# The Effectiveness of Early Sacral Nerve Stimulation in Improving Bladder-Related Complications and Quality of Life after Acute Traumatic Spinal Cord Injury (Central IRB)

## Protocol Summary

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| **IRB Approval Date of Current Version:** | 12/21/2018 |
| **University of Utah IRB #:** | IRB_00096153 |
| **Sponsor:** | DOD DEFENSE ADVANCED RESRCH PRJCTS AGCY |
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| **Principal Investigator:** | Jeremy Myers |
| **Internal Staff and Sub-Investigators:** | Sara Lenherr<br>Jeff Redshaw<br>Ashlea Wilkes |
| **External Sub-Investigators:** | Sean Elliott<br>Spendley James<br>Ian Schwartz<br>John Stoffel |

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## Background and Introduction

University of Utah is the Central IRB.

Urinary bladder dysfunction and incontinence have a significant clinical, physical, and quality of life (QoL) burden in patients with spinal cord injury (SCI). Contemporary studies reports bladder problems are the second leading reason SCI patients seek medical care. Nearly 250,000 Americans live with SCI and approximately 74-80% of SCI patients report some degree of bladder dysfunction within 1 year of injury1-4. In addition, spinal trauma was present in 11% of all injuries sustained by military personal deployed to Iraq and Afghanistan; 9% of those injuries resulted in significant spinal cord injury5. The average age of those injured with spinal trauma was 27 years, meaning that there is a high current prevalence and future burden of wounded American Veterans with bladder dysfunction due to spinal cord injury.

Loss of descending input from the spinal cord results in predictable changes in the neurological control of bladder function6. Normal bladder control is a balance of the sympathetic and parasympathetic nervous systems. The sympathetic system is tonically active the majority of time and allows storage of urine and maintains continence. Conversely, when the parasympathetic nervous system is activated, bladder contraction occurs allowing for bladder emptying7. There are two types of afferent nerve fibers (those that carry nerve impulses from the bladder to the central nervous system), A-delta fibers and C-fibers. Under normal physiological conditions, bladder distention activates A-delta fibers, which triggers a spinobulbospinal micturition reflex and allows voiding. The other type of afferent fibers (C-fibers) are silent during normal voiding 8. Injury to the spinal cord above the sacral segments interrupts the connection between the brain and spinal autonomic centers and interrupts any ability to volitionally void. Immediately after SCI, the bladder becomes flaccid or atonic. Over the next several weeks following injury, neuroplasticity alters bladder afferents causing a proliferation of C-fiber afferent fibers within the lining of the bladder or the urothelium. As a result, a new C-fiber-mediated voiding reflex emerges and becomes sensitive to bladder distention, while the A-delta fiber afferent input becomes ineffective at allowing the bladder to store urine. The end result of these changes is a bladder that spasms leading to urinary leakage at even low volumes and has poor compliance such that it will not store a normal amount of urine. Depending on the location of the spinal injury, detrusor-sphincterdyssynergia (DSD) may also occur. When DSD occurs, the bladder and the urinary sphincter contract simultaneously during a bladder spasm resulting in high bladder pressures due to increased outlet resistance.

Collectively these changes in the neurological control of the bladder comprise the development of the clinical neurogenic bladder (NGB). Patients with NGB carry a heavy burden of disease and over 42% of SCI patients are hospitalized for urinary problems every year 4. The goals of NGB management are wellestablished in the literature: (1) prevention of kidney damage or failure by

keeping bladder pressures low (2) preservation of urinary continence and (3) optimizing quality of life. Clinicians use anticholinergic medications or onabotulinum toxin A to relax or paralyze the bladder musculature and minimize bladder spasticity. By decreasing bladder spasticity, a low-pressure system is established, which protects renal function and allows patients to store urine without significant incontinence. Patients must also employ some form of assisted bladder emptying, such as an indwelling catheter or clean intermittent catheterization (CIC) to drain the bladder. These strategies can significantly reduce urinary complications and related hospitalizations, especially in those patients who tolerate the medications and have the dexterity to perform CIC independently. However, there is a significant inconvenience, potential dependence on others, and often continued leakage that leads to patient noncompliance and discontinuation of CIC4,9,10. Patients who fail these less invasive treatments may require surgical bladder augmentation or urinary diversion in order to preserve renal function11. Bladder augmentation and urinary diversion surgery are both effective, but are associated with significant surgical morbidity and a 1-3% risk of death from complications. Furthermore patients often require additional surgical care during their lifetime to maintain their complex reconstructed urinary system12.

Complications associated with NGB dysfunction and management. In the past, renal failure and urinary sepsis were the major causes of death in SCI patients after recovery from initial injury13. However, advances in urologic care, specifically the introduction of CIC in the 1970's revolutionized the care of SCI patients14,15. In contemporary studies, the leading causes of death in SCI patients are now pneumonia and influenza rather than renal failure16-18. As a result of longer life expectancy, the chronic complications of NGB management are more prevalent and cause significant morbidity19. Five primary risks of NGB dysfunction and associated management are described below, namely: urinary tract infection, urinary calculi, bladder cancer, renal dysfunction and pressure ulcers.

Urinary tract infection (UTI): Between 20-56% of persons with SCI experience a UTI annually20,21. UTIs are associated with a high rate of hospitalization. The urinary tract of most SCI patients is chronically colonized despite meticulous technique with CIC. Persons with SCI are at high risk for symptomatic UTIs and sepsis because of the structural and functional urinary tract abnormalities (e.g., elevated urine storage pressures, vesicoureteral reflux) that often accompany SCI.

Urinary calculi: Renal calculi are common in patients with SCI with a 7-20% risk of developing a stone over a period of 8-10 years22-24, significantly higher than in the general population25. SCI-associated stones are frequently large, can require multiple procedures to treat and have a high incidence of recurrence26. Renal calculi are associated with an increased odds of death (OR 1.3, 95%CI 1.0-1.7) 18. Bladder calculi are also frequent in SCI, with reported prevalence rates of 18-65%27 and pathogenesis attributed to foreign bodies (either chronic indwelling or CIC), urinary stasis and infection28. Management of urinary calculi in patients with SCI carries a higher risk of urosepsis and respiratory failure than the same

procedures in the general population. This morbidity is directly associated with the level of SCI injury29.

Bladder cancer: The risk of bladder cancer is elevated in SCI patients, especially when managed with an indwelling catheter30. The relative risk of bladder cancer is 4.9 (95% CI 1.3-13.8) in those SCI patients managed with an indwelling catheter as compared to those without indwelling catheters31. In SCI, bladder cancer also typically presents at a younger age and more advanced stage, so survival is poor compared with the general population30,32,33.

Renal dysfunction: Historically, renal failure was a frequent cause of mortality in SCI, but has significantly improved bladder pressure management. In addition to chronic health conditions, renal failure in SCI results from recurrent UTIs and pyelonephritis, urinary calculi, hydronephrosis and NGB dysfunction. Current prevalence of chronic kidney disease (eGFR <60ml/min/1.73 m2) in the US veterans administration SCI population is 10.2%.

Pressure ulcers (PrU): The relationship between NGB dysfunction, bladder management method and PrU is less direct. Bladder and bowel incontinence have been suggested as risk factors for PrU in some studies but not in others34-36. A proposed mechanism of PrU resulting from incontinence is wetness of the skin resulting in softening of the protective nature of the dermis and accelerating the impact of pressure on the skin, an effect which is more pronounced when the wetness is due to urine37. PrU prevalence is 39% over three years in Veterans with SCI38, and grade 3-4 PrU are well established risk factors for mortality in SCI18.

Previous study of NGB treatment has focused on how to best control pressures in the bladder, as well as minimize complications once chronic NGB dysfunction has developed after the acute phase of SCI has past. Very few studies have attempted to prevent or ameliorate the adverse sequelae of NGB dysfunction in the acute phase of SCI. Since chronic NGB cannot be reversed, prevention of the development of some of the worst aspects of NGB such as high pressures and spasticity may be the next best strategy.

Sacral neuromodulation (SNM) is an available technology, which may mitigate the effects of SCI on the bladder. Over the past 20 years SNM has become an established treatment for refractory urinary urge incontinence, urinary frequency/urgency syndrome, non-obstructive idiopathic urinary retention and chronic fecal incontinence39-42. Since first FDA approval in 1997 for refractory urinary urge incontinence, more than 40,000 people have been implanted with SNM devices43. The surgical procedure is minimally invasive and has very few risks. A quadripolar electrode is placed with fluoroscopic guidance adjacent to the S3 nerve routes within the sacral foramen. An internal pulse generator (IPG), much like a cardiac pacemaker, is connected to the electrode and the S3 nerve is stimulated with varying patterns and intensity. The mechanism of action of neuromodulation in humans is not well understood, but it is thought to be through the same afferent sensory nerve fibers (A-delta and C), which are implicated in the development of NGB.

Sacral neuromodulation has a very well established track record in the treatment of patients with non-neurogenic urinary and fecal dysfunction. In the US, the

InterStim Therapy System (Medtronic, Minneapolis, MN, USA) has been FDA approved for use in idiopathic overactive bladder (OAB) since 1997, urinary frequency/urgency syndrome and non-obstructive idiopathic urinary retention since 1999, and for chronic fecal incontinence since 201144. Efficacy is well established for all three uses. In idiopathic OAB, SNM achieves sustained therapeutic success in 85% of patients with a greater than 60% reduction in leaks per day. From a quality of life standpoint, 80% of subjects report significant improvement in their urinary symptoms45. Similar improvements with SNM are noted when treating chronic fecal incontinence, with 86% of patients achieving therapeutic success. In this study, patients had decrease in fecal incontinence episodes from a mean of 9.4 at baseline to 1.7, which was durable after 3 years of follow up46.

While the effectiveness of SNM has been well established in non-neurogenic disorders variable success has been achieved in the treatment of chronic NBG47-52. In regards to the treatment of neurogenic overactivity specifically, results from several studies demonstrate improvement40,53. In one study of 39 patients with mixed NGB etiologies, 80% of patients were able to achieve complete continence and 43% no longer required anticholinergic medications40. Both bladder capacity and bladder compliance have also been shown to improve with SNM. Chartier-Kastler et al were able to demonstrate a mean increase in bladder capacity of ~206 ml in a population of partial SCI patients who had motor function below their injury. SNM in patients with NGB from multiple sclerosis (MS) has been the most studied indication and group in the literature. SNM has been found to reduce frequency of voids per day, reduce incontinence by 4-10 episodes per day, and increase voided volume by 77-84mL per void in this popultation54,55. Multiple studies in MS patients also cite significant improvements in quality of life and patient satisfaction of 75-86%54-56. Importantly, treatment failure in patients with progressive neurologic diseases (such as MS) is thought to be due to disease progression rather than device failure, something that is not present in SCI. The current data in the NGB patient population needs to be interpreted with caution however, due to heterogeneous patient populations, small sample sizes, and lack of randomization. Prospective controlled trials are needed. A randomized clinical trial with a goal enrollment of 54 subjects is currently ongoing to further establish the ideal chronic NGB patient population for SNM57. An important aspect of the treatment of patients with chronic NGB with SNM is that largely the patient groups have good motor function, which is thought to be a fair proxy for a largely intact spinal cord. For instance, ability to ambulate with good motor function below injury or disease has been an important predictor in some studies for success of the procedure.

Despite the success of the above studies in selected populations of patients with chronic NGB, once changes in the neurological control of the bladder have occurred following SCI they are mostly irreversible. In chronic NGB, treatments must be directed at the local muscle level in order to control the high bladder pressures, incontinence and other symptoms. Consequently, the majority of research into the effects of spinal cord injury on the urinary bladder has focused on patients with well-established chronic neurogenic bladder physiology.

Interventions during the acute phase of SCI aimed at preventing the development of, or reducing the symptoms of NGB, remain an understudied area of research.

## Purpose and Objectives

AIM 1: To determine the effect of sacral neuromodulation on urodynamic parameters following acute spinal cord injury. The following outcomes will be evaluated by urodynamic assessment at one year post-SCI: (1) maximum cystometric capacity, (2) bladder compliance, (3) presence of detrusor overactivity, and (4) volume and pressure for first detrusor contraction.

AIM 2: To assess the impact of sacral neuromodulation on patient-reported quality of life after acute spinal cord injury. Patient-reported QoL will be assessed using the SCI-QOL bladder question bank and bladder/voiding diaries (Appendix B). Mean SCI-QOL score, daily number of catheterizations, average catheterization volume, and episodes of incontinence per day will be compared between groups at one year post-SCI.

AIM 3: To examine the impact of sacral neuromodulation on quantifiable clinical outcomes. Patients will be followed longitudinally during the study period and assessed for the following: (1) need for anti-cholinergic medications and/or onabotulinum toxin A treatment, (2) number of symptomatic UTIs per year, (3) complications attributable to the device, (4) need for revision of device or leads due to lead migration or failure, (5) development of hydronephrosis.

## Study Population

**Age of Participants:** 18+

**Sample Size:**

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| At Utah: | 20 |
| All Centers: | 60 |

**Inclusion Criteria:**

Inclusion Criteria
Age > 18 years
Ability to implant device less than 12 weeks post-SCI
Presence of acute SCI at or above T12
ASIA Scale A or B
Expectation to perform CIC personally or have caretaker perform CIC

**Exclusion Criteria:**

Exclusion Criteria
Inability to perform CIC
Pre-existing SCI
Pre-existing progressive neurological disorder
Autonomic dysreflexia
Prior sacral back surgery
Posterior pelvic fracture with distortion of the sacroiliac joint
Prior urethral sphincter or bladder dysfunction
Chronic urinary tract infections prior to SCI
Pregnancy at the time of enrollment
Presence of coagulation disorder or need for anticoagulation that they cannot be stopped temporarily for procedure
Any significant co-morbidity or illness that would preclude their participation or increase the risk to them having a surgical procedure
Active untreated infection
Traumatic injury to the genitourinary system
Prior pelvic radiation, bladder cancer or other surgical procedure to the bladder that would effect baseline bladder physiology

## Design

Prospective Clinical Research
Randomized
Phase I Clinical Trial

## Study Procedures

**Recruitment/Participant Identification Process:**

PI and Research coordinators/Assistants will review charts for study eligibility. Then patients will be consented by a member of the study team.

We have also created flyers to be left in clinics with information about the study. The flyers will contain the coordinators contact information and inclusion/exclusion details about the study.

We will also recruit with the assistance via a Facebook advertisement. The Facebook ad will route to the NBRG.org site, Neurogenic Bladder Research Group, which is a site maintained by the study PI Jeremy Myers. All site PI's are part of the Neurogenic Bladder Research Group. The Facebook ad will route to a page that contains 2 educational videos about the study, as well as the inclusion and exclusion information and a form to complete if someone is interested in participating in the study. Once the potential participant enters their

information and clicks on "Submit" button, the completed form information will be emailed directly to ashlea.wilkes@hsc.utah, Ashlea Wilkes, who is the research coordinator at the University of Utah. Ashlea Wilkes will be responsible to responding to all inquiries about the study via the Facebook advertisement.

We have had success with previous studies involving participants with a spinal cord injury with advertising through Facebook. The advertisement will allow us to reach a larger population of possible participants and their friends and family.

**Informed Consent:**

**Description of location(s) where consent will be obtained:**

Patients will be identified and consented in physical medicine and Rehab or neurosurgery or Urology clinics.

**Description of the consent process(es), including the timing of consent:**

Once screened for inclusion and exclusion criteria (see above), patients will be approached and asked if they would like to participate in a randomized, non-blinded study within 12 weeks of the acute spinal cord injury event. Participants screened online through the Facebook advertisement will still require to be seen by the the site PI in clinic prior to consent to the study. They will then be given study material and informational video and allowed sufficient time to make an informed decision regarding participation. In the event that the participant is unable to read or sign the consent form because the participant is illiterate, visually impaired, or physically unable to sign, we will use a witness to confirm the consent process and sign/date the consent form. Not only will this help us achieve enrollment goals, but it will ensure patient safety and prevent discrimination.

**Procedures:**

PI and Research coordinators/Asistants will review charts for study eligibility. Future participants will have a choice to view an information video about the study. Then patients will be consented by a member of the study team.

Pregnant women will be excluded from participation. Women who are at risk of pregnancy will be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy. Women of childbearing potential must use an effective contraceptive during the course of this study. Acceptable methods of birth control include abstinence, oral contraceptives, the contraceptive patch, the contraceptive ring and condoms.

60 patients will be enrolled and randomized (30 per arm) to either standard

neurogenic bladder management or standard management plus implantation of the Medtronic PrimeAdvanced Surescan 97702 Neurostimulator.
All patients will receive usual standard of care bladder management for neurogenic bladder. Specifically, standard treatment entails the following: (1) CIC at regular timed intervals if the patient is physically able to do so, if not able to physically perform self catheterization patients will have the option to have this performed by a caregiver (2) treatment with anticholinergic medicine or onabotulinum toxin A as indicated to increase bladder compliance, decrease urinary leakage, and lower bladder pressures to prevent renal damage, (3), undergo routine follow up in the urology and physical medicine and rehabilitation clinic, (4) upper tract imaging (typically consisting of a renal ultrasound) will be

performed at one year follow-up to monitor for the development of hydronephrosis, (5) and serum creatinine as an estimate of renal function will be collected annually per recommended screening protocols.62

The PrimeAdvanced Surescan 97702 Neurostimulator is an implantable device marketed by Medtronic (Minneapolis, MN) for use in the United States. It has several components: a internal pulse generator (IPG) which delivers an electrical signal to the sacral nerve; a quadripolar electrical lead that is implanted alongside the S3 nerve root; and a programmer that is used to control the electrical pulse delivered by the IPG. The IPG and the lead are permanent implants. The programmer is a handheld device that is not implanted. The PrimeAdvanced 97702 is an FDA approved device for spinal cord stimulation rather than sacral nerve root stimulation, which is the intention of this study. The PrimeAdvanced 97702 is conceptually and functionally, similar to the InterStim II Model3058 neurostimulator which is FDA approved for sacral neurostimulation in the United States. Unlike the Interstim II, the PrimeAdvanced has the ability to accommodate and simultaneously stimulate bilateral leads. All the preliminary studies in acute spinal cord injury have utilized bilateral sacral stimulation.
A standardized surgical procedure will be implemented across all three study centers. Specifically, all patients will receive pre-procedural antibiotics of weightbased dosed Vancomycin and Gentamycin unless allergy precludes use of these antibiotics. In those cases, Clindamycin or other broad-spectrum antibiotics will be used. All antibiotics will be administered within 60 minutes of incision. Depending on patient factors, the procedure will be performed under either local or general anesthesia. All cases will have a surgical prep consisting of betadine scrub and paint over the surgical site followed by chlorhexadine prep application. Surgical transparent drape will be used to cover the surgical field and still allow for visualization of perianal area. Antibiotic irrigation will be used for all steps of the procedure. We will localize the S3 foramen with fluoroscopy and the tined lead will be placed with the curved stylet after demonstration of an optimal motor response (anal bellows). Importantly, tined lead stimulation of the S3 nerve roots activates striated fibers via efferent motor nerves. This pathway remains intact even during spinal shock when the spinal reflex arc is inactive. Therefore, the method to perform lead placement can proceed as in a neurologically intact patient. Tined leads will be placed bilaterally. Both leads will be tunneled to a subcutaneous pocket located in a non-pressure bearing location depending on patient body habitus, generally near the posterior iliac crest or anterior abdomen. Leads will be attached to the Prime Advanced IPG. We will permanently save fluoroscopic images in the lateral and anterior-posterior position to allow for comparison in case of suspected lead migration. Patients will take oral cephalosporin or equivalent for 7 days post-operatively.
NOTE: Implantation is usually accomplished via a two-step process involving a placement of the permanent quadripolar electrode alongside the S3 nerve root under local or general anesthesia. This permanent lead is controlled by a temporary external programming device for 7-14 days. If greater than 50% improvement in clinical symptoms over that test period, the IPG is implanted subcutaneously under during a second surgical procedure. Because the study hypothesis dictates early stimulation of the sacral nerve roots with a primary outcome evaluated one year post implant, the quadripolar electrical lead and IPG will be placed in the same procedure. This will avoid delay in stimulation of the sacral nerves during the critical window for preventing adverse neuroplastic changes. Patients will be mostly insensate due to their SCI or being under general anesthesia for the procedure. Therefore, to confirm intraoperative placement we will rely upon expected motor responses (anal bellows and toe flexion). If correct motor responses cannot be elicited intraoperatively than the patients will not undergo implantation and will be included in the randomized arm

but in an ‘intention-to-treat’ manner.

FDA approved programming parameters for the Interstim II system will be utilized in this study as follows. The device will provide continuous stimulation (i.e. always on) without discrete treatment periods. The PrimeAdvanced Surescan IPG is capable of generating a maximum voltage of 10.5 volts, 2 volts higher than the Interstim II system, however, it will be programed to function within the normal Interstim II system parameters (maximum 8.5 volts). Additionally, it will be programed to use the same stimulation pulsewidth (210 msec) and frequency (14Hz) as the Interstim II system. The area under the stimulation curve will be the same or less than intended by the Interstim II parameters.
Each patient will be evaluated intraoperatively as is standard clinical practice to select stimulation parameters that result in typical, consistent physiological responses (e.g. anal bellows and first toe rotation). The default 14 Hz frequency will be maintained. The electrode with the lowest amplitude stimulation as a proxy for the most closely placed electrode to the S3 nerve. This electrode be trialed first. The stimulation amplitude will be set at 0.7V per protocol as was utilized in the one prior bilateral SNM study in acute SCI. Note: If the subject has S3 sensation (incomplete SCI), the amplitude will be set 0.1V lower than the level of sensation. In such sensate patients, each lead will be programmed individually and then both leads will be activated simultaneously to determine whether further amplitude reduction is needed. These parameters will be set during the initial programming session and will remain constant for the duration of the study. All study centers will utilize the same protocol.

Standardized demographic data based on the National Institutes of Neurological Disorders and Stroke (NINDS) Common Data Elements (CDEs) will be collected via patient interview and evaluation of the electronic medical record including mechanism of SCI and medical comorbidities. All measured outcomes are listed in Table 1 by Aim. At enrollment, all participants will complete the following: (1) standardized 3-day voiding diary to annotate the catheterization time, amount and time of fluid intake, and incontinence events, (2) 24 hour pad weight test, (3) 3-day bowel diary to quantify baseline bowel habits; (4) inventory of current medications; and (5) the SCI-QOL questionnaires (Appendix B). (6) 24 hour pad weight test averaged over 3 days. Repeat measurements will be obtained during clinic visits at 3, 6, 9, and 12 months after enrollment. (7) All participants will undergo baseline urodynamic testing at enrollment. For patients randomized to the intervention arm, urodynamic testing will be completed less than 2 weeks before implantation of the device. Urodynamic testing will be repeated at 3 months and then again at 12 months.
At each time point, a retrospective review since the prior time point will be performed in order to capture major events such as hospitalizations, additional surgery or death as well as additional subjective data. Those additional subjective data will include: (1) current usage of anti-cholinergic medications and/or onabotulinum toxin A treatment (2) number of culture proven symptomatic UTIs per year (3) complications attributable to the device, (4) need for revision of device or leads.
A renal ultrasound will be obtained at the end of 12 months to evaluate for the development of hydronephrosis. This will be compared with baseline CT or US imaging obtained during their initial trauma evaluation.

There will be a video available for participants to view for additional information.

**Procedures performed for research purposes only:**
Implantation of sacral neuromodulator and leads

## Statistical Methods, Data Analysis and Interpretation

Sample size calculations for this study were based on a mean maximum cystometric capacity of 220.7 mL (SD=103.3), as reported by Sievert et al 60, and a feasibility of enrolling 30 patients per arm within the study period. After accounting for a 15% loss to follow-up we expect 25 evaluable patients per arm. To achieve 80% power at a 5% significance level with 25 patients per arm (N=50), we can detect an effect size of a 38% treatment effect (84 mL increase in capacity). This calculation was simulated for a two-tailed t-test incorporating one interim and one final look at the data using the O'Brien and Fleming (OBF) method and running 50000 simulations (using PASS v. 11.0.8 software). An interim analysis will be conducted at 50% enrollment (N=26 after loss to followup, 13 patients per arm) accrual, and the decision to stop early will be governed by an OBF significance level of 0.003. A 0.051 significance level will be used to evaluate the final analysis. The DSMB's decision to stop early will be guided both by interim results and clinical judgment, especially in the context of emerging, relevant literature.