SUMMARY OF SAFETY AND PROBABLE BENEFIT

A. GENERAL INFORMATION

Device Generic Name: Implantable Stimulator

Device Trade Name: *VOCARE Bladder System*

Applicant's Name and Address:

NeuroControl Corporation
8333 Rockside Road
Valley View, OH 44125

Humanitarian Device Exemption (HDE) Number: H980008

Date of HDE: December 8, 1998

Date of Humanitarian Use Device Designation (secondary indication): October 6, 1998

Date of Panel Recommendation: Not Applicable. (refer to section J for discussion)

Date of Good Manufacturing Practices Inspection: December 10, 1998

Date of Notice of Approval to Applicant: FEB 19 1999

B. INDICATIONS FOR USE

The NeuroControl Corporation *VOCARE Bladder System* is indicated for the treatment of patients who have clinically complete spinal cord lesions (ASIA Classification) with intact parasympathetic innervation of the bladder and are skeletally mature and neurologically stable, to provide urination on demand and to reduce post-void residual volumes of urine. Secondary intended use is to aid in bowel evacuation.

C. DEVICE DESCRIPTION

The *VOCARE Bladder System* is a sacral anterior root stimulator intended to provide bladder evacuation by delivering electrical stimulation to a patient's intact spinal nerve roots in order to elicit functional contraction of the muscles innervated by them. It consists of implantable, external, and surgical components, as described below:

The Implanted Components include the Implantable Receiver-Stimulator, and the Extradural Electrodes. The Implantable Receiver-Stimulator is a two-channel passive electronic device. It is powered by RF magnetic fields delivered by coils in an External Transmitter outside the body. The Implantable Receiver-Stimulator delivers current pulses to the Extradural Electrodes which are attached to the sacral anterior nerve roots. The dimensions of the Implantable Receiver-Stimulator are approximately 50 mm x 80 mm x 8 mm with a weight of approximately 12 grams. The Extradural Electrodes are produced from cables which consist of three helices of wire wound over silicone rubber tubing. The wire is 75μ in diameter, 80% platinum, 20% iridium with a polyimide coating. The leads are then backfilled with silicone elastomer. The Extradural Electrode bifurcates to form two tripolar electrodes, one is placed on the left and one is placed on the right nerve root of a particular spinal segment. The overall length of the Extradural Electrode lead is approximately 440 mm and the diameter is about 2 mm. The Implantable Receiver-Stimulator has no internal batteries and no software.

The External Components consist of an External Controller (battery powered), External Transmitter, Battery Charger and Power Cord, External Cable and Transmitter Tester. The External Controller (a plastic enclosure approximately 16 cm x 8 cm x 3 cm and weighing 420 grams) has two external controls; an On/Off slide switch and a three-position Operating Mode slide switch. The Operating Mode switch positions allows for up to three programs, with Mode 1 typically used for Bladder function, Mode 2 for Bowel function, and Mode 3 as an alternate. The External Controller generates and delivers a sequence of electrical pulses that are emitted as electromagnetic fields from the External Transmitter. The External Transmitter is placed on the skin over the Implantable Receiver-Stimulator, such that the A and B channels of the External Transmitter are aligned with the A and B channels of the Implantable Receiver-Stimulator, to communicate the stimulus parameters to be delivered to the Extradural Electrodes. The clinician adjusts stimulus parameters through a series of dials and switches inside the External Controller. The External Cable connects the External Controller to the External Transmitter or the External Controller to the Battery Charger. The Battery Charger is provided for recharging batteries when the *VOCARE Bladder System* is not in use. The *VOCARE Bladder System* cannot be used while connected to the mains power.

The Surgical Components consist of the Surgical Stimulator, the Extradural Surgical Probe, the Intradural Surgical Probe, the Electrode Test Cable and Silicone Adhesive. These components are used intraoperatively to facilitate the identification of the correct sacral root nerves for posterior rhizotomy (Intradural Surgical Probe), the optimal placement of the Extradural Electrodes (Extradural Surgical Probe), and the functional testing of the Extradural Electrodes after they are secured in place (Electrode Test Cable). The Probes, Test Cable, and Silicone Adhesive are supplied sterile for single use. The Surgical Stimulator is a single channel, voltage output stimulator which delivers pulses to the Probes or to the Extradural Electrodes via the Electrode Test Cable. The Surgical Stimulator is powered by a 9-volt alkaline battery that is user replaceable.

D. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

CONTRAINDICATIONS

The NeuroControl Corporation *VOCARE Bladder System* is contraindicated for patients with the following characteristics:

- poor or inadequate bladder reflexes
- active or recurrent pressure ulcers
- active sepsis
- implanted cardiac pacemaker

The warnings and precautions can be found in the Professional Labeling (Attachment 1).

E. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Devices similar to the *VOCARE Bladder System* have been implanted in patients in Europe, Australia, Asia and the U.S. Published reports (Brindley 1994a) describe relevant adverse events including implant infection (1%), exposure of the implanted components via dehiscence or ulceration (1%), and component failures (Brindley 1994b). About 30% of patients (Brindley 1990) have noticed an increase in sweating over the lower part of the body and/or undesirable changes in the pattern of their lower limb reflexes. These changes have never been permanent and have returned to preimplant status within three months to a year.

A clinical study in the U.S. involved 23 devices (using extradural electrodes) implanted in 23 patients (median implant duration = 1.2 years, range approximately 1 month to 2 years). Key adverse events (AEs) reported from this clinical trial include temporary anterior nerve root damage which resolved within 3 months (two cases), incomplete rhizotomy (one case), pathological fracture of L2 vertebra with resulting nerve compression (one case), and post-operative stress incontinence not present preoperatively (two cases). Refer to the clinical section for a complete discussion of adverse events.

F. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative treatments for spinal cord injured patients with neurogenic bladder include a variety of approaches to emptying the bladder, including intermittent catheterization, permanent catheterization (urethral and suprapubic), manual expression of urine from the bladder and the use of reflex bladder contractions, and surgical procedures such as external sphincterotomy or urinary diversion. None of these approaches, however, have proven completely satisfactory. Further discussion of the problems associated with these modalities is presented in the risk/benefit section (section 2.3).

Assisting the spinal cord injured patient with bowel emptying is a secondary use of the *VOCARE Bladder System*. Available alternatives to the use of the *VOCARE Bladder System* include the use of laxatives, stool softening agents, suppositories, digital stimulation, and manual evacuation.

G. MARKETING HISTORY

The Implanted and External components of the *VOCARE Bladder System* are manufactured by Finetech Medical, Ltd., an ISO 9002 manufacturer located near London, England. The Surgical Components of the *VOCARE Bladder System* are manufactured by NeuroControl Corporation of Cleveland, Ohio. The device has been marketed in Europe, Australia, New Zealand and Singapore. It has been on the market outside of the United States for over 16 years, where it is known as the Finetech-Brindley Sacral Anterior Root Stimulator, and it has been implanted in over 1400 patients. The *VOCARE Bladder System* has not been withdrawn from marketing for any reason related to safety or probable benefit of the device.

H. SUMMARY OF STUDIES

1. Non-Clinical Studies

1.1 Biocompatibility

Tissue contacting materials used in the *VOCARE Bladder System* Implantable Receiver-Stimulator and Extradural Electrodes include silicone elastomers, polyester reinforced silicone sheeting, silicone tubing, silicone adhesive, and electrode wire composed of 80% platinum and 20 % iridium. These materials have been used in similar clinical applications and have well known biocompatibility characteristics. NeuroControl Corporation referenced supplier master files and provided biocompatibility test results in support of the biocompatibility of the silicone and polyester materials, and provided references supporting the long history of use and safety of the platinum/iridium materials used for the electrodes. Although no long-term biocompatibility studies were performed on the silicone materials or the final sterilized device, the extensive clinical experience with the Finetech-Brindley Sacral Anterior Root Stimulator as reported in the published literature do not identify any potential long-term biocompatibility issues.

1.2 Qualification Testing

1.2.1 Silicone Encapsulants

Long-term immersion testing at 37°C was performed to evaluate the silicone materials used to encapsulate the VOCARE implanted electronics. Test circuits were encapsulated and tested prior to immersion and at intervals throughout the experiment. No circuit failures occurred during the 12 to 24 months of immersion.

In addition, accelerated tests were performed to determine the mechanical strength of the bond between the silicone adhesive and test sections of alumina. The mechanical strength of the bond between the silicone adhesive and the base material was tested after exposure to 100°C in the presence of aqueous solutions of various pH heated to the boiling point in a closed vessel at atmospheric pressure. These tests were repeated until failure of the bond. Very low failure rates were found before 100 days of exposure to the boiling solutions. Life testing of such adhesions for 100 days corresponds to more than ten years of stress at 37°C.

1.2.2 Mechanical Endurance Testing of Implantable Cable

The implantable cable (Cooper Cable) was exposed to the following series of mechanical endurance tests:

Stretch: Samples of the cables were subjected to axial stretching to 20 percent beyond resting length, in air, at 4 cycles per second. Failure of the cable (visible damage) occurred after $>7 \times 10^7$ cycles.

Flexion: Samples of the cable were bent around a free pulley which is oscillated back and forth in saline over the test section at 3 cycles per second. Tests were performed with bend radii of 3 mm and 5 mm (wrap angle of 360°). For the 3 mm bend radius, failure of the rubber occurred after 4×10^7 cycles. For the 5 mm radius, failure of the wire occurred after 6.5×10^7 cycles.

Compression: Samples of the cable were squeezed in air between two parallel surfaces with compression forces of 100, 200, and 400 grams per mm of cable length. Failure of the cable occurred after 7×10^5 cycles, 5×10^4 cycles, and 1.6×10^3 cycles, respectively.

The above endurance tests are described in a Technical Note, The Cooper Cable: an implantable multi-conductor cable for neurological prosthesis, P.E.K. Donaldson, *Medical & Biological Engineering & Computing*, May 1983, Vol. 21, pgs 371-374.

Repeat testing is currently being completed on the currently manufactured cables, which have had minor changes in materials. To date, cables have been subjected to stress cycles in excess of maximum required life with no failures; thus, supporting the continued suitability and reliability of this design.

1.2.3 Mechanical Testing of Implantable Connector

Six implantable 3-pin connectors and one 4-pin connector were implanted into test animals for periods of 6 to 22 months. After this period the connectors were tested for intact insulation and contact resistance. All 22 conductors were intact.

1.2.4 Pull Testing of Connections

Wire-to-pin crimp connections and wire-to-ceramic substrate brazed connections were pull tested. In all of these tests, the wire failed in tension before the wire pulled out.

1.3 Electromagnetic Compatibility Testing

No specific testing was conducted to test for electromagnetic compatibility. To address this concern, the labeling contains a precaution related to the possibility of unintended stimulation of the device from external electronic devices.

1.3.1 Electrostatic Discharge (ESD) Testing

ESD testing was conducted on the implanted, external, and surgical components using IEC 601-1-2 and IEC 1000-4-2 for general guidance. The *VOCARE Bladder System* components passed these ESD tests.

1.4 Battery Life

Testing was conducted to determine the life of the External Controller rechargeable battery. The testing showed that the battery charge and discharge cycles are very repeatable. It was confirmed that weekly charging for 8-10 hours would be more than adequate to ensure appropriate *VOCARE Bladder System* function.

1.5 Electrical Safety

The *VOCARE Bladder System* passed the requirements of IEC 601-1 for leakage current and dielectric strength.

1.6 Safety of Stimulation

NeuroControl Corporation conducted electrochemical, cyclic voltametry, and scanning electron microscopy (SEM) evaluations to determine if the stimulus parameters delivered by the *VOCARE Bladder System* to the electrodes are within safe stimulation limits.

Electrodes that were stimulated under maximum clinical conditions for time periods equivalent to 5, 10, 15, and 30 years of patient use showed on SEM no signs of dissolution or deleterious changes in behavior. Electrode potentials were significantly below the electrochemical potentials that might cause corrosion, and the charge densities were well below the maximum safe charge densities cited in published literature. Compared to controls, there was no micropitting of the electrodes and no measurable changes in diameter. It was concluded that the *VOCARE Bladder System* delivers safe electrical stimulation parameters to the Extradural Electrodes.

1.7 Animal Studies

NeuroControl Corporation cited studies performed by Brindley and colleagues (Brindley GS. An implant to empty the bladder or close the urethra. *Journal of Neurology, Neurosurgery, and Psychiatry.* 1977;40:358-369) on 26 baboons. In these studies stimulation of the anterior roots produced micturition with low residual volumes of urine. The device design and techniques used by Brindley in these studies form the basis for the *VOCARE Bladder System.*

2.0 Clinical Studies

2.1 Introduction

To support the safety and probable benefit of the *VOCARE Bladder System*, NeuroControl Corporation submitted clinical data from a prospective multi-center clinical study along with information from the peer-reviewed literature.

2.2 U.S. Multi-Center Clinical Study

2.2.1 Study Overview

The prospective multi-center clinical study was conducted at six investigational sites under IDE G960022. A total of 23 patients were enrolled in the study and implanted with the *VOCARE Bladder System.* The primary endpoints for the study involved improvements in bladder function. Improvement in bowel function was evaluated as a secondary endpoint. Each patient served as his/her own control; comparisons were made between bladder function outcomes measured prior to implant and with the *VOCARE Bladder System* ON and OFF post-implant.

2.2.2 Patient Selection/Study Procedures

Spinal cord injured patients with documented complications from the use of conventional bladder emptying methods were enrolled. Preoperative evaluations included medical history, general physical examination, detailed urological and gastrointestinal histories, evaluation of ability to urinate on demand, imaging studies, laboratory tests, quality of life surveys, urodynamic assessment of bladder contractions in response to filling, and

neurological confirmation of bladder innervation. Patients also completed home diaries of bladder and bowel function.

A posterior rhizotomy (cutting of the posterior nerve roots) is performed in conjunction with the implantation of the *VOCARE Bladder System*. An S1-S3 laminectomy is typically performed and electrodes are placed extradurally on the sacral nerves. The electrodes are attached by subcutaneous cables to a stimulator implanted subcutaneously, usually on the lateral aspect of the abdominal wall. The implantation and intraoperative testing procedures are described in detail in the *VOCARE Bladder System* Clinician's Manual. The Surgical Stimulator and Extradural Probe were used to determine optimal electrode placement.

Post-operatively, urodynamic testing was performed, and the *VOCARE Bladder System* was adjusted to set optimal urination parameters. Follow-up sessions were conducted at 3 months, 6 months, and 12 months post-implantation. Urodynamic evaluation of urination on demand was conducted with the *VOCARE Bladder System* ON and with the System OFF. Follow-up evaluations also included medical history since last follow-up, imaging studies, laboratory tests, physical examination, surveys, and completion of patient diaries. Adverse events were recorded at each follow-up visit.

2.2.3 Effectiveness Evaluations and Endpoints

Primary Endpoints:

The primary effectiveness endpoints in the study relate to improvement in bladder emptying. Success was defined as being able to urinate >200 mL on demand with post-void residuals less than pre-surgery or $\leq$ 50 ml.

Secondary Endpoints:

Secondary endpoints evaluated during the study included the following:

- Reduction in time spent in bowel evacuation as documented in patient diaries prior to surgery and prior to each post-operative follow-up milestone.
- Reduction in the use of bowel evacuation methods other than the *VOCARE Bladder System* as documented in patient diaries.
- The proportion of patients who reduced the use of urinary catheters as indicated in follow-up histories and diaries pre-operatively and at each follow-up visit
- Improvement in the number and severity of episodes of urinary incontinence as documented in patient diaries pre-operatively and at each follow-up visit
- Incidence of urinary tract infections before and after surgery
- Reduction in use of anticholinergic medications after surgery
- Reduction in episodes of autonomic dysreflexia after surgery
- Proportion of patients who responded positively to items in User Satisfaction Survey

2.2.4 Patient Population

Data were submitted on a total of 23 patients who were enrolled in the study and had the *VOCARE Bladder System* implanted. All 23 patients had at least 3-month post-implant follow-up and 17 of the 23 patients had 12-month follow-up. The patients ranged in age from 14 to 67 years (median age = 40 years). Sixteen of the patients (70%) were male, which is similar to the gender distribution within the general spinal cord injured patient population. All patients had clinically complete spinal cord injuries. Injury level ranged from the 4th cervical level to the 12th thoracic level. Six of the patients (26%) were quadriplegic and the remainder (74%) were paraplegic. The primary cause of injury was motor vehicle accident (48%). Other causes given for the injury included falls, sports, gun shot wound, diving, helicopter crash, tree fell on patient, and work-related. Time between injury and implant ranged between 2 and 26 years with a median time of 7 years.

2.2.5 Effectiveness Results

2.2.5.1 Improvement in Bladder Function

Success for the key primary endpoint was defined by the ability to urinate on demand with a median voided volume ≥200 ml. Further, to be successful, the Post-Void Residual (PVR) volumes had to be reduced to ≤ 50 ml. Voided volumes and PVR's were measured through clinical urodynamic testing pre-op and at each follow-up visit.

Table 1.0 presents the number of patients who met each of the voided volume and PVR endpoint requirements. At 3 months, 90 percent of patients were able to urinate on demand with the VOCARE ON and 81 percent had post-void residual volumes which were less than 50 ml. Results at 6 months and 12 months were consistent with results obtained at 3 months.

Table 1.0 Results of the VOCARE Bladder System Bladder Function Testing

	Pre-Op (n=23)	3 Month (n=21)	6 Month (n=20)	12 Month (n=12)
Patients who can micturate on demand >200 ml (100% of attempts)				
VOCARE Bladder System **ON**	NA	(90%)	(90%)	(92%)
VOCARE Bladder System **OFF**	(17%)	(0%)	(5%)	(8%)
Patients with PVR ≤ 50 ml				
VOCARE Bladder System **ON**	NA	(81%)	(85%)	(75%)
VOCARE Bladder System **OFF**	(13%)	(.5%)	(0%)	(8%)

2.2.5.2 Secondary Effectiveness Endpoints

Overall, patients also experienced an improvement in the secondary endpoints. These include the following:

- Fifteen of 17 (88%) patients reduced the time they spent on bowel management at 12 months follow-up compared to pre-op.
- Nine of 17 patients (53%) reduced their use of suppositories and 9 (53%) reduced their use of manual evacuation at 12 months follow-up compared to pre-op.
- After device implantation, 78% of the patients reported fewer urinary tract infections (UTIs). While all of the 23 patients had reported UTIs in the year preceding device implantation (many reported three or more infections), six patients had no UTIs and 13 of the remaining 17 patients had three or less infections post-implantation.
- Twenty patients were not using anticholinergics at 6 months post-op, compared to six pre-op.
- Eight patients had experienced autonomic dysreflexia pre-operatively, compared to only one at 6 months post-operatively.
- Eleven patients were using only the VOCARE stimulator for micturition at 6 months post-op compared use of various external devices by all of the 23 patients pre-operatively.
- Urinary incontinence improved at 6 months for 12 of the 19 patients for whom diary data are available.

2.2.6 Adverse Effects

Adverse Events were captured at each follow-up visit or at interim periods where appropriate. Events were categorized as Surgical or Medical. The adverse effects reported during participation in the clinical study which are attributable to the *VOCARE Bladder System* are presented in Table 2.0.

Table 2.0. Summary of Adverse Effects

Surgical Event	# of Incidents	# of Patients	% of Patients
Device Infections	0	0	0%
Implantable Receiver-Stimulator Failures	0	0	0%
Electrode/Lead Failures	0	0	0%
Permanent Nerve Damage	0	0	0%
Temporary Nerve Damage (lasting <3 months)	2	2	9%
Incomplete rhizotomy*	1	1	4%
Compression Fracture of L2 vertebra*	1	1	4%
Post-op pressure sores, swelling, or discomfort	15	12	52%

Medical Event	# of Incidents	# of Patients	% of Patients
Stress Incontinence **	9	7	30%
Irritation over Receiver-Stimulator	2	2	9%
Constipation/Fecal Impaction	11	4	17%
Fecal Incontinence	3	1	4%
Discomfort during stimulation	1	1	4%
Sweating during stimulation	1	1	4%
Increased lower extremity spasticity	2	1	4%
Foot movement during stimulation	1	1	4%
Pyelonephritis from underuse of device	1	1	4%
Overdistended bladder ***	2	2	9%

*patient discontinued use of the device
**five cases of worsening of stress incontinence and two new cases of stress incontinence
***two patients experienced distention of the bladder from inadequate emptying while in the hospital post-operatively. After several days using an indwelling catheter, both recovered and began using the device regularly

2.3 Risk/Benefit Analysis (based on the clinical study and the literature)

Risks Related to the Loss of Bladder and Bowel Control Resulting from Spinal Cord Injury:

Spinal cord injuries are one of the most debilitating and devastating injuries. After spinal cord injury, there is a paralysis below the level of injury along with impairment of voluntary control over voiding and fecal evacuation. Prior to World War II, a spinal cord injury was almost universally fatal, with urosepsis or urinary tract infection (UTI) being the predominant cause of death. UTI results from inadequate bladder emptying which leaves large residual volumes of urine in the bladder. The high bladder pressures built up from the inability to void voluntarily lead to autonomic dysreflexia, vesicoureteral reflux, upper urinary tract dilatation, renal stone formation and hydronephrosis, eventually resulting in renal failure. From autopsies on 122 paraplegic patients, Tribe found that 52% of the deaths were secondary to renal failure (Tribe, CR: Cause of death in early and late stages of paraplegia. Paraplegia, Vol. 1, p. 19, (1963)).

Although surgical (e.g., sphincterotomy, urinary diversion) and nonsurgical techniques (e.g., indwelling or intermittent catheterization) are available for managing neurogenic bladders in spinal cord injury patients, they all have some disadvantages. Ileal conduit operations revealed deterioration of the upper urinary tract in 30% to 48% of patients and a reoperation rate of 32% to 60% (Hollander et al., Urologic Clinics of North America, Vol. 20, pp.465-474, (1993)). External sphincterotomy, a technique developed later, did not improve the situation since many patients required repeat surgery and many developed upper urinary tract deterioration (Hollander et al.). The nonsurgical

alternatives can also cause significant complications. Indwelling urethral or suprapubic catheters have been associated with UTIs, upper tract deterioration and renal failure. The rate of urinary tract infection is approximately 5% to 7% for each day of catheterization (Schaeffer AJ: Catheter Associated Bacteriuria. Urologic Clinics of North America, Vol. 13, p. 735 (1986)) and there is 100% incidence of significant bacteriuria ($>10^5$ organisms/ml) associated with long-term indwelling catheters. Warren et al. (Acute pyelonephritis associated with bacteriuria during long-term catheterization: A prospective clinico-pathological study. Journal of Infectious Diseases, Vol. 158, p. 1341 (1988)) showed that 28 of 75 patients (38%) with a chronic urinary catheter had evidence of acute pyelonephritis, compared to only 5% of those without a catheter. Severe renal infections and renal or perirenal abscesses caused by bacterial, or rarely fungal, infections can occur as well.

Although a preferred method of bladder management in patients who have good hand coordination, intermittent catheterization is not without complications. With every catheter insertion, there is a risk of bacteriuria and UTI. The risk of infection is lower with intermittent catheterization than with an indwelling catheter, but only 30% of patients maintained on long-term self-intermittent catheterization remain free of UTIs (Maynard et al: The prevention and management of urinary tract infections among people with spinal cord injuries: Journal of American Paraplegia Society, Vol. 15, p. 194 (1992); McGuire EJ and Sevastono JA: Long-term follow-up of spinal cord injured patients managed by intermittent catheterization, Journal of Urology, Vol. 123, p. 775 (1983); Stover SL et al.: Neurogenic urinary tract infection, Neurologic Clinics, Vol. 9, p. 741 (1991)).

Traumatic injury to the spinal cord also leads to interruption of normal bowel and sexual function (Guttman, 1973). There may be intractable constipation associated with episodic fecal impaction which may require manual disimpaction and use of enemas and cathartics (Glick et al. 1984). The morbidity that is associated with the disordered bowel habit may be present for years and includes extensive time spent in these interventions, dependence on other health care providers to carry out the defecatory activity and the consequent psychological and physical dependency which evolves (Gore et al. 1981). Complications with bowel care may prevent patients from living and performing in a normal social environment.

Benefits and Risks of VOCARE Bladder System:

In comparison with the risks presented by the alternative techniques, the risks reported for the Sacral Anterior Root Stimulator are outweighed by the benefits of being able to void voluntarily with low residual volumes of urine. Posterior rhizotomy usually precedes the Sacral Anterior Root Stimulator implantation. The purpose of rhizotomy is to identify and cut the posterior (sensory) sacral roots to eliminate or minimize reflex incontinence and autonomic dysreflexia. In NeuroControl's U.S. clinical study, all of the 23 patients had experienced UTIs during the year prior to the VOCARE Bladder System implantation; 10 of them had experienced 5 or more UTIs. The median number was 3.

After 6 months of device implantation, 6 of the 23 patients (26%) had not experienced a UTI and the median number of infections was 1. Three patients, however, reported more UTIs after the device implantation. In the patient survey, 18 of the 23 patients (78%) reported fewer infections after the device implantation. Few patients participating in the study (5 of 23 preoperatively) exhibited vesicoureteral reflux (VUR), hydronephrosis, stones or other upper tract complications either preoperatively (5 of 23) or post-operatively (worsening of VUR in 2 patients at 12 months). There were no electrode/cable lead failures. Preoperatively, 17 patients required anticholinergic medications to control reflex incontinence, but only 2 required these medications post-operatively. None of the patients reported autonomic dysreflexia post-implantation, whereas 8 patients reported this problem preimplantation. While all the patients used an intermittent catheter, indwelling catheter or condom leg bag preoperatively, 12 of the 23 (54%) patients were using only the VOCARE Stimulator at 6 months post-op. Eighteen of 20 (90%) patients at 6 months and 11of 12 patients at 12 months post-op were able to void >200 ml urine. Post-void residual (PVR) urine volume of <50 ml was achieved in 17 of 20 patients at 6 months and 9 of 12 patients at 12 months. Incontinence improved in 12 of 19 patients (63%).

With regard to bowel function benefits, 15 of 17 patients (88%) achieved a reduction in the time spent in bowel evacuation at 12 months follow-up compared to pre-op, with a median difference of 7 minutes. Nine of 17 patients (53%) reduced their use of suppositories and 9 of 17 patients (53%) reduced their use of manual evacuation at 12 months. For all System users, the VOCARE Bladder System was employed as part of their bowel management routine.

Benefits and Risks Reported in Literature:

Data from the U.S. are supported by data from several published articles on the Finetech-Brindley Sacral Anterior Root Stimulator; these articles provide additional information on the safety an probable benefit of the *VOCARE Bladder System.* Although most of the published studies involve intradural implantation of the stimulator electrodes, compared to extradural implantation of electrodes in the U.S. study, these studies do provide an overall perspective of the safety of the surgical procedures and the device. Especially relevant are the articles by Brindley (The first 500 patients with sacral anterior root stimulator implants: General description-Paraplegia, Vol. 32, p. 795 (1994)); Kerrebroeck et al (Worldwide experience with the Finetech-Brindley sacral anterior root stimulator-Neurourology and Urodynamics, Vol.12, p. 497 (1993)), and Borau et al (Spinal Cord, Vol. 1, No.2, p.1 (1995)). Van Kerrebroeck reported on the first 184 patients treated with the Finetech-Brindley Sacral anterior Root Stimulator and Brindley's article reported on the first 500 patients treated with the same device, of which 165 patients were also reported on by Dr. Van Kerrebroeck. The studies discussed by Brindley and Van Kerrebroeck involve mostly intradural implantation of the electrodes, and the article by Borau et al discusses extradural implantation results.

In Brindley's article: Of the 479 surviving patients, 411 (86%) were using the device for micturition and a majority were using it for defecation also. An additional 13 patients were using the device for defecation only. Deterioration of the upper urinary tract deterioration was reported in only 2 (0.55%) of the 365 patients who were fully deafferented (posterior rhizotomy). Among the 135 patients who were not deafferented or partially deafferented, there were 10 cases (7.5%) of upper tract deterioration, indicating that complete rhizotomy is essential to prevent upper tract deterioration. There were 95 (19%) operations to remedy failure of the implants; 75 of these were repair procedures for replacing receiver blocks or rejoining broken cables, and 20 were implantations of new extradural electrodes.

In Van Kerrebroeck's article, the benefits and risks of the procedure are quantified: elimination of reflux in 7/8 patients who had experienced reflux pre-op, improvement in upper urinary tract dilatation in 7/8 patients with pre-op dilatation, spontaneous micturition in 156/184 patients (85%), continence in 86% of patients, increase in bladder capacity in 93% of patients, decrease in infections with fever from 44 to 5 patients, decrease in infections without fever from 83 to 20 patients, decrease in PVR to ≤30 ml in 82% (151/184) of patients and decrease in autonomic dysreflexia from 26 to 10 cases. Of those for whom information was available on defecation, 110 use the device to assist in defecation either alone (36 patients) or in conjunction with other methods (manual evacuation, medication, etc.).

Borau et al in Barcelona, Spain, used the same technique of extradural electrode implantation and intradural posterior rhizotomy at the conus medullaris as the U.S. study. Thirty-four patients were studied with the first 21 patients being reported on in their 1995 article. In an unpublished report on all 34 patients, the adverse events were similar to those reported in the U.S. study. Four patients experienced incomplete rhizotomy requiring a second procedure, 2 implantable receiver-stimulator channels failed and 1 patient had 2 reoperations to reposition the receiver-stimulator. The first patient in this series sustained permanent nerve damage at the time of rhizotomy. Other medical events such as episodes of sweating and increased spasticity, fracture attributed to vertebral instability from laminectomy, and bladder distension with pyelonephritis were experienced by one patient each. Twenty five of the 34 patients emptied their bladders without the aid of bladder appliances.

In the published report on 21 patients, 6 patients were free of infection post-operatively, compared to 14 preoperatively; reflex incontinence dropped from 16 cases at pre-op to 0 at post-op; autonomic dysreflexia disappeared in 3 of 4 pre-op cases; no patient had VUR or upper tract dilation post-op compared to 4 pre-op cases; and average post-void residual urine volume decreased from 227.6 ml to 24.3 ml. Eighteen patients used the device for bowel management. User satisfaction survey results available on 16 patients indicated a high overall level of satisfaction with the device.

Additional publications outlined the effect of sacral anterior root stimulation on defecation in spinal cord injured individuals. Fifty percent are able to achieve complete rectal evacuation with the stimulator while the majority find that the time taken for defecation is reduced and constipation is alleviated (Binnie et al, J Gastro Motility, Vol 2, No 1, p. 12 (1990); MacDonagh et al., Br Med J, Vol 300, p. 1494 (1990)).

Based upon the experience in hundreds of patients implanted with the Finetech-Brindley Sacral Anterior Root Stimulator, there is no evidence that long-term electrical stimulation of the sacral anterior nerve roots causes nerve damage. Creasey (Graham Creasey, Urologic Clinics of North America: Vol. 20, p. 505 (1993)) states in his review "The procedure has now been applied in about 700 patients with spinal cord injury, some of whom have been followed for nearly 15 years. The nerves do not appear to be damaged by long-term stimulation, and technical faults with the equipment are now uncommon."

The information provided by the U.S. study and the medical literature show that implantation of the VOCARE Bladder System offers a positive risk/benefit profile to complete spinal cord injury patients who have lost voluntary bladder control.

I. CONCLUSIONS DRAWN FROM STUDIES

Biocompatibility testing of the materials used in the device, along with the history of the safe use of these materials in similar clinical applications, provide assurance of the biocompatibility of the device. The mechanical testing and clinical experience with the device also support its safety for the proposed intended use. The limited clinical data available from the prospective multi-center clinical trial, along with information from the peer-reviewed literature, indicate that implantation of the VOCARE Bladder System offers a positive risk/benefit profile to complete spinal cord injury patients who have lost voluntary bladder and bowel control.

Information provided in the HDE indicates that the VOCARE Bladder System will not expose patients to an unreasonable or significant risk of illness or injury, and that the probable benefit to health from the use of the device outweighs the risk of injury or illness, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

J. PANEL RECOMMENDATIONS

This HDE was not taken to an Advisory Panel because implantable sacral nerve stimulators for several indications have been in use in the United States for many years, and the clinical issues raised by this HDE are similar to those previously reviewed by this panel.

K. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, The VOCARE Bladder System will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the device outweighs the risks of injury or illness, and issued an approval order on FEB 19 1999.

L. APPROVAL SPECIFICATIONS

Directions for Use: See the Labeling (Attachment 1)

Warnings, Hazards to Health for use of the Device: See indications, contraindications, warnings, precautions and adverse effects in the Labeling (Attachment 1).