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: 30 June 2016, v11.3

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PROTOCOL APPROVAL

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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 Phone Number:

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1 PROTOCOL SYNOPSIS

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Study Phase: Pivotal

Study Design: Open-label, non-randomized, single-arm, multicenter

Study Duration: Primary Endpoint: 6 months post-Scaffold implantation

Long-Term Follow-up Period: 6 months through 10 years post-Scaffold implantation (12 month and 24 month in-clinic visits, and annual phone follow-up through 10 years 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/L1 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 (“Neuro-Spinal Scaffold™” or “Scaffold”) is a porous bioresorbable polymer scaffold comprised of a synthetic biomaterial, poly((lactic-co-glycolic acid)-co-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 intra-spinal post-irrigation contusion 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 four to eight weeks.

**Intended Use:**

The Scaffold is intended for use in patients age 16 – 70 years diagnosed with a T2- T12/L1 (neurological spinal cord level) functionally complete spinal cord injury (AIS A) 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 post-irrigation 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 (≤ 96 hours) spinal cord injuries that do not involve penetrating injury to the cord or complete severing of the cord.

**Number of Subjects:**

Up to 30 subjects to ensure 20 subjects in the Primary Endpoint Analysis Set (defined as subjects with a successful Scaffold implant, 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

**Study Assessments**

**Screening:**

Subjects with recent (≤ 96 hours) T2 –T12/L1 (neurological spinal cord level) 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:**

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 96 hours from the time of injury. Electrophysiological monitoring studies will be performed intraoperatively according to institutional standard of care. For T2 and T3 neurological level injuries, intraoperative neuromonitoring will be conducted during the investigational portion of the open spine surgery. Changes in ventilator parameters due to worsening of pulmonary function will be documented during the investigational portion of the open spine surgery. 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.

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. 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. Following irrigation, the surgeon will collect a sample of the spontaneous exudate or post-irrigation debris if present, and submit to pathology for routine examination/testing, for example Hematoxylin and Eosin (H&E) staining for histology. The Scaffold is wetted and trimmed, if necessary, on one end only to obtain the desired length needed to fit the post-irrigation 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 intra-spinal post-irrigation 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. 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 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 (First 3 Months Assessments): Follow-up assessments will occur post-implantation of the Scaffold 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 (including hip abduction/adduction and great toe flexion/extension at Hospital Discharge through 3 Month Follow-up Visits)
  - 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

- MRI without contrast (72 hour and 3 Month Follow-up Visits)
- Physical examination (Hospital Discharge)

Primary Endpoint Analysis (6 Month 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

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)

Safety event monitoring including potential complications related to the procedure to implant the Scaffold and Scaffold related complications

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**Long-Term Follow-up (Post 6 Months through 10 Year Assessments):**

The Long-Term Follow-up period begins after the 6 month Primary Endpoint Analysis and has both 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, 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 phone 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.

**Inclusion Criteria:**

1. AIS A classification of traumatic spinal cord injury at neurological spinal cord level T2 to T12/L1 confirmed by a qualified medical professional at the time of open spine surgery
2. Recent injury (must receive Scaffold within 96 hours 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

**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. 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
6. 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
7. Subjects with clinically significant pre-existing respiratory disease not related to the contusion being treated (e.g., COPD)
8. Subjects requiring long-term ongoing mechanical ventilation
9. Subjects with documented immune deficiency disorders, including a known diagnosis of HIV infection/AIDS
10. Recent (according to DSM IV or DSM V criteria) history of abuse of narcotics or other significant substance abuse
11. Significant injury complications where, in the view of the Investigator, participation in the study could further complicate subject care
12. 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)

13. 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

14. Current or impending incarceration

15. Radiographic or visual evidence of parenchymal dissociation or anatomic transection as determined by the Investigator where the contusion completely bridges a full cross-section of the spinal cord

16. Subjects with spinal cord injuries directly due to gunshot, knife, or other penetrating wounds.

17. Known hypersensitivity to PLGA or PLL (e.g., hypersensitivity to absorbable sutures containing PLGA)

18. History of severe mental illness (according to DSM IV or V)

19. Evidence of pre-trauma active local or systemic infection

20. Participation in another interventional clinical trial for six months after Scaffold implantation

21. BMI over 39

22. Having a medical condition, or receiving medical treatment, or having any other reason that, in the judgment of the Investigator, precludes successful participation or confounds collection or interpretation of study safety, feasibility, or efficacy data

23. Subjects receiving tetracyclines, such as minocycline (subjects must discontinue tetracyclines to be enrolled in the study; tetracyclines can be resumed after 6 months post-Scaffold implant)

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. 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. Post-operative 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**
Proportion of subjects with improvement in AIS grade of one or more levels

**Secondary Efficacy Endpoints**
1. Proportion of subjects with improvement in sensory scores
2. Proportion of subjects with improvement in motor scores
3. Proportion of subjects with improvement in hip abduction, hip adduction or great toe flexion/extension
4. Proportion of subjects with improvement in bowel function
5. Proportion of subjects with improvement in bladder function
6. Proportion of subjects with decreased pain
7. Proportion of subjects with improvement in SCIM III
8. Proportion of subjects with improvement in QLI-SCI III

Statistical Analysis:
The primary analysis (safety and efficacy) of the study will employ data up to and including the 6 Month Primary Endpoint Follow-up Visit (6 months post-Scaffold implantation). Additional Long-Term Follow-up analyses will be performed for information 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 Amendment 9 and subjects < 22 years old (i.e., pediatric population) will be clearly identified in the data tabulations.

Study population and safety assessment will be tabulated based on the Safety Set which includes all enrolled subjects (i.e., subjects who have signed an Informed Consent Form). Safety events will be coded by system-organ-class and preferred term using the most current Medical Dictionary for Regulatory Activities (MedDRA). Safety events will be tabulated for the first six months post-Scaffold implantation and separately for the Long-Term Follow-up after the first 6 months post-Scaffold implantation.

The primary efficacy analysis will utilize the Primary Endpoint Analysis Set, which includes all subjects who have a successful Scaffold implant, no major protocol deviations, and have completed the 6 Month Primary Endpoint Visit. The primary efficacy analysis will employ the proportion of subjects from the Primary Endpoint Analysis Set who do and who do not demonstrate an increase of at least 1 grade on AIS assessment at the 6 Month Primary Endpoint Follow-up Visit. If the proportion of subjects who demonstrate an increase 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 ≥ 25% as a measure of success. Additional efficacy evaluations will be based on the All Treated Analysis Set that includes all subjects who have the Scaffold successfully implanted.

Reference time point (e.g., Screening or Discharge or 1 month post-Scaffold implant) for each efficacy endpoint will be identified to assess change and identify subjects with maintenance or improvement. Observed scores and change from the identified reference time point will be included in the data tabulation.

Subjects for whom the Scaffold implant is attempted but not successful and a durotomy is performed will undergo safety assessments according to the same visit schedule as subjects who have a Scaffold implanted, and will discontinue the study at the 6 Month Primary Endpoint Follow-up Visit. These subjects
will not be followed during the Long-Term Follow-up Period. Available safety information for these subjects will be provided in data listings.
2 INTRODUCTION

Each year, hospitals in the United States receive over 12,000 new cases of spinal cord injuries (SCI), and more than 273,000 people in the nation are currently living with SCI [1]. Annual global incidence rate is estimated to be 22 per million population, which adds to the total of nearly 2.5 million current survivors [2]. Moreover, researchers across all recent studies of SCI incidence have noted increasing trends in both the percentage of tetraplegics and percentage of complete lesions [3].

Initial spinal cord injury is most often caused by blunt mechanical injury, which may result from contusion or compression [2]. 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 [4]. Throughout the secondary injury, substantial loss of myelin has also been noted [5]. 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) [6]. 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 (≤ 96 hours 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 7.1.3, 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 comprised of poly((lactic-co-glycolic acid)-co-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 [7] 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 intra-spinal post-irrigation contusion cavity if necessary. The Scaffold is placed into the epicenter of the post-irrigation 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 Section 7.1.

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. The first pre-clinical study was conducted in the rat with surgically induced spinal cord injury [8]. While this trial successfully demonstrated the baseline safety and efficacy of the Scaffold, it was felt that moving to the recommended non-human primate with a larger spinal cord and more complex neurological system was necessary to better simulate results more translatable to humans. As a result, a small (4 animal) pilot study in the African Green monkey was undertaken in 2008 (RX08.02). The pilot
African Green monkey study was successful in producing a consistent injury via cord hemisection and in demonstrating a consistently positive response to Scaffold intervention [9].

To demonstrate reproducibility and establish a reliable basis for moving forward with an early feasibility study in a human population, a second, larger randomized study (18 animals) in the African Green monkey (RX09.11) was conducted. A final study in 25 African Green monkeys (RX11.01) was conducted to provide further support for the results observed in the two prior African Green monkey studies. When the results of two of the African Green monkey studies (RX09.11 and RX11.01) were combined and analyzed, Scaffold implantation was found to promote a significant increase in newly formed or remodeled tissue in the region of the hemisection compared with non-implant controls and to improve recovery of locomotion when subjects had a full hemisection lesion.

Due to the limitations presented by using a surgically induced spinal cord injury and the difficulties related to conducting a contusion study in non-human primates, the company conducted several contusion injury studies in rats. The first rat study evaluated the progression of a contusion injury over the first 96 hours in order to select an optimal time for implantation and an appropriate size for a Scaffold. A second pilot study trialed the implantation surgery, and demonstrated that Scaffolds of 1.0 and 1.5 mm diameter matched the size of the contusion lesion based on both histological evaluation and ex vivo MRI techniques.

Larger rat contusion studies were subsequently conducted, two internal studies and an outsourced study. In these studies Scaffold implantation was not associated with any change in latency to respond to a thermal stimulus (no thermal hyperalgesia) or a decrease in body weight. In the outsourced study, 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. In the first internal study, a higher percentage of rats implanted with Scaffolds of 1.0 mm diameter reached a predetermined measure of functional recovery compared with controls, however, this did not reach statistical significance. In the second internal study, histological analysis at 12 weeks revealed that rats in the non-treated control group developed large cavities surrounded by a thin rim of spared tissue. In contrast, in rats implanted with Scaffolds, cavity volume decreased by 86% and spared tissue width increased by 44%. Although Scaffolds were fully resorbed by 12 weeks after implantation, the amount of remodeled tissue at the site of implantation in the lesion epicenter increased by 111%. These results demonstrate that biodegradable Scaffold implantation in the acutely injured spinal cord can reduce cavitation and promote tissue sparing and remodeling.

Finally, the neurosurgical technique for implanting the Scaffold into the recently injured spinal cord was evaluated in the Gottigen pig, a clinically relevant, large animal model. At 4, 6 and 24 hours following
contusion injury, the necrotic injury center was gently debrided following internal decompression via myelotomy and a Scaffold was implanted. In each animal, contusion injury resulted in an intraparenchymal cavity which readily accommodated the Scaffold. In addition, the surgical technique provided the added benefit of reducing 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, the results from these pre-clinical studies in two injury models (hemisection and contusion injury) and three species (the rat, the pig, and the African Green monkey) suggest that following implantation the Scaffold is well tolerated, may serve as a locus for appositional healing and neuropermissive tissue remodeling that can preserve spinal cord architecture, and may play a role in the treatment of SCI.

### 3.3 Potential Risks of 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

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, the potential of occurrence of which may be increased, decreased or the same with Scaffold implantation. Note that a syrinx is defined as an area of fluid within the spinal cord whose rostral and caudal margins are cone shaped and not blunt, considered by some authors to suggest the potential for enlargement, possibly resulting in neurological deterioration or increased pain. Similarly, a syrinx will also appear isointense with CSF on all MRI sequences. It is preferred to reserve the term “syrinx” for a clinical diagnosis of rostral neurologic deterioration correlated to a radiologically established progression of a fluid-filled region within the spinal cord.

9. 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. 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 level of injury 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/L1 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.

**Intended Use:** The Scaffold is intended for use in patients age 16 – 70 years diagnosed with a T2-T12/L1 (neurological spinal cord level) functionally complete spinal cord injury (AIS A) 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 post-irrigation 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 (≤ 96 hours) 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)-co-poly-(L-lysine)) Scaffold (“Scaffold”) in subjects with thoracic AIS A traumatic spinal cord injury.

Subjects who have experienced a recent (must receive Scaffold within 96 hours from injury) spinal cord injury (AIS A) from T2 to T12/L1 (neurological spinal cord level) 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 ASIA. The 5-grade ASIA Impairment Scale will be used to determine the completeness of a subject’s injury. The ISNCSCI examination includes sensory and motor function assessments. A rectal examination will be used to assess deep anal pressure sensation and voluntary anal contraction to determine the completeness of the 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). Furthermore, magnetic resonance imaging (MRI) studies without contrast will be performed to measure and characterize the contusion and its location. The contusion dimensions (length and anteroposterior diameter) will be estimated. 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. Other baseline assessments at screening will include subject demographics, general medical/medication history, physical examination, neurological exam, resting vital signs, Vital Capacity (VC) for subjects who are not ventilator dependent, and baseline clinical laboratory tests. Body mass index (BMI) at screening will be calculated based on actual, self-reported or family-reported weight and height.

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.
Within approximately 8 hours prior to open spine surgery, the AIS classification of the subject will be confirmed to ensure only subjects with a reliable AIS A classification will be implanted with the Scaffold. The Scaffold will be implanted at the time of open spine surgery and not during a second or separate surgery, and ideally within 24 hours from the time of injury but no longer than 96 hours from the time of injury.

After completion of the spine surgery, the Investigator will ensure the subject continues to meet eligibility criteria.

For subjects with a T2 or T3 neurological level of injury, bilateral intraoperative median and ulnar nerve somatosensory evoked potential (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 can 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. 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 motor evoked potentials (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, as initially assessed by the preoperative MRI. Based upon the contusion cavity size, the Investigator will select and prepare an appropriately sized Scaffold. The Investigator will then perform a durotomy, arachnoid/pial resection, and after the epicenter of the contusion cavity has been identified/reached (e.g., by myelotomy), further irrigate the contusion with isotonic saline for the purposes of debridement as necessary to remove additional areas of hemorrhage and necrotic tissue within the cavity. During gentle irrigation, 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. Next, the Scaffold will be placed into the epicenter of the intra-spinal post-irrigation contusion cavity.

A second intraoperative ultrasound, with photograph, should be performed to confirm placement of the Scaffold in the spinal cord. The dura will be closed in standard surgical fashion. 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. The surgical wound will then be closed and dressed according to standard clinical practice. See Section 7.1 and Appendix E (Instructions for Use) for more details on the preparation of the Scaffold and implant procedure.

Following surgery, vital signs will be monitored and qualified medical personnel will perform neurological examinations in a manner consistent with standard post-anesthesia care. Subjects will be cared for in the hospital and after discharge following the standard medical care practice for SCI patients.

The cylindrical-shaped 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. Therefore, the post-Scaffold implantation Follow-up study visits will be determined based on the date/time the Scaffold implantation procedure was finished and will be at 24 hours, 48 hours, 72 hours, 1 week, at hospital discharge, 1 month, 2 months, 3 months, and 6 months. The Long-Term follow-up visits will be in clinic at 12 months and 24 months, and annually by phone for years 3 through 10.

Post-Scaffold implantation Follow-up assessments will consist of ISNCSCI, neurological examinations (including hip abduction/adduction and great toe flexion/extension at Discharge through 6 Month Primary Endpoint Follow-up Visit), Spinal Cord Independence Measure (SCIM III), Ferrans and Powers Quality of Life Index - Spinal Cord Injury (QLI-SCI III), Beck Depression Inventory-II (BDI-II), bowel and bladder function, routine laboratory tests, Vital Capacity (VC) for subjects who are not ventilator dependent, and resting vital signs. In addition, an MRI without contrast will be performed at the 72 Hour, 3 Month and 6 Month Primary Endpoint Follow-up Visits, and a physical exam will be performed at the Discharge Visit and the 6 Month Primary Endpoint Follow-up Visit. Safety event monitoring including procedure and Scaffold related complications will occur at all Follow-up Visits and will include adverse device effects (ADEs), unanticipated adverse device effects (UADEs), and all serious safety events (SAEs/SADEs). Subjects will participate in comprehensive rehabilitative programs for spinal cord surgery patients (Section 7.1.3) and a Rehabilitation Therapy Log will be completed.

Long-Term Follow-up assessments will be conducted in clinic at 12 months and 24 months post-Scaffold implantation, and annually for years 3 – 10. In-clinic Long-Term Follow-up Visits will consist of ISNCSCI, neurological examinations including hip abduction/adduction and great toe flexion/extension, MRI without
contrast, routine laboratory tests, resting vital signs and a physical exam. At the 12 Month Long-Term Follow-up Visit only, SCIM III, QLI-SCI III, BDI-II, and bowel and bladder function will be assessed. The Rehabilitation Therapy Log will be completed through the 12 month Long-Term Follow-up Visit. Safety event monitoring including procedure and Scaffold related complications will occur at the 12 Month and 24 Month Long-Term Follow-up visits and will include adverse device effects (ADEs), unanticipated adverse device effects (UADEs), and all serious safety events (SAEs/SADEs). An annual telephone Long-Term Follow-up Visit will be conducted for years 3 – 10 and will collect general health information. If at any time 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.

The safety of the Scaffold will be assessed by incidence of all safety events of any kind/seriousness, all serious safety events, all unanticipated ADEs, and incidence of specified risks (See Section 8.3) associated with the use of the Scaffold and/or associated with the neurosurgical procedures. Findings from clinical laboratory tests, resting vital signs, and the BDI-II will also be examined.

The efficacy of the Scaffold will be measured by improvements in AIS grade, ISNCSCI motor and sensory scores, bowel and bladder function, hip abduction/adduction, great toe flexion/extension, SCIM III, and QLI-SCI III at follow-up visits.

An independent Data Safety Monitoring Board (DSMB) will monitor subject safety on an on-going basis. The DSMB will be notified of all Serious Safety Events, Safety Events of Interest (Section 8.3), and Study Stopping Rules (Section 7.11). The DSMB may recommend that the study enrollment be put on hold or the study be terminated should safety events occur that are Scaffold-related and distinct from a safety event that may be associated with standard of care open spine surgery or sequelae considered part of the normal course of a non-penetrating SCI (contusion injury) following such surgery (See Section 7.11).

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 7.1.3). 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 phone.

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 continuously being updated. A recent paper including almost 400 subjects with thoracic (T2-T12) complete (AIS A) SCI (same population evaluated in this study) [10] 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 change, 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 [2, 10, 11]. 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 neurological spinal cord level T2 to T12/L1 confirmed by a qualified medical professional at the time of open spine surgery
2. Recent injury (must receive Scaffold within 96 hours 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. 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
6. 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

7. Subjects with clinically significant pre-existing respiratory disease not related to the contusion being treated (e.g., COPD)

8. Subjects requiring long-term ongoing mechanical ventilation

9. Subjects with documented immune deficiency disorders, including a known diagnosis of HIV infection/AIDS

10. Recent (according to DSM IV or DSM V criteria) history of abuse of narcotics or other significant substance abuse

11. Significant injury complications where, in the view of the Investigator, participation in the study could further complicate subject care

12. 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)

13. 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

14. Current or impending incarceration

15. Radiographic or visual evidence of parenchymal dissociation or anatomic transection as determined by the Investigator where the contusion completely bridges a full cross-section of the spinal cord

16. Subjects with spinal cord injuries directly due to gunshot, knife, or other penetrating wounds.

17. Known hypersensitivity to PLGA or PLL (e.g., hypersensitivity to absorbable sutures containing PLGA)

18. History of severe mental illness (according to DSM IV or V)

19. Evidence of pre-trauma active local or systemic infection
20. Participation in another interventional clinical trial for six months after Scaffold implantation

21. BMI over 39

22. Having a medical condition, or receiving medical treatment, or having any other reason that, in the judgment of the Investigator, precludes successful participation or confounds collection or interpretation of study safety, feasibility, or efficacy data

23. Subjects receiving tetracyclines, such as minocycline (subjects must discontinue tetracyclines to be enrolled in the study; tetracyclines can be resumed after 6 months post-Scaffold implant)

6.3 Duration of the Study

Subjects who are enrolled will be followed for ten years after Scaffold implantation. The Screening period is a maximum of 96 hours between the time of injury and the time 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 Primary Endpoint Analysis is at the 6 Month Primary Endpoint Follow-up Visit post-Scaffold implantation. The Long-Term Follow-up is after the 6 Month Primary Endpoint Follow-up Visit through 10 years, with a 12 Month and a 24 Month Long-Term Follow-up visit at the study center, and the remaining annual Long-Term Follow-up visits are conducted over the phone. 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 30 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 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 FDA 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 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 FDA 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 7.10.6). 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 which includes all Visit 13 (24 Month Long-Term Follow-up Visit) protocol-required assessments (see Section 7.10.7). 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 phone 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 phone 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 Scaffold Implantation

7.1.1 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 subject 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 in the study. The Investigator conducts procedures specific to the study protocol that are needed to evaluate the subject’s eligibility (screening), 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 7.8.8). 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.

### 7.1.2 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 96 hours from the time of injury. 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. 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.

Sites should bring all available Scaffolds and sterilized Cupped Forceps to the Scaffold implant procedure.

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.

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.

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 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 post-irrigation 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. If a penetrating injury to the spinal cord is identified, the Scaffold should not be implanted. In this case, the Investigator should close the dura and the surgical wound, and dress the wound according to standard clinical practice, and the subject is considered enrolled with procedure but not treated (Section 6.5).

An arachnoid/pial incision will be made over the contusion allowing direct access to the injured parenchyma. After the epicenter of the contusion cavity has been identified/reached (e.g., by myelotomy), the contusion is further 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. Following irrigation, 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.

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 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 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 operation. 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 post-irrigation cavity in the epicenter of the contusion using bayoneted forceps and/or the size-matched Cupped Forceps. An appropriate size Scaffold must allow insertion into the post-irrigation contusion 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 post-irrigation contusion 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 surgery start date/time (the date/time of the first incision) and stop date/time (the date/time of closing the skin after all surgical procedures and the Scaffold implant are complete), Scaffold implant start date/time (the date/time the dura is opened) and stop date/time (the date/time the dura is closed), Scaffold length, implant location and any problems encountered (e.g., Scaffold fracture, inability to place Scaffold, Scaffold migration, need to secure Scaffold). In addition, 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.

7.1.3 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, and as early as 96 hours after surgery. 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 7.8.11).

### 7.2 Method of Assigning Treatment Groups

Not Applicable.

### 7.3 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.

### 7.4 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 ±10% range for the length (Table 1).

<table>
<thead>
<tr>
<th>Scaffold Diameter</th>
<th>Scaffold Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>2mm (1.7 – 2.1mm)</td>
<td>10mm (9.0 – 11.0mm)</td>
</tr>
<tr>
<td>3mm (2.55 – 3.15mm)</td>
<td>10mm (9.0 – 11.0mm)</td>
</tr>
</tbody>
</table>

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 surgical procedure with corresponding figures.

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

7.5 Prior and Concomitant Medications

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 on the Concomitant Medication eCRF 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. The information documented will include the medication name, indication, dosage, and the dates of start and discontinuation.

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 on the Prior and Concomitant Medications eCRF. Subjects may receive medications to treat safety events and routine treatment for underlying medical conditions as deemed necessary by the Investigator.

7.6 Prior and Concomitant Interventions and Procedures

All interventions or procedures, whether diagnostic or therapeutic, which were administered to a subject beginning 30 days before Scaffold implantation and continuing throughout the subject’s participation will be recorded on the Concomitant Intervention and Procedure eCRF 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. The intervention or procedure 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.

7.7 Demographics and Baseline Assessments

7.7.1 Demographics

Demographics information will be collected during the screening visit including age, sex, ethnicity, and race.
7.7.2 Medical and Surgical History

The Investigator or designee will document each subject’s general medical and surgical history during 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) or serious safety event (SAE/SADE), and if so, will be documented on the Safety Event eCRF.

7.7.3 Spinal Cord Injury Assessment

The spinal cord injury related data will include: date, time, and cause of the injury; neurological level of injury, complete ISNCSCI exam size and location of the injury identified by MRI, prior SCI therapies/procedures in the field and before study participation. All spinal cord injury data will be documented on the appropriate eCRF.

7.8 Safety Assessments Description

7.8.1 Intraoperative Ultrasound

An ultrasound will be performed intraoperatively and immediately prior to the Scaffold implantation to confirm the contusion size and location, and presence or absence of a cavity, and the data will be documented in the eCRF. A second intraoperative ultrasound will also be performed after Scaffold implantation to confirm correct placement of the Scaffold. Ultrasound images of the spinal cord post-irrigation contusion/cavity and the Scaffold in the spinal cord, as well as ultrasound recordings (if ultrasounds are recorded), should be included in the source documents and provided to the Sponsor.

7.8.2 Intraoperative Neuromonitoring (subjects with T2 or T3 neurological level SCI only)

As an additional safety measure, intraoperative neuromonitoring 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 intraoperative neuromonitoring will consist of median and ulnar nerve SSEP monitoring 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 it 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. 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 indicate in the eCRF the neuromonitoring performed during the investigational procedure, if there was a deterioration in the signal, and if any actions were taken.

7.8.3 Monitoring of Pulmonary Function

Changes in pulmonary function, as indicated by changes in ventilator parameters, will be monitored during the investigational portion of the 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.
7.8.4 Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (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. MRI studies will be performed prior to the open spine surgery (Screening MRI), and following Scaffold implantation at the 72 Hour, 3 Month, 6 Month Primary Endpoint Follow-up Visits, and at the 12 Month and 24 Month Long-Term Follow-up Visits. All study MRIs should be conducted without contrast.

The Screening MRI is required for all study subjects. The Investigator will use the Screening MRI to estimate the contusion dimensions (length and anteroposterior diameter), determine the contusion location, presence or absence of a cavity, parenchymal sparing, atrophic changes of the cord, and identify areas of edema and hemorrhage. The Screening MRI and any other available imaging study such as CT or intraoperative ultrasound should be used to estimate that a minimum 4 mm diameter spinal contusion is present per the study eligibility criteria.

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 conducted.

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

MRI 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.
7.8.5 Physical Examination, including Weight and Height

The Investigator or designee will perform a complete physical examination (Head, Ears, Eyes, Nose and Throat (HEENT), cardiovascular, respiratory, gastrointestinal, neurological unrelated to SCI, dermatologic, and musculoskeletal systems) at screening, discharge, 6 months, 12 months, and 24 months post-Scaffold Implantation. 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.

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 reported in the eCRF (through 24 Month Long-Term Follow-up) or the annual General Health Assessment (Long-Term Follow-up years 3 – 10).

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.

7.8.6 Clinical Laboratory Tests

During the screening visit, on the day of the open spine surgery, and at every Follow-Up/Primary Endpoint Follow-up/Long-Term Follow-up Visit up to and including the 24 Month Long-Term Follow-up Visit, subjects will have blood samples collected for routine clinical laboratory testing.

Laboratory tests will include:

- **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.

Additional laboratory tests to be performed at Screening only include:

- Serum pregnancy testing
- Blood alcohol and urine drug toxicology
- Blood type and coagulation tests (PT, PTT, INR)
The site must have received the results of the screening laboratory tests before the subject receives Scaffold implantation.

The following laboratory tests will be performed at screening, discharge, 1 month, 2 months, and 3 months:

- Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP)

### 7.8.7 Vital Sign Measurements

Resting vital signs, including the resting blood pressure, resting pulse, respiratory rate, and temperature will be measured at screening and before surgery.

Following surgery, vital signs will be monitored in a manner consistent with standard post-anesthesia care per ICU routine.

Vital signs will be taken at all study visits up to and including Month 24, and recorded in the eCRFs.

### 7.8.8 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 portable hand-held 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.

### 7.8.9 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.

7.8.10 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 is comprised of 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

The BDI-II will be used to assess the subject’s mood at hospital discharge and at months 1, 2, 3, 6 and 12. A score of 17 or higher may indicate the presence of major 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.

7.8.11 Rehabilitation Therapy Log

A comprehensive rehabilitation program is recommended for all study subjects as outlined in Section 7.1.3.

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 Discharge and through the 12 Month Long-Term Follow-up Visit.
7.8.12 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 phone 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.

7.9 Efficacy Assessments Description

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

The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) Exam will be assessed at screening, within the 8 hours prior to surgery, at discharge, and at each Follow up/Long-Term Follow-up Visit after discharge up to and including 24 Month Long-Term Follow-up Visit. 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). AIS classification, and ISNCSCI motor and sensory scores will be recorded in the eCRF.

7.9.2 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. Neurological examinations will be performed at Screening, on the day of open spine surgery per site Standard of Care, and after implantation of the Scaffold at 24 hours, 48 hours, 72 hours, and 1 week.

Beginning at Hospital Discharge and through remaining in-clinic Follow-up/Long-Term Follow-up Visits, the presence/absence of hip abduction/adduction and great toe flexion/extension on the left and right sides will be assessed using a 2-point scale (0=absent; 1=present).
7.9.3 Pain Assessment (Appendix G)

Pain assessment will focus on the worst pain problems that a subject had during the last 7 days. The site will interview the subject regarding their worst pain problems including the location of the pain and the frequency of occurrences of pain, and complete the required assessments.

Pain assessment will be performed at Discharge and at each Follow up/Long-Term Follow-up Visit up to and including the 12 Month Long-Term Follow-up Visit. The pain assessment at hospital discharge visit will be used as the baseline.

7.9.4 Bowel and Bladder Function Assessments (Appendix H)

Bowel and bladder function assessments will be performed and recorded in the eCRF at 1 month, 2 months, 3 months, 6 months, and 12 months post-Scaffold implantation.

7.9.5 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), Mobility Indoors and Outdoors (0-30). The final score ranges from 0 to 100, with 0 being requiring total assistance and 100 being completely independent. SCIM III will be used to assess the subject’s quality of life at hospital discharge and at months 1, 2, 3, 6 and 12.

7.9.6 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 used to assess the subject’s quality of life at hospital discharge and at months 1, 2, 3, 6 and 12.

7.10 Study Observations and Procedures by Visits

7.10.1 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 96 hours 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 7.7.1)
- Medical and surgical history (Section 7.7.2)
- Complete physical examination (Section 7.8.5)
- Laboratory tests including screening laboratory tests - serum pregnancy test, blood alcohol and urine drug toxicology, blood type and coagulation test (Section 7.8.6)
- Erythrocyte Sedimentation Rate (ESR) & C-Reactive Protein (CRP)
- Measurement of resting vital signs (Section 7.8.7)
- Vital Capacity for subjects not ventilator dependent (Section 7.8.8)
- Neurological exam (Section 7.9.2)
- ISNCSCI Exam (Section 7.9.1)
- MRI without contrast (Section 7.8.3)
- Prior and concomitant medications, interventions and procedures (Section 7.5, 7.6)
- 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 7.8.8). X-rays obtained during the preoperative period may be used for this assessment.

7.10.2 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 ≤ 96 hours from the time of the spinal cord injury.
**Before Surgery:** On the day of surgery, the following safety assessments will be conducted in all subjects before surgery:

- Confirmatory ISNCSCI Exam within the 8 hours prior to surgery (Section 7.9.1)
- Clinical laboratory tests (Section 7.8.6)
- Measurement of resting vital signs (Section 7.8.7)
- Neurological exam (Section 7.9.2)

**Surgery:** After eligibility is confirmed, the following assessments will be conducted intraoperatively:

- For subjects with a T2 or T3 neurological level of injury, intraoperative neuromonitoring minimally consisting of median and ulnar nerve SSEPs (Section 7.8.2)
- Documentation of changes in ventilator parameters due to worsening of pulmonary function (Section 7.8.3). 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.
- Scaffold implantation procedure according to the Instructions for Use (Appendix E) including:
  - Collection of a sample of the spontaneous exudate, if present during gentle irrigation of contusion, 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 07.8.1)
  - Intraoperative ultrasound with photograph after Scaffold implantation to document placement of Scaffold in the spinal cord (Section 7.8.1)
  - Video of the Scaffold implant procedure (Section 7.1.2)
- Safety events monitoring of (Section 8)

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

- Clinical laboratory tests (Section 7.8.6)
- Measurement of resting vital signs (Section 7.8.7)
- Neurological exam (Section 7.9.2)
- Concomitant medications, interventions and procedures (Section 7.5, 7.6)
- 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. (Section 7.8.3)

- Safety event monitoring (Section 8)

### 7.10.3 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):

- Clinical laboratory tests (Section 7.8.6)
- Measurement of resting vital signs (Section 7.8.7)
- Vital Capacity for subjects not ventilator dependent (Section 7.8.8)
- Neurological exam (Section 7.9.2)
- Concomitant medications, interventions and procedures (Section 7.5, 7.6)
- Safety event monitoring (Section 8)
- MRI without contrast at 72 Hour Follow-up Visit only (Section 7.8.3)

### 7.10.4 Hospital Discharge (Visit 7)

On the day of hospital discharge the following procedures will be performed:

- Complete physical examination (Section 7.8.5)
- Clinical laboratory tests (Section 7.8.6)
- Erythrocyte Sedimentation Rate (ESR) & C-Reactive Protein (CRP)
- Measurement of resting vital signs (Section 7.8.7)
- Vital Capacity for subjects not ventilator dependent (Section 7.8.8)
- Neurological examinations including hip abduction/adduction and great toe flexion/extension (Section 7.9.2)
- Baseline pain assessment (Section 7.9.3)
- ISNCSCI Exam (Section 7.9.1)
- SCIM III (Section 7.9.5)
- QLI-SCI III (Section 7.9.6)
- BDI-II (Section 7.8.10)
- Rehabilitation Therapy Log (Section 7.8.11)
- Concomitant medications, interventions and procedures (Section 7.5, 7.6)
• Safety event monitoring (Section 8)
• For subjects ages 16, 17, if not already completed, assessment of skeletal maturity must be performed prior to hospital discharge (Section 7.8.7)
  
  Note that the assessments must be performed on the date of discharge, and there is no visit window.

7.10.5 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:

• Clinical laboratory tests (Section 7.8.6)
• Erythrocyte Sedimentation Rate (ESR) & C-Reactive Protein (CRP) (Section 7.8.6)
• Measurement of resting vital signs (Section 7.8.7)
• Neurological examinations including hip abduction/adduction and great toe flexion/extension (Section 7.9.2)
• Pain assessment (Section 7.9.3)
• ISNCSCI Exam (Section 7.9.1)
• Bowel and bladder function assessments (Section 7.9.4)
• SCIM III (Section 7.9.5)
• QLI-SCI III (Section 7.9.6)
• BDI-II (Section 7.8.10)
• MRI without contrast at 3 months (Section 7.8.3)
• Rehabilitation Therapy Log (Section 7.8.11)
• Concomitant medications, interventions and procedures (Section 7.5, 7.6)
• Safety event monitoring (Section 8)

7.10.6 Primary Endpoint - 6 Month Follow-up (Visit 11)

The 6 Month Primary Endpoint Follow-up Visit at 6 months post-Scaffold implantation (±30 days) is the primary endpoint assessment visit. The following study assessments will be conducted:

• Clinical laboratory tests (Section 7.8.6)
• Measurement of resting vital signs (Section 7.8.7)
• Neurological examinations including hip abduction/adduction and great toe flexion/extension (Section 7.9.2)
• Complete physical examination (Section 7.8.5)
- Pain assessment (Section 7.9.3)
- ISNCSCI Exam (Section 7.9.1)
- Bowel and bladder function assessments (Section 7.9.4)
- SCIM III (Section 7.9.5)
- QLI-SCI III (Section 7.9.6)
- BDI-II (Section 7.8.10)
- MRI without contrast (Section 7.8.3)
- Rehabilitation Therapy Log (Section 7.8.11)
- Concomitant medications, interventions and procedures (Section 7.5, 7.6)
- Safety event monitoring (Section 8)

7.10.7 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:

- Clinical laboratory tests (Section 7.8.6)
- Measurement of resting vital signs (Section 7.8.7)
- Neurological examinations including hip abduction/adduction and great toe flexion/extension (Section 7.9.2)
- ISNCSCI Exam (Section 7.9.1)
- Safety event monitoring (Section 8)
- MRI without contrast (Section 7.8.3)
- Complete physical examination (Section 7.8.5)

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

- Pain assessment (Section 7.9.3)
- Bowel and bladder function assessments (Section 7.9.4)
- SCIM III (Section 7.9.5)
- QLI-SCI III (Section 7.9.6)
- BDI-II (Section 7.8.10)
- Rehabilitation Therapy Log (Section 7.8.11)
**Telephone (Visits 14 – 21)**

For years 3 through 10, the site will contact the subjects via phone on or about the annual anniversary of the date of their Scaffold implantation (date of Scaffold implantation ± 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.

**7.10.8 End of Study Assessment (Year 10/Visit 21 or final Study Visit for withdrawn subjects)**

An end of study assessment will be conducted over the phone at the final study Long-Term Follow-up Visit at year 10 (±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. 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.

**7.11 Study Stopping Rules**

The study will 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 (contusion injury) following such surgery, as determined by the DSMB. Following urgent consultation with the DSMB and FDA, the study will 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 sensory deterioration at more than 2 dermatome levels, on two successive examinations at least 8 hours apart.

5. Motor deterioration of at least a 5-point change of the motor score compared with baseline.

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 or motor deterioration of less than a 5-point change of the motor score compared with baseline). 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 sensory score indicating a greater than 2-dermatome 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), further subject enrollment will be held to allow for review of the event by the Sponsor, FDA, and the DSMB.

7.12 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be formed to monitor and review the study results. The DSMB will be comprised of an independent group of at least three members (ideally a neurosurgeon, a physical medicine and rehabilitation physician, and a statistician) that have 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 their 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 7.11) 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 a safety events that meet Study Stopping Rules (Section 7.11). 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.

7.13 Appropriateness of Assessments

The efficacy measures utilized include the AIS grading, and the ISNCSCI motor and sensory scores. Safety measures used in this study are standard for clinical studies of investigational product 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 which 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)

A 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

- 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

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 7.11), 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.
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 Event that Meet Study Stopping Rules.

E-mail transmission is the preferred method to transmit SAE/SADE/UADE/Safety Event of Interest/Safety Event 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 Event 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 Event 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 Event 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 Event 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 the either 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: jbara@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 30 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 are 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 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
   - 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

The primary efficacy endpoint will be the proportion of subjects in the Primary Endpoint Analysis Set with an AIS improvement from baseline of one or more grades at the 6 Month Primary Endpoint Follow-up Visit (6 months post-Scaffold implantation).

Additional efficacy endpoints include:

1. Proportion of subjects with improvement in sensory scores
2. Proportion of subjects with improvement in motor scores
3. Proportion of subjects with improvement in hip abduction, hip adduction or great toe flexion/extension
4. Proportion of subjects with improvement in bowel function
5. Proportion of subjects with improvement in bladder function
6. Proportion of subjects with decreased pain
7. Proportion of subjects with improvement in SCIM III
8. Proportion of subjects with improvement 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 provided informed consent). The Safety Set will be used for the study population summary and safety endpoints summary.

**All Treated Set:** The All Treated Set includes all subjects in the Safety Set who have a successful Scaffold implant. The All Treated Set will be used for efficacy analyses.

**Primary Endpoint Analysis Set:** The Primary Endpoint Analysis Set includes all subjects in the All Treated 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 be used for the primary efficacy analysis and to determine whether the objective performance criterion has been met.

Separate efficacy tabulations will be performed for the subjects enrolled prior to initiation of Amendment 9 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.

For the All Treated Set, 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 last 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 implantation will result in the event being considered as having started after the initiation of device implantation.

Safety events will be coded by system-organ-class and preferred term using the most current Medical Dictionary for Regulatory Activities (MedDRA). Events will be tabulated for the first six months post implantation and separately for the study period after the first six month post implant period.
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 system organ class and preferred term, that subject will be tabulated under the worst severity for that safety event category. 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.

9.3.4 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 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 7.10 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 screened subjects, subjects treated with the Scaffold, subjects who had attempted but unsuccessful implantation of the Scaffold (treated/durotomy performed or untreated/durotomy not performed), subjects who completed the 6 Month Primary Endpoint Follow-up period of the study, 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 Disease Characteristics

The demographic summary will include descriptive statistics for age, sex, race, weight, height, and BMI at the baseline.

Baseline disease characteristics will include levels of spinal cord injury, baseline neurological exam, ISNCSCI motor and sensory scores, 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 or that may significantly affect a subject’s rights, safety, or well-being. 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. Final decisions will be documented and databased.

The Primary Endpoint Analysis Set includes all subjects in the All Treated Set who have no major protocol deviations as described above and have completed the 6 Month Primary Endpoint Follow-up Visit. The Primary Endpoint Analysis Set will be used for the primary efficacy analysis and to determine whether the objective performance criterion has been met.

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.

Summaries will be separated by medications and interventions, and will be presented for data up to the primary endpoint at the 6 Month Primary Endpoint Follow-up Visit (post-Scaffold implantation) separately.

9.5 Safety Evaluations

9.5.1 Extent of Exposure

The Scaffold is a biodegradable 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

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 be presented for data up to the primary endpoint at the 6 Month Primary Endpoint Follow-up Visit (post-Scaffold implantation) separately and 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 intensity for that safety event category. 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 study visits up to and including Month 24, with a separate analysis being performed using data up to the 6 Month Primary Endpoint Follow-up Visit (post-Scaffold implantation). Observed values at each time point, and change from screening, pre-surgery, 24-hour post-Scaffold implant, and hospital discharge will be summarized without formal statistical testing.

9.5.4 Vital Sign Measurements

Observed resting vital sign values, change from screening, change from the day of open spine surgery (as measured before the surgery) and change from hospital discharge in vital signs at each visit will be summarized without formal statistical testing. A separate analysis will be performed using data up to the 6 Month Primary Endpoint Follow-up Visit (post-Scaffold implantation).
9.5.5 Beck Depression Inventory II (BDI-II)

BDI-II will be assessed at discharge and at months 1, 2, 3, 6, and 12. BDI-II results at discharge will be used as the reference time point (baseline) to assess changes in subjects’ severity of depression at months 1, 2, 3, 6, and 12. Analysis will include total score and subjects with changes will be identified. Question 9 on the BDI-II that deals with suicidal thoughts will be tabulated separately. In addition, a separate analysis will be performed using data up to the primary endpoint at the 6 Month Primary Endpoint Follow-up Visit (post-Scaffold implantation).

9.5.6 Subgroup Analyses for Safety Endpoints

Separate Safety Event tabulations will be performed for the subjects enrolled prior to initiation of Amendment 9.

9.6 Efficacy Analysis

The Primary Endpoint Analysis Set and the All Treated Set (successful Scaffold implant) will be used for efficacy analyses. For the All Treated Set, there will be no imputation of missing 6 Month Primary Endpoint Follow-up Visit AIS assessment. For the purpose of this 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.

9.6.1 Primary Efficacy Analysis

The primary efficacy analysis will employ the proportion of subjects from the Primary Endpoint Analysis Set who do and who do not demonstrate an increase of at least 1 grade on AIS assessment at the primary endpoint 6 Month Primary Endpoint Follow-up Visit. If the proportion of subjects who demonstrate an increase of at least 1 grade on AIS 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.

9.6.2 AIS Grade Improvement

The efficacy analyses will include assessment of any AIS grade improvement. The confirmatory ISNCSCI exam performed within 8 hours prior to surgery will be used as the reference time. Change from 8 hours prior to surgery will be evaluated at each follow-up time point. A positive value indicates an improvement and a negative value indicates a deterioration of the condition. Summaries will provide descriptive statistics for AIS grade, observed change in AIS grades, and cumulative changes in AIS grade at each time point.
Again, the primary analysis for this study will be performed for information up to and including the 6 Month Primary Endpoint Follow-up Visit.

### 9.6.3 ISNCSCI Motor and Sensory Scores

The efficacy analysis will include ISNCSCI motor and sensory scores at 1 month, 2 months, 3 months, 6 months, 12 months and 24 months post Scaffold implantation. The confirmatory ISNCSCI exam performed within 8 hours prior to surgery (confirmatory screening) and at hospital discharge will be used as the reference time points to assess changes in the motor score (maximum score = 100), pin prick score (maximum score = 112), light touch score (maximum score = 112), and total sensory score (sum of pin prick score and light touch score). Change from confirmatory screening and change from hospital discharge will be calculated at each time point (Change = Visit – Reference (Confirmatory screening or Discharge)). A positive value indicates an improvement and a negative value indicates a deterioration of the condition. Summaries will provide descriptive statistics for observed score, observed change in score, and cumulative changes in score at each time point for each category. If data permit, data could also be tabulated at each item level.

ISNCSCI scores over time for each subject will be graphically displayed. Again, the primary analysis for this study will be performed for information up to and including the 6 Month Primary Endpoint Follow-up Visit. A separate analysis will be performed for information obtained after the 6 Month Primary Endpoint Follow-up Visit.

### 9.6.4 Improvement in Motor Score

Tabulations will be prepared to show number of points improved at each post-Scaffold implantation Primary Endpoint Follow-up and Long-Term Follow-up time point through 24 months, and total number of points improved for each subject. Percent of improvement as compared to the screening visit and as compared to the hospital discharge will be presented. The primary analysis for this endpoint will be performed for information up to and including the 6 Month Primary Endpoint Follow-up Visit. A separate analysis will be performed for information obtained after the 6 Month Primary Endpoint Follow-up Visit.

### 9.6.5 Improvement in Sensory Score

Tabulations will be prepared to show number of points improved at each post-Scaffold implantation Primary Endpoint Follow-up and Long-Term Follow-up time point through 24 months, and total number of points improved for each subject. Percent of improvement as compared to the screening visit and as compared to the hospital discharge will be presented. The primary analysis for this endpoint will be
performed for information up to and including the 6 Month Primary Endpoint Follow-up Visit. A separate analysis will be performed for information obtained after the 6 Month Primary Endpoint Follow-up Visit.

**9.6.6 Improvement in Hip Abduction/Adduction and Great Toe Flexion/Extension**

Hip abduction/adduction and great toe flexion/extension will be assessed at all study visits beginning at Hospital Discharge through the 24 Month Long-Term Follow-up Visit. The hip abduction/adduction and great toe flexion/extension results at Hospital Discharge will be used as the reference time point (baseline) to assess changes at months 1, 2, 3, 6, 12, and 24. Subjects with improvement will be identified. The primary analysis for this endpoint will be performed for information up to and including the 6 Month Primary Endpoint Follow-up Visit. A separate analysis will be performed for information obtained after the 6 Month Primary Endpoint Follow-up Visit.

**9.6.7 Improvement in Bowel Function**

Bowel function will be assessed at 1 month, 2 months, 3 months, 6 months, and 12 months post-Scaffold implantation. Bowel function at the 1 Month Follow-up Visit will be used as the reference time point (baseline) to identify any improvement at the 2, 3, 6, and 12 months data points. Degree of improvement and temporal pattern to implantation will be evaluated. The primary analysis for this endpoint will be performed for information up to and including the 6 Month Primary Endpoint Follow-up Visit. A separate analysis will be performed for information obtained after the 6 Month Primary Endpoint Follow-up Visit.

**9.6.8 Improvement in Bladder Function**

Bladder function will be assessed at 1 month, 2 months, 3 months, 6 months, and 12 months post-Scaffold implantation. Bladder function at the 1 Month Follow-up Visit will be used as the reference time point (baseline) to identify any improvement at the 2, 3, 6, and 12 months data points. Degree of improvement and temporal pattern to implantation will be evaluated. The primary analysis for this endpoint will be performed for information up to and including the 6 Month Primary Endpoint Follow-up Visit. A separate analysis will be performed for information obtained after the 6 Month Primary Endpoint Follow-up Visit.

**9.6.9 Improvements in Pain**

Pain assessment findings by time profile will be prepared for each subject. Pain score at the hospital discharge will be used as the reference time point (baseline) for the assessment of change in pain intensity. Subjects with decreased pain at each follow-up visit after hospital discharge will be identified and listed. A separate primary analysis will be performed for information up to and including the 6 Month Primary Endpoint Follow-up Visit.
9.6.10 Improvements in SCIM III

SCIM III will be assessed at discharge and at months 1, 2, 3, 6, and 12. SCIM III results at discharge will be used as the reference time point (baseline) to assess changes in subjects’ quality of life at months 1, 2, 3, 6, and 12. Subjects with improvement will be identified. Analysis will include total score as well as scores for each sub-domain. The primary analysis for this endpoint will be performed for information up to and including the 6 Month Primary Endpoint Follow-up Visit. A separate analysis will be performed for information obtained after the 6 Month Primary Endpoint Follow-up Visit.

9.6.11 Improvements in QLI-SCI III

QLI-SCI III will be assessed at discharge and at months 1, 2, 3, 6, and 12. QLI-SCI III results at discharge will be used as the reference time point (baseline) to assess changes in subjects’ quality of life at months 1, 2, 3, 6, and 12. Subjects with improvement will be identified. Analysis will include total score as well as scores for each sub-domain. The primary analysis for this endpoint will be performed for information up to and including the 6 Month Primary Endpoint Follow-up Visit. The primary analysis for this endpoint will be performed for information up to and including the 6 Month Primary Endpoint Follow-up Visit. A separate analysis will be performed for information obtained after the 6 Month Primary Endpoint Follow-up Visit.

9.6.12 Covariate Analyses for Efficacy

No covariance analysis is planned.

9.6.13 Subgroup Analyses for Efficacy

Separate efficacy tabulations will be performed for the subjects enrolled prior to initiation of Amendment 9. 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 is planned at the time the first 5 subjects who have received a Scaffold implant have completed the 6 Month Follow-up Visit post-Scaffold implantation. The purpose of this interim evaluation is to support conversion of the pilot study into a HDE probable benefit study enrolling up to 30 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. 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 7.12 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 may have already 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 that a study site is located in). 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


### APPENDIX A: Summary of Study Procedures

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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 phone 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 21 CFR 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 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 _____ / _______ / ______

Principal Investigator Name (print)………………………………………… Title…………………………

Institution at which study will be conducted………………………………………………………………………

Address………………………………………………………………………………………………………………

City, State……………………………………………………………. Zip Code……………………………………

Email………………………………………………………. Phone…………………………………….
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 12 dated 30 June 2016)

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 comprised of poly(lactic-co-glycolic acid)-co-poly-L-lysine (PLGA-PLL), a synthetic biomaterial that is designed to naturally degrade 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 in a cylindrical shape, comes in two sizes (2mm diameter x 10mm length; 3mm diameter x 10mm length), and is intended to be selected and trimmed to the appropriate length to fit the intra-spinal post-irrigation contusion cavity. The Scaffold should 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 96 hours from the time of injury. A durotomy is performed to expose the contusion site. Then, the contused cord is irrigated with isotonic saline to wash away any superficial hemorrhagic material or devitalized tissue. During gentle irrigation, 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. An arachnoid/pial incision will then be made over the contusion cavity allowing direct access to the injured parenchyma. After the epicenter of the contusion cavity has been identified/reached (e.g., by myelotomy), the contusion 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 post-irrigation contusion cavity such that there is space within the cavity to avoid undue tension on the spinal cord surrounding the contusion site. The Scaffold is then gently implanted into the epicenter of the post-irrigation contusion 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/L1 (neurological spinal cord level) functionally complete spinal cord injury (AIS A) 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 post-irrigation 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 (≤ 96 hours) spinal cord injuries that do not involve penetrating injury to the cord or complete severing of the cord.

D. INCLUSION CRITERIA
1. AIS A classification of traumatic spinal cord injury at neurological spinal cord level T2 to T12/L1 confirmed by a qualified medical professional at the time of open spine surgery
2. Recent injury (must receive Scaffold within 96 hours 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. In these studies no safety concerns were identified. 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 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
1. Spinal cord injury outside of T2 – T12/L1 (neurological spinal cord level)
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. Known hypersensitivity to PLGA or PLL (e.g., hypersensitivity to absorbable sutures containing PLGA)
5. Hemodynamic instability
6. 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.

G. PRECAUTIONS
CAUTION: Investigational device. Limited by Federal (or 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 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.

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, the potential of occurrence of which may be increased, decreased or the same with Scaffold implantation. Note that a syrinx is defined as an area of fluid within the spinal cord whose rostral and caudal margins are cone shaped and not blunt, considered by some authors to suggest the potential for enlargement, possibly resulting in
neurological deterioration or increased pain. Similarly, a syrinx will also appear isointense with CSF on all MRI sequences. It is preferred to reserve the term “syrinx” for a clinical diagnosis of rostral neurologic deterioration correlated to a radiologically established progression of a fluid-filled region within the spinal cord.

9. 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. 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

<table>
<thead>
<tr>
<th>SYMBOL</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Manufactured by]</td>
<td>Manufactured by</td>
</tr>
<tr>
<td>![Catalogue Number]</td>
<td>Catalogue Number</td>
</tr>
<tr>
<td>![Lot Number]</td>
<td>Lot Number</td>
</tr>
<tr>
<td>![Date of Manufacture]</td>
<td>Date of Manufacture</td>
</tr>
<tr>
<td>![Use by]</td>
<td>Use by</td>
</tr>
<tr>
<td>![Storage Temperature Range]</td>
<td>Storage Temperature Range</td>
</tr>
<tr>
<td>![Single use only]</td>
<td>Single use only</td>
</tr>
</tbody>
</table>

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

M. PREPARATION OF INVESTIGATIONAL PRODUCT

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 and that the Cupped Forceps completely encircle to 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](image)

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](image)

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

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).
Note: Hold Cupped Forceps so that the cupped closure is facing downwards and the Scaffold is fully encircled when grasping. 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.

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

**Note:** 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. Irrigate the contused cord with isotonic saline to wash away any superficial hemorrhagic material or devitalized tissue. During gentle irrigation, 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.

**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., 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 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 to select an optimal area for Scaffold placement.

4. Perform an arachnoid/pial incision over the contusion cavity allowing direct access to the injured parenchyma.

5. After the epicenter of the contusion cavity has been identified/reached (e.g., by myelotomy), the contusion 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 post-irrigation cavity for Scaffold implantation.

6. Using direct visualization and intraoperative ultrasound, confirm the size of the post-irrigation contusion cavity and confirm that the Scaffold was trimmed appropriately to allow for adequate space between the Scaffold and surrounding contused spinal cord tissue to avoid tissue tension when Scaffold is implanted lengthwise into spinal cord.

Note: If the Scaffold size does not fit the post-irrigation 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. Using standard surgical forceps, retract the cord edges to expose the post-irrigation cavity.

8. Using bayonetted forceps and/or the size-matched Cupped Forceps, remove the Scaffold from the tray/pan/petri dish and gently place lengthwise into the mid-portion (epicenter) of the contusion where the post-irrigation cavity was observed/created.

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.
APPENDIX G: PAIN ASSESSMENT


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:
<table>
<thead>
<tr>
<th>Pain locations/sites</th>
<th>R</th>
<th>M</th>
<th>L</th>
<th>Type of pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>(can be more than one, so check all that apply):</td>
<td></td>
<td></td>
<td></td>
<td>Intensity and duration of pain</td>
</tr>
<tr>
<td>right (R), midline (M), or left (L)</td>
<td></td>
<td></td>
<td></td>
<td>Treatment of pain</td>
</tr>
<tr>
<td>Head</td>
<td></td>
<td></td>
<td></td>
<td>Type of pain (check one):</td>
</tr>
<tr>
<td>Neck/shoulders</td>
<td></td>
<td></td>
<td></td>
<td>Nociceptive</td>
</tr>
<tr>
<td>throat</td>
<td></td>
<td></td>
<td></td>
<td>□ Musculoskeletal</td>
</tr>
<tr>
<td>neck</td>
<td></td>
<td></td>
<td></td>
<td>□ Visceral</td>
</tr>
<tr>
<td>shoulder</td>
<td></td>
<td></td>
<td></td>
<td>□ Other</td>
</tr>
<tr>
<td>Arms/hands</td>
<td></td>
<td></td>
<td></td>
<td>Neuropathic</td>
</tr>
<tr>
<td>upper arm</td>
<td></td>
<td></td>
<td></td>
<td>□ At-level SCI</td>
</tr>
<tr>
<td>elbow</td>
<td></td>
<td></td>
<td></td>
<td>□ Below-level SCI</td>
</tr>
<tr>
<td>forearm</td>
<td></td>
<td></td>
<td></td>
<td>□ Other</td>
</tr>
<tr>
<td>wrist</td>
<td></td>
<td></td>
<td></td>
<td>□ Unknown</td>
</tr>
<tr>
<td>hand/fingers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal torso/genitals</td>
<td></td>
<td></td>
<td></td>
<td>□ Other</td>
</tr>
<tr>
<td>chest</td>
<td></td>
<td></td>
<td></td>
<td>□ Unknown</td>
</tr>
<tr>
<td>abdomen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pelvis/genitalia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back</td>
<td></td>
<td></td>
<td></td>
<td>Date of onset: YYYY/MM/DD</td>
</tr>
<tr>
<td>upper back</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lower back</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buttocks/hips</td>
<td></td>
<td></td>
<td></td>
<td>Are you using or receiving any treatment for your pain problem:</td>
</tr>
<tr>
<td>buttocks</td>
<td></td>
<td></td>
<td></td>
<td>□ No □ Yes</td>
</tr>
<tr>
<td>hip</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper leg/thigh</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower legs/feet</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>knee</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>shin</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>calf</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ankle</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>foot/toes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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
|---------------------------------------------------------------|---|---|---|------------------------
| Head                                                          |   |   |   | Intensity and duration of pain |
| Neck/shoulders throat neck shoulder                             |   |   |   | Treatment of pain |
| Arms/hands upper arm elbow forearm wrist hand/fingers          |   |   |   | Type of pain (check one): |
| Frontal torso/genitals chest abdomen pelvis/genitalia          |   |   |   | Nociceptive |
| Back upper back lower back                                     |   |   |   | □ Musculoskeletal |
| Buttocks/hips buttocks hip anus                                 |   |   |   | □ Visceral |
| Upper leg/thigh                                                |   |   |   | □ Other |
| Lower legs/feet knee shin calf ankle foot/toes                  |   |   |   | Neuropathic |
|                                                               |   |   |   | □ At-level SCI |
|                                                               |   |   |   | □ Below-level SCI |
|                                                               |   |   |   | □ Other |

Intensity and duration of pain:
Average pain intensity in the last week:
0 = no pain; 10 = pain as bad as you can imagine
□ 0; □ 1; □ 2; □ 3; □ 4; □ 5;
□ 6; □ 7; □ 8; □ 9; □ 10

Date of onset: YYYY/MM/DD

Are you using or receiving any treatment for your pain problem:
□ No □ Yes
INTERNATIONAL SCI PAIN BASIC DATA SET Version 2.0 incl. training cases-2013-06-11

Third worst pain problem:

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

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

---

<table>
<thead>
<tr>
<th>International Spinal Cord Injury Data Sets</th>
<th>Bowel Function Basic Data Set — Data Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date performed: YYYYMMDD</td>
<td>□ Unknown</td>
</tr>
<tr>
<td>Gastrointestinal or anal sphincter dysfunction unrelated to the spinal cord lesion:</td>
<td>□ No □ Yes, specify __________________</td>
</tr>
<tr>
<td>Surgical procedures on the gastrointestinal tract:</td>
<td>□ Unknown</td>
</tr>
<tr>
<td>□ No □ Appendectomy, date performed YYYYMMDD</td>
<td></td>
</tr>
<tr>
<td>□ Cholecystectomy, date performed YYYYMMDD</td>
<td></td>
</tr>
<tr>
<td>□ Colostomy, date last performed YYYYMMDD</td>
<td></td>
</tr>
<tr>
<td>□ Ileostomy, date last performed YYYYMMDD</td>
<td></td>
</tr>
<tr>
<td>□ Other, specify: __________________, date last performed YYYYMMDD</td>
<td></td>
</tr>
<tr>
<td>Awareness of the need to defecate (within the last four weeks):</td>
<td></td>
</tr>
<tr>
<td>□ Normal (direct) □ Indirect (For example: Abdominal cramping or discomfort—Abdominal muscle spasms—Spasms of lower extremities—Perspiration—Piloerection—Headache—Chills)</td>
<td></td>
</tr>
<tr>
<td>□ None □ Unknown</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Method</th>
<th>Main</th>
<th>Supplementary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal defecation</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Straining/bearing down to empty</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Digital ano-rectal stimulation</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Suppositories</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Digital evacuation</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Mini enema (Clysm ≤150 ml)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Enema (&gt;150 ml)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Colostomy</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Sacral anterior root stimulation</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Other method, specify ______________________</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>□ Unknown</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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:** YYYYYMMDD

**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:**

<table>
<thead>
<tr>
<th>Bladder emptying</th>
<th>Main</th>
<th>Supplementary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal voiding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder reflex triggering</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voluntary (tapping, scratching, anal stretch, etc.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Involuntary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder expression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Straining (abdominal straining, Valsalva’s manoeuvre)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>External compression (Credé manoeuvre)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermittent catheterisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-catheterisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheterisation by attendant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indwelling catheter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transurethral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suprapubic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacral anterior root stimulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-continent urinary diversion/ostomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other method, specify</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
- □ 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)


<table>
<thead>
<tr>
<th>SCIM-SPINAL CORD INDEPENDENCE MEASURE</th>
<th>DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-Care</strong></td>
<td></td>
</tr>
<tr>
<td>1. Feeding (cutting, opening containers, pouring, bringing food to mouth, holding cup with fluid)</td>
<td></td>
</tr>
<tr>
<td>0. Needs parenteral, gastrostomy, or fully assisted oral feeding</td>
<td></td>
</tr>
<tr>
<td>1. Needs partial assistance for eating and/or drinking, or for wearing adaptive devices</td>
<td></td>
</tr>
<tr>
<td>2. Eats independently; needs adaptive devices or assistance only for cutting food and/or pouring and/or opening containers</td>
<td>1</td>
</tr>
<tr>
<td>3. Eats independently; does not require assistance or adaptive devices</td>
<td>2</td>
</tr>
<tr>
<td>2. Bathing (soaping, washing, drying body and head, manipulating water tap). A-upper body; B-lower body</td>
<td>3</td>
</tr>
<tr>
<td>A. Requires total assistance</td>
<td></td>
</tr>
<tr>
<td>1. Requires partial assistance</td>
<td></td>
</tr>
<tr>
<td>2. Washes independently with adaptive devices or in a specific setting (e.g., bars, chair)</td>
<td>4</td>
</tr>
<tr>
<td>3. Washes independently; does not require adaptive devices or specific setting (not customary for healthy people) (ads)</td>
<td>5</td>
</tr>
<tr>
<td>B. Requires total assistance</td>
<td></td>
</tr>
<tr>
<td>1. Requires partial assistance</td>
<td></td>
</tr>
<tr>
<td>2. Washes independently with adaptive devices or in a specific setting (ads)</td>
<td></td>
</tr>
<tr>
<td>3. Washes independently; does not require adaptive devices (ads) or specific setting</td>
<td></td>
</tr>
<tr>
<td>3. Dressing (clothes, shoes, permanent ortheses: dressing, wearing, undressing). A-upper body; B-lower body</td>
<td></td>
</tr>
<tr>
<td>A. Requires total assistance</td>
<td></td>
</tr>
<tr>
<td>1. Requires partial assistance with clothes without buttons, zippers or laces (cwoбл)</td>
<td></td>
</tr>
<tr>
<td>2. Independent with cwoбл; requires adaptive devices and/or specific settings (ads)</td>
<td></td>
</tr>
<tr>
<td>3. Independent with cwoбл; does not require ads; needs assistance or ads only for bzl</td>
<td>6</td>
</tr>
<tr>
<td>4. Dresses (any cloth) independently; does not require adaptive devices or specific setting</td>
<td>7</td>
</tr>
<tr>
<td>B. Requires total assistance</td>
<td></td>
</tr>
<tr>
<td>1. Requires partial assistance with clothes without buttons, zippers or laces (cwoбл)</td>
<td></td>
</tr>
<tr>
<td>2. Independent with cwoбл; requires adaptive devices and/or specific settings (ads)</td>
<td></td>
</tr>
<tr>
<td>3. Independent with cwoбл; does not require ads; needs assistance or ads only for bzl</td>
<td></td>
</tr>
<tr>
<td>4. Dresses (any cloth) independently; does not require adaptive devices or specific setting</td>
<td></td>
</tr>
<tr>
<td>4. Grooming (washing hands and face, brushing teeth, combing hair, shaving, applying makeup)</td>
<td></td>
</tr>
<tr>
<td>0. Requires total assistance</td>
<td></td>
</tr>
<tr>
<td>1. Requires partial assistance</td>
<td></td>
</tr>
<tr>
<td>2. Grooms independently with adaptive devices</td>
<td></td>
</tr>
<tr>
<td>3. Grooms independently without adaptive devices</td>
<td></td>
</tr>
<tr>
<td><strong>SUBTOTAL</strong> (0-20)</td>
<td></td>
</tr>
<tr>
<td><strong>Respiration and Sphincter Management</strong></td>
<td></td>
</tr>
<tr>
<td>5. Respiration</td>
<td></td>
</tr>
<tr>
<td>0. Requires tracheal tube (TT) and permanent or intermittent assisted ventilation (IAV)</td>
<td>8</td>
</tr>
<tr>
<td>2. Breaths independently with TT; requires oxygen, much assistance in coughing or TT management</td>
<td>9</td>
</tr>
<tr>
<td>4. Breaths independently with TT; requires little assistance in coughing or TT management</td>
<td>10</td>
</tr>
<tr>
<td>6. Breaths independently without TT; requires oxygen, much assistance in coughing, a mask (e.g. peep) or IAV (bipap)</td>
<td>11</td>
</tr>
<tr>
<td>8. Breaths independently without TT; requires little assistance or stimulation for coughing</td>
<td>12</td>
</tr>
<tr>
<td>10. Breaths independently without assistance or device</td>
<td></td>
</tr>
<tr>
<td><strong>6. Sphincter Management - Bladder</strong></td>
<td></td>
</tr>
<tr>
<td>0. Indwelling catheter</td>
<td></td>
</tr>
<tr>
<td>3. Residual urine volume (RUV) &gt; 100cc; no regular catheterization or assisted intermittent catheterization</td>
<td>13</td>
</tr>
<tr>
<td>6. RUV &lt; 100cc or intermittent self-catheterization; needs assistance for applying drainage instrument</td>
<td>14</td>
</tr>
<tr>
<td>9. Intermittent self-catheterization; uses external drainage instrument; does not need assistance for applying</td>
<td>15</td>
</tr>
<tr>
<td>11. Intermittent self-catheterization; continent between catheterizations; does not use external drainage instrument</td>
<td>16</td>
</tr>
<tr>
<td>13. RUV &lt; 100cc; needs only external urine drainage; no assistance is required for drainage</td>
<td></td>
</tr>
<tr>
<td>15. RUV &lt; 100cc; continent; does not use external drainage instrument</td>
<td></td>
</tr>
<tr>
<td><strong>7. Sphincter Management - Bowel</strong></td>
<td></td>
</tr>
<tr>
<td>0. Irregular timing or very low frequency (less than once in 3 days) of bowel movements</td>
<td></td>
</tr>
<tr>
<td>5. Regular timing, but requires assistance (e.g., for applying suppository); rare accidents (less than twice a month)</td>
<td>17</td>
</tr>
<tr>
<td>8. Regular bowel movements, without assistance; rare accidents (less than twice a month)</td>
<td>18</td>
</tr>
<tr>
<td>10. Regular bowel movements, without assistance; no accidents</td>
<td></td>
</tr>
<tr>
<td>8. <strong>Use of Toilet</strong> (perineal hygiene, adjustment of clothes before/after, use of napkins or diapers)</td>
<td></td>
</tr>
<tr>
<td>0. Requires total assistance</td>
<td>19</td>
</tr>
<tr>
<td>1. Requires partial assistance; does not clean self</td>
<td></td>
</tr>
<tr>
<td>2. Requires partial assistance; cleans self independently</td>
<td></td>
</tr>
<tr>
<td>4. Uses toilet independently in all tasks but needs adaptive devices or special setting (e.g., bars)</td>
<td></td>
</tr>
<tr>
<td>5. Uses toilet independently; does not require adaptive devices or special setting</td>
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<tr>
<td><strong>SUBTOTAL</strong> (0-40)</td>
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</table>
### Mobility (room and toilet)

<table>
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9. Mobility in Bed and Action to Prevent Pressure Sores
- 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
- Performs one of the activities without assistance
- Performs two or three of the activities without assistance
- 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)
- Requires total assistance
- Needs partial assistance and/or supervision, and/or adaptive devices (e.g., sliding board)
- 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)
- Requires total assistance
- Needs partial assistance and/or supervision, and/or adaptive devices (e.g., grab-bars)
- Independent (or does not require wheelchair)

### Mobility (indoors and outdoors, on even surface)

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</table>

12. Mobility Indoors
- Requires total assistance
- Needs electric wheelchair or partial assistance to operate manual wheelchair
- Moves independently in manual wheelchair
- Requires supervision while walking (with or without devices)
- Walks with a walking frame or crutches (swinging)
- Walks with crutches or two canes (reciprocal walking)
- Walks with one cane
- Needs leg orthosis only
- Walks without walking aids

13. Mobility for Moderate Distances (10-100 meters)
- Requires total assistance
- Needs electric wheelchair or partial assistance to operate manual wheelchair
- Moves independently in manual wheelchair
- Requires supervision while walking (with or without devices)
- Walks with a walking frame or crutches (swinging)
- Walks with crutches or two canes (reciprocal walking)
- Walks with one cane
- Needs leg orthosis only
- Walks without walking aids

14. Mobility Outdoors (more than 100 meters)
- Requires total assistance
- Needs electric wheelchair or partial assistance to operate manual wheelchair
- Moves independently in manual wheelchair
- Requires supervision while walking (with or without devices)
- Walks with a walking frame or crutches (swinging)
- Walks with crutches or two canes (reciprocal walking)
- Walks with one cane
- Needs leg orthosis only
- Walks without walking aids

15. Stair Management
- Unable to ascend or descend stairs
- Ascends and descends at least 3 steps with support or supervision of another person
- Ascends and descends at least 3 steps with support of handrail and/or crutch or cane
- 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)
- Requires total assistance
- Needs partial assistance and/or supervision and/or adaptive devices
- Transfers independent; does not require adaptive devices (or does not require wheelchair)

17. Transfers: ground-wheelchair
- Requires assistance
- Transfers independent with or without adaptive devices (or does not require wheelchair)

**TOTAL SCIM SCORE (0-100)**

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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 1. 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.

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

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© Copyright 1984 & 1998 Carol Estwing Ferrans and Marjorie J. Powers
<table>
<thead>
<tr>
<th>HOW SATISFIED ARE YOU WITH:</th>
<th>Very Dissatisfied</th>
<th>Moderately Dissatisfied</th>
<th>Slightly Dissatisfied</th>
<th>Slightly Satisfied</th>
<th>Moderately Satisfied</th>
<th>Very Satisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>18. The emotional support you get from your family?</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>5</td>
<td>6</td>
</tr>
<tr>
<td>19. The emotional support you get from people other than your family?</td>
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<td>5</td>
<td>6</td>
</tr>
<tr>
<td>20. Your ability to take care of family responsibilities?</td>
<td>1</td>
<td>2</td>
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<td>6</td>
</tr>
<tr>
<td>21. How useful you are to others?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<td>6</td>
</tr>
<tr>
<td>22. The amount of worries in your life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>23. Your neighborhood?</td>
<td>1</td>
<td>2</td>
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<td>6</td>
</tr>
<tr>
<td>24. Your home, apartment, or place where you live?</td>
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<td>2</td>
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<td>6</td>
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<tr>
<td>25. Your job (if employed)?</td>
<td>1</td>
<td>2</td>
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<td>6</td>
</tr>
<tr>
<td>26. Not having a job (if unemployed, retired, or disabled)?</td>
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<td>2</td>
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</tr>
<tr>
<td>27. Your education?</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>6</td>
</tr>
<tr>
<td>28. How well you can take care of your financial needs?</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>5</td>
<td>6</td>
</tr>
<tr>
<td>29. The things you do for fun?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>30. Your chances for a happy future?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<td>6</td>
</tr>
<tr>
<td>31. Your peace of mind?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<td>6</td>
</tr>
<tr>
<td>32. Your faith in God?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>33. Your achievement of personal goals?</td>
<td>1</td>
<td>2</td>
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<td>5</td>
<td>6</td>
</tr>
<tr>
<td>34. Your happiness in general?</td>
<td>1</td>
<td>2</td>
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<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>35. Your life in general?</td>
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<td>6</td>
</tr>
<tr>
<td>36. Your personal appearance?</td>
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<td>2</td>
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<td>6</td>
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<tr>
<td>37. Yourself in general?</td>
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</tbody>
</table>

(Please Go To Next Page)
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.

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

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Page 3
<table>
<thead>
<tr>
<th>HOW IMPORTANT TO YOU IS:</th>
<th>Very Unimportant</th>
<th>Moderately Unimportant</th>
<th>Slightly Unimportant</th>
<th>Slightly Important</th>
<th>Moderately Important</th>
<th>Very Important</th>
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<tbody>
<tr>
<td>18. The emotional support you get from your family?</td>
<td>1</td>
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<td>20. Taking care of family responsibilities?</td>
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<td>6</td>
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<tr>
<td>21. Being useful to others?</td>
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<td>6</td>
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<tr>
<td>22. Having no worries?</td>
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<td>23. Your neighborhood?</td>
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<td>27. Your education?</td>
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<tr>
<td>28. Being able to take care of your financial needs?</td>
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<td>6</td>
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<tr>
<td>29. Doing things for fun?</td>
<td>1</td>
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</tr>
<tr>
<td>30. Having a happy future?</td>
<td>1</td>
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<td>6</td>
</tr>
<tr>
<td>31. Peace of mind?</td>
<td>1</td>
<td>2</td>
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<td>4</td>
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<td>6</td>
</tr>
<tr>
<td>32. Your faith in God?</td>
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<td>2</td>
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<td>5</td>
<td>6</td>
</tr>
<tr>
<td>33. Achieving your personal goals?</td>
<td>1</td>
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<td>6</td>
</tr>
<tr>
<td>34. Your happiness in general?</td>
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<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>35. Being satisfied with life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>36. Your personal appearance?</td>
<td>1</td>
<td>2</td>
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<td>5</td>
<td>6</td>
</tr>
<tr>
<td>37. Are you to yourself?</td>
<td>1</td>
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APPENDIX K: BECK DEPRESSION INVENTORY II (BDI-II)

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).

1. **Sadness**
   0 I do not feel sad.
   1 I feel sad much of the time.
   2 I am sad all the time.
   3 I am so sad or unhappy that I can’t stand it.

2. **Pessimism**
   0 I am not discouraged about my future.
   1 I feel more discouraged about my future than I used to be.
   2 I do not expect things to work out for me.
   3 I feel my future is hopeless and will only get worse.

3. **Past Failure**
   0 I do not feel like a failure.
   1 I have failed more than I should have.
   2 As I look back, I see a lot of failures.
   3 I feel I am a total failure as a person.

4. **Loss of Pleasure**
   0 I get as much pleasure as I ever did from the things I enjoy.
   1 I don’t enjoy things as much as I used to.
   2 I get very little pleasure from the things I used to enjoy.
   3 I can’t get any pleasure from the things I used to enjoy.

5. **Guilty Feelings**
   0 I don’t feel particularly guilty.
   1 I feel guilty over many things I have done or should have done.
   2 I feel quite guilty most of the time.
   3 I feel guilty all of the time.

6. **Punishment Feelings**
   0 I don’t feel I am being punished.
   1 I feel I may be punished.
   2 I expect to be punished.
   3 I feel I am being punished.

7. **Self-Dislike**
   0 I feel the same about myself as ever.
   1 I have lost confidence in myself.
   2 I am disappointed in myself.
   3 I dislike myself.

8. **Self-Criticalness**
   0 I don’t criticize or blame myself more than usual.
   1 I am more critical of myself than I used to be.
   2 I criticize myself for all of my faults.
   3 I blame myself for everything bad that happens.

9. **Suicidal Thoughts or Wishes**
   0 I don’t have any thoughts of killing myself.
   1 I have thoughts of killing myself, but I would not carry them out.
   2 I would like to kill myself.
   3 I would kill myself if I had the chance.

10. **Crying**
    0 I don’t cry any more than I used to.
    1 I cry more than I used to.
    2 I cry over every little thing.
    3 I feel like crying, but I can’t.
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<tr>
<th>11. Agitation</th>
<th>17. Irritability</th>
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<tbody>
<tr>
<td>0 I am no more restless or wound up than usual.</td>
<td>0 I am no more irritable than usual.</td>
</tr>
<tr>
<td>1 I feel more restless or wound up than usual.</td>
<td>1 I am more irritable than usual.</td>
</tr>
<tr>
<td>2 I am so restless or agitated that it’s hard to stay still.</td>
<td>2 I am much more irritable than usual.</td>
</tr>
<tr>
<td>3 I am so restless or agitated that I have to keep moving or doing something.</td>
<td>3 I am irritable all the time.</td>
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<tr>
<th>12. Loss of Interest</th>
<th>18. Changes in Appetite</th>
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<tbody>
<tr>
<td>0 I have not lost interest in other people or activities.</td>
<td>0 I have not experienced any change in my appetite.</td>
</tr>
<tr>
<td>1 I am less interested in other people or things than before.</td>
<td>1a My appetite is somewhat less than usual.</td>
</tr>
<tr>
<td>2 I have lost most of my interest in other people or things.</td>
<td>1b My appetite is somewhat greater than usual.</td>
</tr>
<tr>
<td>3 It’s hard to get interested in anything.</td>
<td>2a My appetite is much less than before.</td>
</tr>
<tr>
<td></td>
<td>2b My appetite is much greater than usual.</td>
</tr>
<tr>
<td></td>
<td>3a I have no appetite at all.</td>
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<tr>
<td></td>
<td>3b I crave food all the time.</td>
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<tr>
<th>13. Indecisiveness</th>
<th>19. Concentration Difficulty</th>
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<tbody>
<tr>
<td>0 I make decisions about as well as ever.</td>
<td>0 I can concentrate as well as ever.</td>
</tr>
<tr>
<td>1 I find it more difficult to make decisions than usual.</td>
<td>1 I can’t concentrate as well as usual.</td>
</tr>
<tr>
<td>2 I have much greater difficulty in making decisions than I used to.</td>
<td>2 It’s hard to keep my mind on anything for very long.</td>
</tr>
<tr>
<td>3 I have trouble making any decisions.</td>
<td>3 I find I can’t concentrate on anything.</td>
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<tr>
<th>14. Worthlessness</th>
<th>20. Tiredness or Fatigue</th>
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<tbody>
<tr>
<td>0 I do not feel I am worthless.</td>
<td>0 I am no more tired or fatigued than usual.</td>
</tr>
<tr>
<td>1 I don’t consider myself as worthwhile and useful as I used to.</td>
<td>1 I get more tired or fatigued more easily than usual.</td>
</tr>
<tr>
<td>2 I feel more worthless as compared to other people.</td>
<td>2 I am too tired or fatigued to do a lot of the things I used to do.</td>
</tr>
<tr>
<td>3 I feel utterly worthless.</td>
<td>3 I am too tired or fatigued to do most of the things I used to do.</td>
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<tbody>
<tr>
<td>0 I have as much energy as ever.</td>
<td>0 I have not noticed any recent change in my interest in sex.</td>
</tr>
<tr>
<td>1 I have less energy than I used to have.</td>
<td>1 I am less interested in sex than I used to be.</td>
</tr>
<tr>
<td>2 I don’t have enough energy to do very much.</td>
<td>2 I am much less interested in sex now.</td>
</tr>
<tr>
<td>3 I don’t have enough energy to do anything.</td>
<td>3 I have lost interest in sex completely.</td>
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<tr>
<th>16. Changes in Sleeping Pattern</th>
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<tbody>
<tr>
<td>0 I have not experienced any change in my sleeping pattern.</td>
<td>Subtotal Page 2</td>
</tr>
<tr>
<td>1a I sleep somewhat more than usual.</td>
<td>Subtotal Page 1</td>
</tr>
<tr>
<td>1b I sleep somewhat less than usual.</td>
<td>Total Score</td>
</tr>
<tr>
<td>2a I sleep a lot more than usual.</td>
<td></td>
</tr>
<tr>
<td>2b I sleep a lot less than usual.</td>
<td></td>
</tr>
<tr>
<td>3a I sleep most of the day.</td>
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<tr>
<td>3b I wake up 1–2 hours early and can’t get back to sleep.</td>
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