



Medtronic

Medtronic® DBS™ Therapy for Epilepsy

Indication-specific information
for implantable neurostimulators

FDA CLEAN DRAFT 2015-AUG-20

Information for prescribers addendum

USA Rx only

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This information for Prescribers (IFP) addendum contains information that is specific to Medtronic DBS Therapy for Epilepsy. Additional information, including common DBS contraindications, therapy warnings, and precautions, can be found in the primary IFP booklet.

PLEASE REFER TO THE PRIMARY IFP BOOKLET FOR COMPLETE INFORMATION.

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Contraindications

There are no therapy-specific contraindications for DBS Therapy for Epilepsy. Refer to the primary IFP for common DBS contraindications.

Warnings

Risk of depression, suicidal ideations, and suicide - Depression, suicidal ideations, and suicide have been reported in patients receiving Medtronic DBS Therapy for Epilepsy, although no direct cause and effect relationship has been established. Preoperatively, assess patients for depression and suicide risk, and carefully balance this risk with the potential clinical benefit. Postoperatively, monitor patients closely for new or changing symptoms of depression and suicidal thoughts or behaviors, and manage these symptoms appropriately. If DBS therapy is stopped for any reason, patients should continue to be monitored. Emphasize the importance of sustained follow-up and support with all patients, their caregivers, and family members.

Increase in seizures - Cessation, reduction, or initiation of stimulation may potentially lead to an increase in seizure frequency, severity, and new types of seizures. Symptoms may return with an intensity greater than was experienced prior to system implant, including the potential for status epilepticus. Emphasize the importance of contacting the patient's physician if they experience worsening of seizure frequency or severity or if they experience new types of seizures.

It is also important that the patient or caregiver knows how to use the patient programmer in case the neurostimulator is accidentally turned off.

Precautions

Physician training

Prescribing physicians - Prescribing physicians should be experienced in the diagnosis and treatment of epilepsy and should be familiar with the use of the Medtronic DBS System for Epilepsy.

Implanting physicians - Implanting physicians should have expertise with functional stereotactic neurosurgical treatment of epilepsy. Such expertise should include knowledge of the anatomical and neurophysiological characteristics of the anterior nucleus of the thalamus (ANT), surgical and/or implantation techniques for the brain stimulation system, operational and functional characteristics of the brain stimulation system, and experience in the continued management of patients by stimulation parameter adjustment. Physicians may contact Medtronic before prescribing or implanting a brain stimulation system for the first time and request a referral to a physician experienced in the use of Medtronic DBS Therapy for Epilepsy.

All programming of a Medtronic DBS System for Epilepsy should be by or under the supervision of a physician or other experienced medical personnel familiar with the use of the programming software and equipment. Physicians should be thoroughly familiar with Medtronic DBS System for Epilepsy supporting material, including all product labeling and education and training materials.

Clinician programming

Selecting stimulation parameters for DBS Therapy for Epilepsy - When stimulation is adjusted the following side effects may occur:

- increase in seizure frequency
- change in seizure type or characteristics
- tingling sensation
- change in mood, increased confusion

Ask the patient to wait in the clinic for a period of time after ending the programming session to monitor the patient for any immediate adverse events due to programming changes. If necessary, reprogram the neurostimulator by reducing the amplitude or pulse width settings or both.

Instruct patients to carefully monitor their seizure frequency, seizure types or seizure characteristics during the first few days and weeks after stimulation is modified.

Cognitive effects

Memory impairment - Patients should be monitored for memory impairment. Memory impairment has been reported in patients receiving Medtronic DBS Therapy for Epilepsy, although no direct cause and effect relationship has been established. The consequences of failing to monitor patients are unknown.

Long-term safety and effectiveness

Long-term safety and effectiveness - The long-term safety and effectiveness of Medtronic DBS Therapy for Epilepsy has not been established beyond 84 months (7 years).

System implant

Preoperative MRI and surgical planning

Perform a preoperative stereotactic MRI for image-guided surgical planning to determine the target coordinates, entry points, and trajectories for DBS lead placement. Use the preoperative MRI to evaluate the possible impact of anatomical variations or disordered anatomy due to prior surgery, trauma, or congenital conditions on the planned DBS implant procedure. Reference information on stereotactic coordinates for the anterior nucleus of the thalamus (ANT) must be combined with information on individual patient anatomy obtained during the preoperative MRI.

The preoperative MRI should include an imaging series that provides sufficient differentiation between gray matter and white matter to identify the ANT. One possible

example is a T1-weighted 3D image acquisition sequence. **Do not conduct an MRI on a patient with any implanted devices without reading and fully understanding all MRI information in the MRI guidelines manual.** The MRI should be performed in accordance with these guidelines.

Refer to the VNS manufacturer's physician manual for information on preventing patient injury. No test data are available to establish the effect of MRI exposure on abandoned vagus nerve stimulation (VNS) leads. For information regarding abandoned systems, refer to the MRI guidelines for Medtronic deep brain stimulation systems.

In the SANTÉ (Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy) clinical study of DBS for epilepsy, fluoroscopy was also used intraoperatively to confirm lead placement.

Determining targets for lead placement

The bilateral stimulation targets should correspond to the posterior-inferior portion of each ANT to ensure that at least two lead electrodes reside within the anterior nucleus. For the Model 3387 Lead, place the gap interval between electrodes 1 and 2 at the target coordinates.

The lead insertion cannula and stylet should be placed all the way to the target to make certain that the lead follows the intended trajectory to the ANT through the ventricle. The target coordinates will vary according to each patient's anatomy. The following coordinates are offered **for reference only**. Variations in individual anatomy identified on the preoperative MRI must be considered in surgical planning. In individual patients, target coordinates may lie outside the predicted range based upon brain atlases.

- X = 5-6 mm lateral to the midline
- Y = 0-2 mm anterior to the midcommissural plane
- Z = 12 mm superior to the intercommissural line

Postoperative MRI

A postoperative MRI is recommended to confirm proper lead placement within the target. Do not conduct an MRI on a patient with any implanted devices without reading and fully understanding all MRI information in the MRI guidelines manual. The MRI should be performed in accordance with these guidelines.

Alternatively, coregistration of the preoperative planning MRI with a postoperative CT image can be utilized to confirm proper lead placement.

Vagus nerve stimulation (VNS)

Refer to the manufacturer's instructions for explant of a VNS system prior to implanting a Medtronic DBS System for Epilepsy.

Patient counseling

Medtronic DBS Therapy for Epilepsy is an active therapy that requires both physician and patient involvement to be successful. Ensure the patient understands this will be a long-term relationship between physician, medical staff, patient, and family. Physicians

should carefully monitor patients for new or changing symptoms of depression. Such symptoms may include a change in sleep or eating behavior or suicidal ideation.

Physicians should inform patients who are recipients of Medtronic DBS Therapy for Epilepsy that it may take time (perhaps several months or more) to achieve maximum therapeutic effect from the stimulation. Patients should be reminded that a seizure diary or seizure counting on the patient programmer are essential for the optimization of the therapy and should be considered a long-term commitment.

Physicians should also instruct patients to contact their physician if they notice an increase in seizure frequency, a change in seizure characteristics, new or changing symptoms of depression, signs of infection, or new neurological symptoms.

Patient selection

Selection of patients who have other brain stimulation systems implanted is not recommended as it is unknown how the operation of Medtronic DBS Therapy for Epilepsy will affect the operation of those devices. If patients with other brain stimulation systems are selected, it is recommended that the other systems be turned off.

It is recommended that implanters refer to the manufacturer's instructions for explant of a vagus nerve stimulation system prior to implanting a Medtronic DBS System for Epilepsy. Careful consideration should be exercised when determining if a patient is appropriate for a Medtronic DBS System for Epilepsy. The following should be considered for the expected duration of the implant period:

- Patient's or caregiver's ability to use the patient programmer.
- Patient's or caregiver's ability to accurately locate their implanted neurostimulator and properly position the patient programmer.
- Patient's ability to undergo a preoperative MRI for surgical planning purposes.

Special consideration should be given to:

- Patient's mental capacity, or availability of a caregiver, as patients with cognitive impairment would likely have difficulty performing device-related tasks without assistance.
- Patient's history of depression or suicidal ideation, as new onset and worsening depression have been reported in patients receiving DBS Therapy for Epilepsy.
- Patient's previous brain surgeries for treatment of epilepsy, as patients who have had previous brain surgeries may have an altered anterior nucleus of the thalamus (ANT) location making it difficult to locate the target site.
- Patient's anatomic area of seizure onset, as patients with multilobar onset (more than 3 anatomic areas of seizure onset) were excluded from the SANTÉ study, and therefore not studied.

Note: If a patient had bilateral onset in the same lobe (eg, bitemporal onset), this was counted as one anatomic area in the study.

- Patient's physical size, as patients who are very thin or small may experience erosion at the neurostimulator implant site.
- Patient's existing infections, as patients with existing infections may be more likely to develop infections at the implant site.

Clinical studies and adverse events

The clinical use of implantable deep brain stimulation systems for epilepsy is supported by the SANTÉ study.

The following adverse events may occur with deep brain stimulation for epilepsy.

Adverse event summary

Blinded phase adverse events

There was a statistically significant difference between the active and control groups (regardless of relationship to the surgical procedure, programming/stimulation, or device/device tract) for the following events:

- Self-reported worsening or new-onset depression (14.8% of the active subjects and 1.8% of the control subjects; $p=0.016$).
- Self-reported worsening or new-onset memory impairment (13.0% of the active subjects and 1.8% of the control subjects; $p=0.032$).
- Epilepsy-related injury, which occurred more frequently in the control group (25.5%) than in the active group (7.4%), $p=0.019$.

Risks (potential adverse events) related to the lead, extension, and/or neurostimulator implant or explant procedure:

- Immediate intracranial hemorrhage, which could be asymptomatic, or which could result in temporary or permanent neurological injury or death.
- Complications or effects related to the device implantation or removal procedure, including lead(s) not within target requiring replacement.
- Mechanical complications of the device, including extension fracture and neurostimulator setscrews not adequately tightened.
- Complications related to anesthesia including nausea and vomiting, headache, and other symptoms.
- General medical complications such as postoperative fever, postprocedural pain including incision site pain, and hypoesthesia.

Risks (potential adverse events) after implantation of the lead(s), extension(s), and/or neurostimulator(s):

- Complications of the incision/surgical site, including infection, transient or persistent pain, inflammation, effusion, wound dehiscence, and hematoma.
- Erosion of the skin at the lead, extension, or neurostimulator site.
- Lead, extension, or neurostimulator device complications, including lead or extension fracture and high impedance.
- Migration or dislodgement of the lead, extension, or neurostimulator.
- Fibrosis at the extension or neurostimulator site.
- Seizures:
 - Status epilepticus.
 - Changes that may be transient or permanent including new seizure type or increased frequency, duration, and/or severity of seizures.
- Psychiatric and behavioral disorders, including agitation, anger, anxiety, depression, and panic attack.
- Neurological symptoms, new or exacerbation of existing symptoms which may be transient or permanent, including:
 - Mentation impairment: memory impairment, confusional state, abnormal thinking, déjà vu.
 - Motor and balance disorders: dizziness, dyskinesia.

- Sleep disorders: insomnia.
- Sensory disturbance: paresthesia, hypoesthesia, burning sensation, other abnormal sensations.
- General sense of discomfort, headache.
- Lack of effective therapy.

[USA] For a comprehensive summary of adverse events, refer to the clinical summary.

Risks (potential adverse events) that were not reported in the SANTÉ study:

- Leakage of cerebrospinal fluid.
- Allergic or immune system response to the implanted material.

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Definition of Terms

Anatomy

Anterior nucleus of the thalamus (ANT) – The anterior nuclear group (anterior nucleus) of the thalamus is an area located at the dorsal surface of the rostral extent of the thalamus. The anterior nuclei receive limbic inputs from the mammillary bodies (hypothalamus) via the mammillothalamic tract. The output of the anterior nuclei is primarily to the cingulate gyrus (and frontal cortex) which connects via the cingulum back to the entorhinal cortex and hippocampus (temporal lobe). The hippocampus projects to the hypothalamus via the fornix, completing a neuronal loop known as the circuit of Papez.

Programmable parameters

Amplitude – A measure, in volts or milliamps, of the electrical intensity delivered in a stimulating pulse.

Cycling – Turns the neurostimulator on and off at programmed intervals.

Parameter, programmable – A selectable value of amplitude, rate, pulse width, or cycling that enables the tailoring of the stimulating pulses.

Pulse width – A measure, in microseconds, of the duration of each stimulating pulse.

Rate – A measure, in Hertz, of the number of times stimulating pulses are delivered each second.

Epilepsy and Seizures

Epilepsy – A neurological disorder with recurrent seizures, which may include episodes of sensory disturbance, loss of consciousness, or convulsions.

Seizure – Excessive and abnormal electrical activity in the brain marked by sudden changes in behavior or sensations/perceptions. Clinical manifestations depend on the region of the brain initially affected and on the degree of spread to other regions.

Partial seizures – Seizures with onset limited to one hemisphere of the brain. Partial seizures are further classified according to degree of impaired consciousness and other symptoms:

Simple partial – Seizures where no impairment of consciousness is associated with a patient's symptoms. A simple partial seizure may remain simple or evolve into a complex or secondarily generalized seizure depending on the extent of its spread.

Complex partial – Seizures where there is any associated impairment of consciousness. A complex partial seizure may begin as a simple partial seizure and evolve into a complex seizure.

Partial seizures evolving to secondarily generalized – Seizures that start as a simple partial seizure or a complex partial seizure (including those with a simple partial onset) and spread to involve both hemispheres.

Generalized seizures – Seizures where clinical findings are associated with electroencephalogram (EEG) changes that indicate synchronous (simultaneous) involvement of both hemispheres at onset. Consciousness may be impaired, and motor manifestations, if present,

are bilateral and symmetrical. Generalized seizures can be classified as absence, myoclonic, clonic, tonic, and atonic.

Terms used in clinical study and analysis

AED – antiepileptic drug

Anticonvulsant toxicity – The Medical Dictionary for Regulatory Activities (MedDRA®) term that all antiepileptic drug side effects are coded to regardless of severity.

Baseline phase – A 12-week period used to establish subject baseline seizure frequency. Subjects qualifying for device implant were implanted within 14 days after the end of the Baseline phase. Antiepileptic medications were kept stable during this phase.

Blinded phase – A 3-month period beginning with randomization of subjects to active or control groups at week 4 after device implant. The stimulation amplitude for subjects in the active group was set at 5 volts, while the amplitude for subjects in the control group was set at 0 volts. Antiepileptic medications were kept stable during this phase. Adjustments to stimulation parameters were made only if the subject experienced an intolerable adverse event that was deemed possibly due to the stimulation. Study subjects, the investigator, and study center staff were blinded to the treatment assignment.

Complete system – A complete system includes all implanted components that are connected together (lead, neurostimulator, and extension).

Explant – Removal of a system or component without replacement.

Generalized estimating equation (GEE) – An extension of the generalized linear model, in this case, used for repeated count data (ie, seizure counts over time).

Long-term follow-up phase (LTFU) – A phase beginning at Month 13 following the Unblinded phase in which subjects were seen for follow-up every 6 months. Stimulation parameters and AEDs could be changed at the discretion of the investigator.

Operative phase – A 4-week period that began with implantation of the leads, extensions, and neurostimulator.

Patient programmer – A portable, handheld device used by patients to check the status of the implanted neurostimulator and reset the stimulation cycle.

QOLIE-31 (Quality of life in epilepsy) – A validated survey of health-related quality of life for adults (18 years or older) with epilepsy. There are 31 questions about health and daily activities.

Replacement – Removal and replacement of a system or component either during the same or a subsequent procedure (eg, device explanted and subsequently replaced 2 months later).

Responder – A subject who experiences a seizure frequency reduction greater than or equal to 50% as compared to baseline.

Revision – Repositioning or adjustment of the system or component without removal.

SAE – serious adverse event

Std – standard deviation

SUDEP – Sudden unexplained death in epilepsy.

SOC – System Organ Class

Treatment failure – A subject who 1) required 3 or more doses of rescue medication within 48 hours, 3 times during the Blinded phase; or 2) had 3 episodes of convulsive status epilepticus during the Blinded phase.

Unblinded phase – A 9-month period that began after completion of the Blinded phase. All subjects were eligible to receive active stimulation. Restricted changes in stimulation parameters were allowed. Antiepileptic medications were kept stable during this phase. Study subjects, the investigator, and study center staff remained blinded to the treatment received during the Blinded phase.

Vagus nerve stimulation (VNS) – The delivery of electrical pulses to the vagus nerve for therapeutic purposes.

SANTÉ Study

Introduction

The Medtronic Deep Brain Stimulation (DBS) system uses an implantable neurostimulator to deliver electrical stimulation to specific targets in the brain. The system consists of at least one neurostimulator, lead, and extension.

The purpose of the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTÉ) study was to assess the safety and effectiveness of bilateral stimulation of the anterior nucleus of the thalamus (ANT) using the Medtronic DBS System for Epilepsy as an adjunctive therapy in adults diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization. Subjects in the SANTÉ study had an average of 6 or more partial seizures per month, were refractory to at least 3 antiepileptic drugs (AEDs), and were taking 1 to 4 AEDs at the time of enrollment.

This Clinical Summary summarizes data from the SANTÉ study.

Study objectives

The primary effectiveness objective was to demonstrate that the reduction in the total seizure rate in the active group was greater than in the control group.

Secondary objectives were to demonstrate the following:

- The proportion of responders in the active group was greater than in the control group
- The percentage of seizure-free days and maximum length of seizure-free intervals in the active group was greater than in the control group
- The proportion of treatment failures in the active group was less than in the control group

Additional study measures included characterization of the following:

- Seizure type and severity experienced during the Baseline and Blinded phases in the active and control groups
- The number of patient programmer activations during the Blinded phase in the active and control groups
- The scores of the Quality of Life in Epilepsy-31 survey (QOLIE-31), the subject satisfaction, and subject outcome questions in the active and control groups

- The results of the neuropsychological testing in the active and control groups
- Health care resource utilization in the active and control groups
- The number of times subjects in the active and control groups used rescue medications

Safety objectives were to characterize the following:

- The adverse events experienced with the DBS system stimulating the anterior nucleus in subjects with refractory epilepsy
- The incidence of sudden unexplained death in epilepsy (SUDEP) with the DBS system stimulating the anterior nucleus in subjects with refractory epilepsy

Study design

SANTÉ was a multicenter, prospective, randomized, double-blind, parallel groups study to evaluate the safety and effectiveness of bilateral stimulation of the ANT. The study was conducted at 17 centers in the US. Subjects were eligible to participate in the study if they were aged 18 to 65 and diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, and had an average of six or more seizures per month with no more than thirty days between seizures. Subjects were required to be refractory to at least 3 AEDs and to be treated with 1 to 4 AEDs at the time of enrollment.

Subjects collected baseline seizure data for 3 months prior to implantation of the DBS system. Subjects received a DBS system as adjunctive therapy if they met all inclusion and no exclusion criteria during the Baseline phase.

Devices were implanted in a single surgical procedure under local or general anesthesia. DBS leads were implanted bilaterally in the ANT and connected subcutaneously to a neurostimulator via lead extensions tunneled down the side of the neck. A postoperative MRI was performed to confirm lead placement. Four weeks after device implant, subjects were randomized to treatment or control groups in a 1:1 ratio. The treatment (active) group received stimulation at 5 V, 145 Hz, 90 μ s, a cycling on interval of 1 minute, and a cycling off interval of 5 minutes. The control group was programmed to 0 V, 145 Hz, 90 μ s, a cycling on interval of 1 minute, and a cycling off interval of 5 minutes. Study subjects, the investigator, and study center staff were blinded to the randomization assignments. One programmer at each site was unblinded for purposes of programming and treatment of adverse events. Subjects kept seizure diaries and were seen in the clinic at 2 months, 3 months, and 4 months postimplant for follow-up during the Blinded (randomized) phase of the study.

At the end of the Month 4 visit, the control group subjects had the stimulation programmed on, and active group subjects continued stimulation. Subjects in both groups continued to be unaware of the stimulation status during the previous Blinded phase. Programming changes were restricted through the Unblinded phase of the study (Months 4-13) and AEDs remained stable. During the Long-term follow-up phase (beyond Month 13), there were no restrictions on programming or AED changes. Visits occurred monthly through the Blinded and Unblinded phases, and every 6 months during the Long-term follow-up phase. In addition to the semi-annual and annual visits, subjects were contacted by phone once a month in the Long-term follow-up phase to review the diary and record health care utilization and adverse events. See [Figure 1](#) for an overview of the study phases.

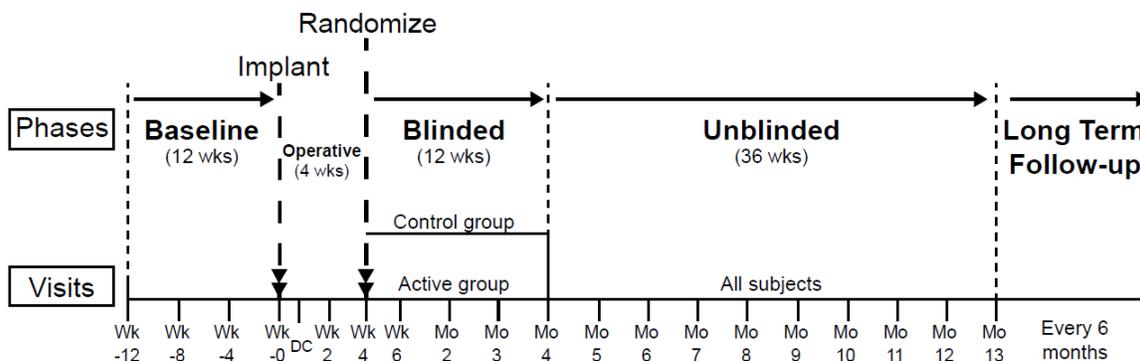


Figure 1. Study design schema.¹

Sample size calculation

The SANTÉ study was designed to have 80% power with an overall 1-sided Type 1 error rate of 0.025 (equivalent to two-sided Type 1 error of 0.05), assuming 25% difference between groups in seizure frequency reduction. To meet these criteria, 102 subjects were required at the end of the Blinded phase. To ensure that patient enrollment was adequate to meet the minimum sample size requirement (taking into account an approximate 30% baseline dropout and losses to follow-up), the recommended enrollment sample size was 150 subjects.

The sample size for the secondary outcome measures and additional study measures was not prespecified to show a statistically significant difference in those measures.

Study population

The following were key inclusion and exclusion criteria for the study.

Inclusion criteria

- Partial-onset seizures with or without secondary generalization.
- An average of 6 or more partial-onset seizures (with or without secondary generalized seizures) per month during the baseline phase, with no more than 30 days between seizures.
- Refractory to antiepileptic drugs (subjects were considered refractory if they failed at least 3 AEDs due to lack of efficacy).
- Receiving 1 to 4 currently marketed AEDs.
- Aged 18 to 65 years, inclusive.
- If female, not pregnant.

Exclusion criteria

- Multilobar (>3 different lobes) anatomic areas of seizure onset.
- Symptomatic generalized epilepsy.
- Averaged more than 10 complex partial seizures/day over the 3-month period prior to baseline.
- Experienced only simple partial seizures that had no outward clinical manifestations observable by either the subject or caregiver.

¹ Abbreviations: wk(s), week(s); mo, month; DC, hospital discharge

- Any episode of convulsive status epilepticus within the 12 months prior to baseline.
- Previous diagnosis of psychogenic/nonepileptic seizures.
- Surgical candidate for, and willing to undergo, partial temporal lobectomy or lesionectomy.
- Diagnosis or evidence of a neurological disorder or condition affecting the brain likely to progress (eg, brain tumor, active encephalitis, active meningitis or abscess, arteriovenous malformations or cavernous angiomas that were likely to progress).
- Intelligence quotient (IQ) less than 70 based on the baseline WASI (Wechsler Abbreviated Scale of Intelligence) test.
- Presence of any of the following: psychiatric illness hospitalization, suicide attempt or symptoms of psychosis (eg, hallucinations, delusions) unrelated to an ictal state, a postictal state or a medication.
- Malignancy or history of malignancy (excluding resected basal cell carcinomas).
- Presence of an implanted electrical stimulation medical device anywhere in the body (eg, cardiac pacemakers, spinal cord stimulator) or any metallic implants in the head (eg, aneurysm clip, cochlear implant). Vagus nerve stimulation (VNS) devices were allowed if the device had been turned off and the subject agreed to have the generator explanted.
- Risk factors that would put the subject at risk for intraoperative or postoperative bleeding
- Condition or disease that was known to require repeat MRIs.

Table 1 and Table 2 describe study population demographics and baseline characteristics at the time of enrollment for all implanted subjects and for all randomized subjects by treatment group.

Table 1. Demographic and baseline characteristics – age, years with epilepsy, baseline seizure counts

	All implanted (n=110)	By treatment group				p-value
		Active (n=54)		Control (n=55)		
	Mean ± std	Mean ± std	Range	Mean ± std	Range	
Age (years)	36.1 ± 11.2	35.3 ± 11.0	18.2 – 55.4	36.8 ± 11.5	19.6 – 60.9	0.484
Years with epilepsy	22.3 ± 13.3	21.6 ± 13.3	2 – 48	22.9 ± 13.5	2 – 60	0.608
Baseline phase seizure counts (per month)	56.1 ± 101.0 median 19.5	57.9 ± 105.2 median 18.4	7 – 555	55.2 ± 98.4 median 20.4	6 – 604	0.985

Table 2. Demographic and baseline characteristics – gender, surgical procedure for epilepsy, number of epilepsy medications, seizure types, seizure onset locations

	All implanted (n=110)		By treatment group				p-value
	No. of subjects	%	No. of subjects	%	No. of subjects	%	
Gender							
Male	55	50.0%	25	46.3%	30	54.5%	0.389
Female	55	50.0%	29	53.7%	25	45.5%	
Surgical procedure for epilepsy							
VNS system implant	49	44.5%	21	38.9%	28	50.9%	0.389
Previous epilepsy surgery	27	24.5%	11	20.4%	16	29.1%	0.292
Number of epilepsy medications							
1	12	10.9%	6	11.1%	6	10.9%	0.287

	All implanted (n=110)		By treatment group				p-value
	No. of subjects	%	Active (n=54)		Control (n=55)		
			No. of subjects	%	No. of subjects	%	
2	54	49.1%	25	46.3%	28	50.9%	
3	41	37.3%	23	42.6%	18	32.7%	
4	3	2.7%	0	0.0%	3	5.5%	
Seizure types^a							
Complex partial	102	92.7%	51	94.4%	50	92.6%	0.716
Partial to generalized	85	77.3%	38	70.4%	46	85.2%	0.115
Simple partial	74	67.3%	37	68.5%	36	66.7%	0.839
Primary generalized	5	4.5%	3	5.6%	2	3.7%	0.679
Other	1	0.9%	0	0.0%	1	1.9%	1.000
Seizure onset locations^b							
Temporal lobe	66	60.0%	35	64.8%	30	54.5%	0.331
Frontal lobe	30	27.3%	15	27.8%	15	27.3%	1.000
Diffuse or multifocal	10	9.1%	5	9.3%	5	9.1%	1.000
Other	10	9.1%	5	9.3%	5	9.1%	1.000
Parietal lobe	5	4.5%	2	3.7%	3	5.5%	1.000
Occipital lobe	4	3.6%	3	5.6%	1	1.8%	0.363

^a Subjects may experience more than 1 seizure type.

^b Subjects may have seizures originating from more than 1 onset location.

Subject disposition

One hundred fifty-seven subjects were enrolled in the study:

- Of the 157 subjects who enrolled in the study, 110 entered the Operative phase and received an implant
- 109 subjects were randomized to the active group (n=54) or the control group (n=55), and completed the Blinded phase
- 108 subjects entered the Unblinded phase
- 105 subjects entered the Long-term follow-up phase

One subject developed an infection after implantation but before randomization, and the device was explanted. After the infection resolved, the subject underwent re-implantation and then entered the Long-term follow-up phase. Another subject randomized to the control group developed an infection during the Blinded phase and the device was explanted. After the infection resolved, the subject underwent re-implantation and then entered the Long-term follow-up phase.

All subjects remaining in the study have been followed for a minimum of 7 years.

Withdrawals and discontinuations

Forty-seven subjects discontinued from the study prior to implant: eligibility or implant criteria not met (24), withdrawal of consent by subject (17), investigator decision due to safety reason (2), adverse event (1), death (1), lost to follow-up (1), and instability after VNS device turned off (1).

No subjects discontinued from the study during the Blinded phase.

Five subjects discontinued from the study in the Unblinded phase: death (1) and adverse event (implant site infection [2], implant site pain [1], and involuntary muscle contractions [1]).

Thirty-six subjects discontinued from the study in the Long-term follow-up phase: death (5), withdrawal of consent by subject (5), investigator decision (3), elective medical device removal (1), and adverse event (therapeutic product ineffective [13], implant site infection [3], anxiety [2], cognitive disorder [1], meningitis [1], psychotic disorder [1], and sensory disturbance [1]).

[Figure 2](#) summarizes the distribution of subjects entering each study phase and the number of subjects active in each phase at the time of the database cutoff.

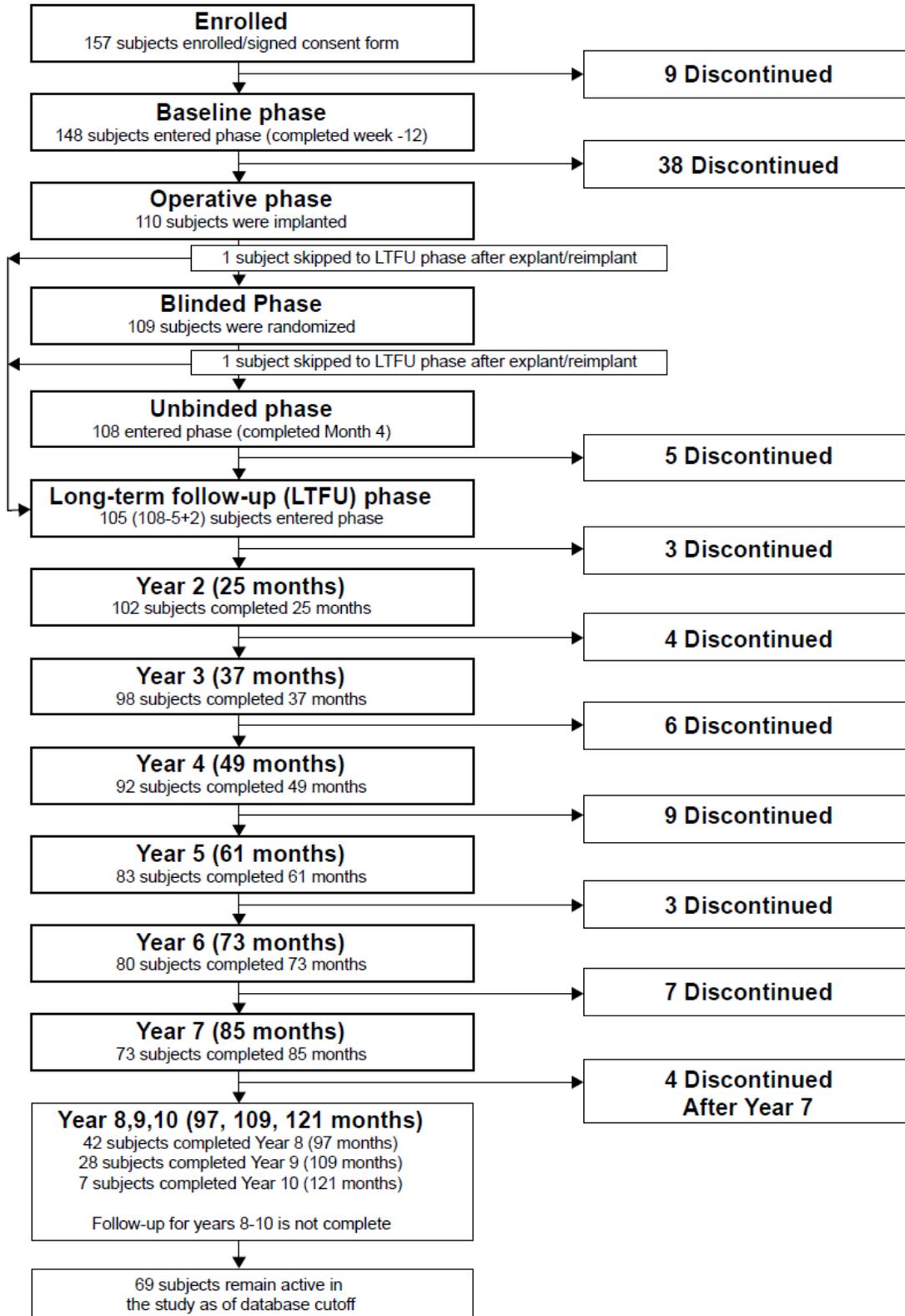


Figure 2. Subject disposition.

Analysis methods

The primary effectiveness objective was to demonstrate that the reduction in the total seizure rate in the active group was greater than in the control group. The prespecified analysis utilized a generalized estimating equations (GEE) model to test for the difference in seizure rates between groups and required that subjects record a minimum of 70 days of diary in the entire Blinded phase. One subject was excluded for having less than the required number of diary days and one subject in the active group was also excluded as this subject was determined to be an outlier.

This “outlier” subject, randomized to the active group, was identified to be an extreme and highly influential observation from a statistical and medical perspective. Inclusion of this subject’s data markedly changes the estimate of the treatment effect. This subject experienced a nearly immediate increase in the occurrence of frequent and brief seizures of a new complex partial type subsequent to the initiation of stimulation (210 seizures in 3 days compared to this subject’s baseline seizure rate of 19 seizures per month) which immediately ceased when voltage was reduced. The subject later had voltage increased beyond the level that was associated with the initial increase in seizures, with no recurrence of those seizures. The subject experienced two more seizures of this type, on the same day, during the Long-term follow-up phase.

Sensitivity analyses were performed to assess the potential impact of missing data on the long-term effectiveness results. Two analyses were performed that included all randomized subjects: LOCF (last observation carried forward) and Worst case. For both of these analyses, if the subject had at least 28 days of diary in the last 3 months prior to the annual visit, the percent change from baseline was calculated from those data. If there were less than 28 days, the percent change from the last visit was used to calculate missing values for the LOCF method. The Worst case imputation used 100% worsening if there were less than 28 days of diary.

For other effectiveness objectives, chi-square tests were used for categorical responses, Wilcoxon rank-sum (for comparison between active and control) and Wilcoxon signed-rank (for change from baseline) tests for non-normally distributed continuous endpoints, and t-tests (for comparison between active and control) or paired t-tests (for change from baseline) for normally distributed continuous endpoints.

Adverse events occurring after implant were presented in summary tables displaying the event coded using the Medical Dictionary for Regulatory Activities (MedDRA[®]) Preferred Term and percentage of subjects per study time period. Adverse event rates use the number of implanted subjects (n=110) as the denominator for calculating percentages. Adverse events were further summarized by their treatment group, seriousness, device-relatedness, and adverse event System Organ Class (SOC).

The number of subjects, person-years at risk, observed number of deaths, observed number of SUDEPs, and SUDEP per 1,000 person-years and the two-sided 95% confidence interval were summarized. Probable and definite SUDEP were included in the incidence rate. The SUDEP rate was determined based on the SANTÉ study experience and on previous studies of anterior thalamic stimulation.

For the Blinded phase effectiveness analyses, randomized subjects who had at least 70 days of diary during the Baseline phase and at least 70 days of diary during the Blinded phase were included in the analyses. The primary effectiveness analysis also excluded the outlier subject. For safety and non-Blinded phase effectiveness analyses, all implanted subjects that were

followed during the time interval of interest were included in the analyses. Sample sizes are shown with each analysis.

Effectiveness results

Primary outcome measure

Primary effectiveness analysis – total seizure frequency

The protocol prespecified a GEE analysis for the evaluation of the treatment effect on seizure frequency, and allowed for subject exclusion in the case of diary non-compliance. With this primary analysis dataset, the GEE analysis showed that the active group experienced 8% fewer seizures compared with the control group over the Blinded phase (95% confidence interval (CI): -29.2%, 20.0%). This difference was not statistically significant.

With post-hoc removal of the outlier subject, the primary objective was met over the entire Blinded phase using the original GEE analysis, demonstrating a statistically significant improvement in the total seizure rate in the active group as compared with the control group ($p=0.045$, two-sided). The active group experienced 17% fewer seizures compared with the control group over the entire Blinded phase (95% CI: -30.8%, -0.4%). There was no correction for multiplicity.

As shown in [Table 3](#), for a subject with 26 seizures per month at baseline and 34 years of age (ie, the average of the model covariates), the number of seizures per month over the Blinded phase as calculated from the GEE model would be 17.5 if that subject was in the active group and 21.1 if that subject was in the control group.

Table 3. Primary objective analysis – GEE model with outlier removed

Treatment group	Treatment effect parameter estimate (log scale) ^a	Estimated number of seizures per day (original scale) ^b	Mean seizure counts per month from GEE model (original scale) [95% confidence interval] ^c
Active (n=53)	-0.4698	0.6251	17.5 [15.2, 20.1]
Control (n=54)	-0.2838	0.7529	21.1 [18.6, 23.8]

^a The estimated treatment effect from the GEE model. The model includes the natural log of age and baseline seizure count as covariates.

^b Exponentiating transforms the estimates from the natural log scale to the original scale.

^c The daily mean seizure count is converted to a monthly count by multiplying by 28.

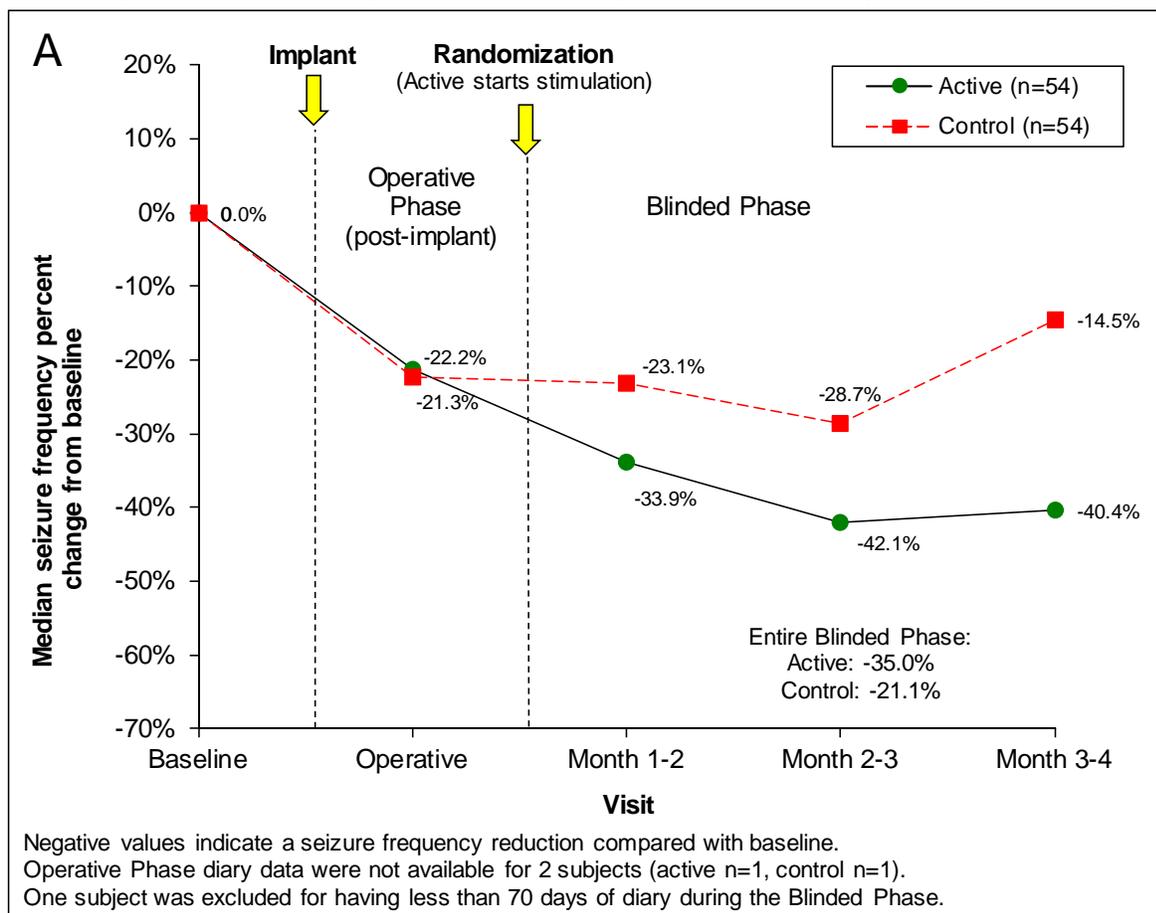
Observed data – median total seizure frequency

[Figure 3](#) displays the median total seizure frequency percent change from baseline in the Operative and Blinded phases using the primary analysis dataset ([Figure 3A](#)) and with the outlier removed ([Figure 3B](#)). The differences between the two figures are small, which is the result of the robustness of medians to extreme values such as for the outlier subject. Interaction between the number of seizures and the post randomization month should be considered when interpreting the results. There was a similar reduction in seizure frequency in both groups postimplant, prior to randomization and initiation of stimulation in the active group. Thereafter, when active stimulation was initiated, the median seizure frequency change from baseline in the active group continued to decrease, whereas the median seizure frequency change from baseline

for the control group initially decreased but then increased at Month 3-4. The net effect was an increasing difference between the active and control groups at each visit in the Blinded phase.

Using the primary analysis dataset, the median percent change from baseline in total seizure frequency over the entire Blinded phase was -35.0% for the active group and -21.1% for the control group (p=0.119, post-hoc Wilcoxon rank sum test). The active group achieved a median percent change from baseline of -40.4% during the final month of the Blinded phase. Table 4 summarizes the median along with the 25th and 75th percentiles (ie, interquartile range).

When removing the outlier subject from the analysis, the median percent change from baseline in total seizure frequency over the entire Blinded phase was -35.0% for the active group and -21.1% for the control group. The active group achieved a median percent change from baseline of -38.0% during the final month of the Blinded phase.



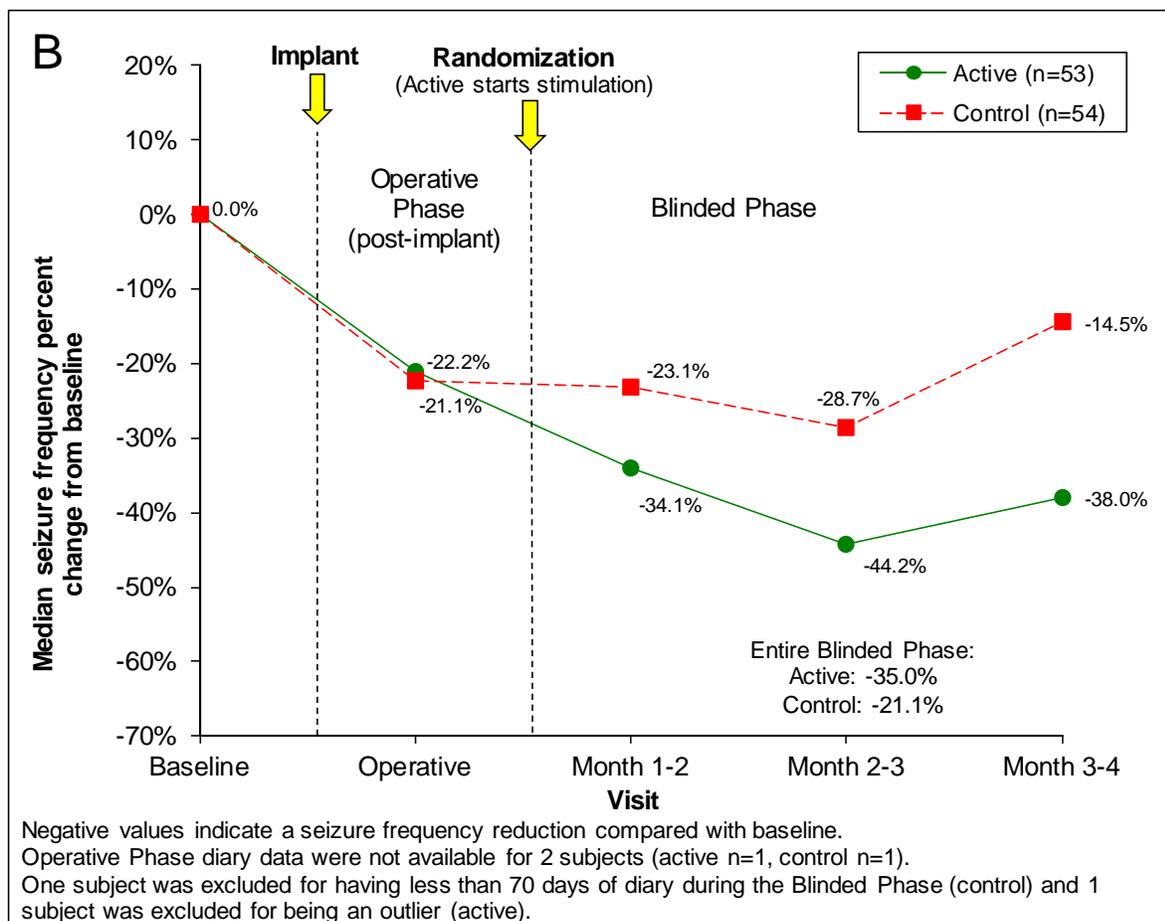


Figure 3. Unadjusted median total seizure frequency percent change from baseline (A) with outlier included and (B) with outlier removed.

Table 4. Unadjusted median total seizure frequency percent change from baseline

Visit	Active				Control			
	n	Median	25th percentile	75th percentile	n	Median	25th percentile	75th percentile
Baseline	54	0.0%	0.0%	0.0%	54	0.0%	0.0%	0.0%
Operative ^a	53	-21.3%	-42.5%	5.3%	53	-22.2%	-62.7%	9.3%
Month 1-2	54	-33.9%	-59.7%	17.3%	54	-23.1%	-51.7%	13.8%
Month 2-3	54	-42.1%	-61.0%	-19.3%	54	-28.7%	-66.4%	-5.0%
Month 3-4	54	-40.4%	-60.9%	-21.6%	54	-14.5%	-51.6%	20.0%
Entire Blinded phase	54	-35.0%	-53.9%	-13.0%	54	-21.1%	-51.5%	7.5%

^a Operative phase diary data were not available for 2 subjects (active n=1, control n=1).

Individual subject results

As shown in Figure 4, 81.5% (44/54) of subjects in the active group and 70.9% (39/55) of subjects in the control group reported any decrease in seizures (ie, any improvement from baseline) during the Blinded phase. This analysis includes all randomized subjects.

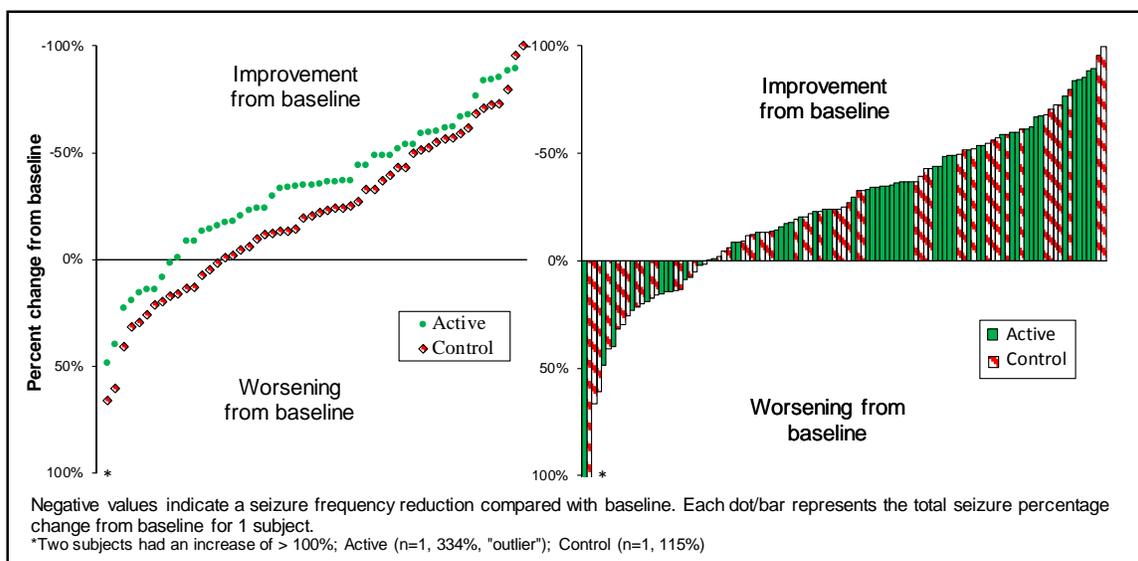


Figure 4. By-subject plot of total seizure frequency percent change from baseline.

Unblinded and Long-term follow-up phases

Since this is open label data, its interpretation is limited by several factors, including:

- All subjects were aware that they were receiving stimulation (expectation bias).
- Those who may not do well could exit the study; 108 out of 110 implanted subjects entered the Unblinded phase, 105 subjects entered the Long-term follow-up phase, and 73 subjects completed the year 7 visit (selection bias).
- Limited programming parameters were allowed during the Unblinded phase. After Month 13, programming parameters and antiepileptic drug changes were allowed (confounding factors).

The control group had stimulation turned on at the Month 4 visit at the same settings as the active group in the Blinded phase. The control group had a median total seizure frequency percent change from baseline of -13.9% during the final month of the Blinded phase (Month 3-4) which improved to -40.7% after 1 month of stimulation (Month 4-5 in [Figure 5](#)). [Figure 5](#) includes subjects with at least 70 days of diary in each 3-month time interval (n=86).

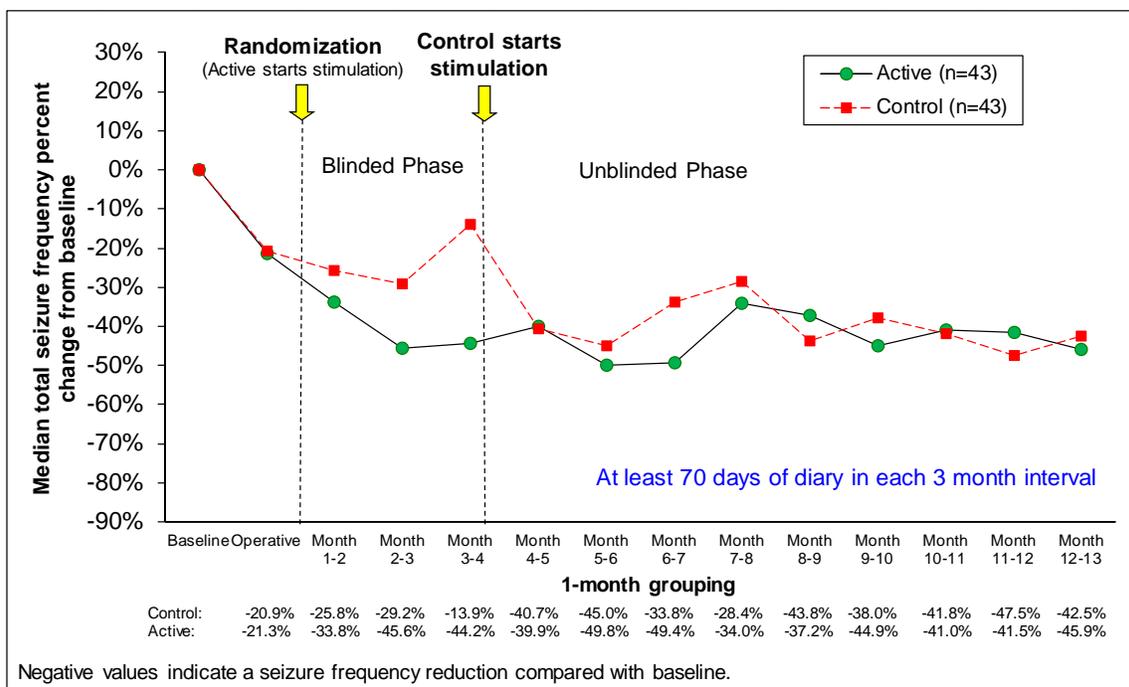


Figure 5. Median total seizure frequency percent change from baseline by treatment group – Operative phase through Year 1.

Seizure reduction continued to improve in the Long-term follow-up phase. Table 5 shows that the median total seizure frequency percent change from baseline ranged from -41% at 1 year to -75% at 7 years after device implant for those subjects with at least 70 days of diary in the 3 months prior to each annual visit. Sensitivity analyses including LOCF and Worst case are also included in Table 5.

Figure 6 shows the distribution of median total seizure frequency percent change from baseline to the most recent 3-month follow-up (as of database cutoff) with at least 70 days during the interval for all implanted subjects. For this interval, 11% (12/110) of subjects were seizure-free and 69% (76/110) were responders.

Table 5. Median total seizure frequency percent change from baseline – Blinded phase through Year 7

Time period	n	Median	25th percentile	75th percentile	Wilcoxon p-value
Analysis using all subjects with at least 70 days of diary during the time period ^{a,b}					
Blinded Phase - Active	54	-35.0%	-53.9%	-13.0%	0.119
Blinded Phase - Control	54	-21.1%	-51.5%	7.5%	
Year 1	99	-41.4%	-76.0%	-12.3%	<0.001
Year 2	82	-55.6%	-78.6%	-25.6%	<0.001
Year 3	75	-52.9%	-79.8%	-31.8%	<0.001
Year 4	76	-65.9%	-85.0%	-25.9%	<0.001
Year 5	59	-69.4%	-96.4%	-41.7%	<0.001
Year 6	64	-74.9%	-90.9%	-46.6%	<0.001
Year 7	50	-74.8%	-92.2%	-39.3%	<0.001
Analysis of long term data using LOCF ^a					
Year 1	109	-44.0%	-74.5%	-12.9%	<0.001
Year 2	109	-56.8%	-76.4%	-17.6%	<0.001

Time period	n	Median	25th percentile	75th percentile	Wilcoxon p-value
Year 3	109	-56.6%	-79.8%	-27.9%	<0.001
Year 4	109	-61.5%	-84.8%	-22.8%	<0.001
Year 5	109	-65.4%	-86.0%	-26.5%	<0.001
Year 6	109	-70.4%	-86.5%	-29.8%	<0.001
Year 7	109	-70.4%	-89.0%	-27.1%	<0.001
Analysis of long term data using Worst case ^a					
Year 1	109	-40.3%	-74.5%	-11.6%	<0.001
Year 2	109	-54.3%	-76.1%	-8.0%	<0.001
Year 3	109	-51.4%	-77.6%	-12.1%	<0.001
Year 4	109	-43.0%	-80.5%	16.1%	0.060
Year 5	109	-49.7%	-82.1%	100%	0.534
Year 6	109	-52.9%	-85.0%	100%	0.961
Year 7	109	-39.3%	-86.4%	100%	0.046

^a Blinded phase p-values are the comparison between Active and Control; Year 1-7 p-values are comparison to zero. The p-values are from post-hoc analyses.

^b No imputation was applied for missing data.

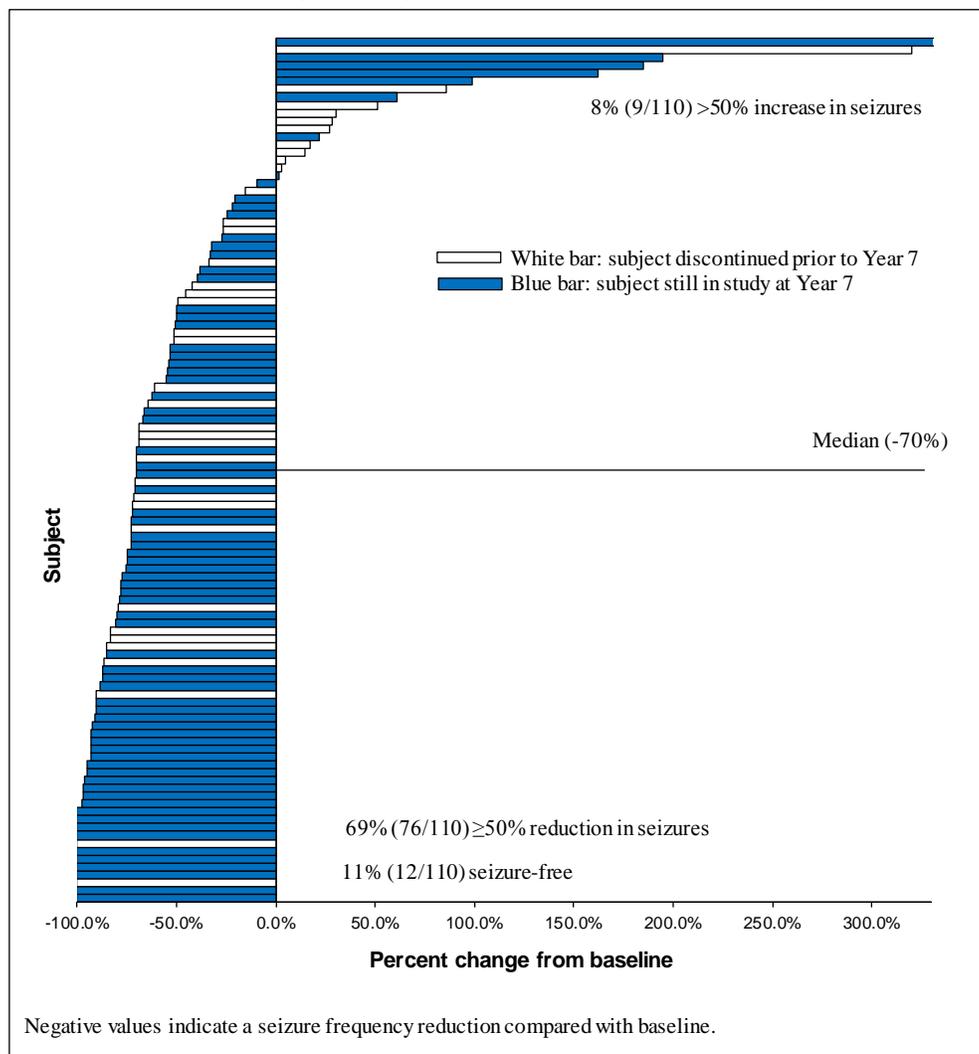


Figure 6. Subject total seizure frequency percent change from baseline to most recent 3 months of follow-up.

Secondary outcome measures

Responder rate

A responder is a subject whose seizure frequency is reduced by $\geq 50\%$ as compared with baseline. The difference in the responder rate between the active and control groups was not statistically significant ($p=0.830$, Fisher’s exact test).

Table 6 shows the responder rates in the Blinded phase and through Long-term follow-up phases for those subjects with at least 70 days of diary in the 3 months prior to each annual visit. By the end of Year 1 the responder rate was 43% and by Year 7 it had increased to 74%.

Table 6. Responder rate – Blinded phase through Year 7 ^a

Time period	n	Responder rate
Blinded Phase - Active	54	29.6%
Blinded Phase - Control	54	25.9%
Year 1	99	43.4%

Time period	n	Responder rate
Year 2	82	53.7%
Year 3	75	56.0%
Year 4	76	56.6%
Year 5	59	67.8%
Year 6	64	71.9%
Year 7	50	74.0%

^a The p-value for active vs control group in the Blinded phase is not statistically significant.

Seizure-free days and seizure-free intervals

As shown in [Table 7](#), there was no statistically significant difference in percent change in seizure-free days or percent change in maximum length of seizure-free intervals between the active and control groups over the Blinded phase.

Table 7. Seizure-free days and seizure-free intervals – Blinded phase

	Active	Control	Wilcoxon p-value
Median % change in seizure-free days ^a	15.3%	8.8%	0.112
Median % change in maximum length of seizure-free intervals	35.0%	25.0%	0.768

^a % change in seizure-free days was not calculated for subjects with no seizure-free days during baseline (active: n=4, control: n=4)

[Figure 7](#) shows that at any time between implant and Year 7, 18% (20/110) of implanted subjects were seizure-free for at least 6 months, this included 9 subjects who were seizure-free for over 2 years. In addition, there were 10 subjects with 2 or more seizure-free intervals of at least 6 months. Ten had an ongoing 6-month or longer seizure-free interval at the time of the Year 7 visit or discontinuation, including one subject who had been seizure-free for over 6 of the 7 total years, and another subject who had been seizure-free for over 5 years. Because the seizure-free interval could be of variable length, only subjects with reliable and complete diary collection were included and the interval was required to have a diary compliance of at least 83.3%.

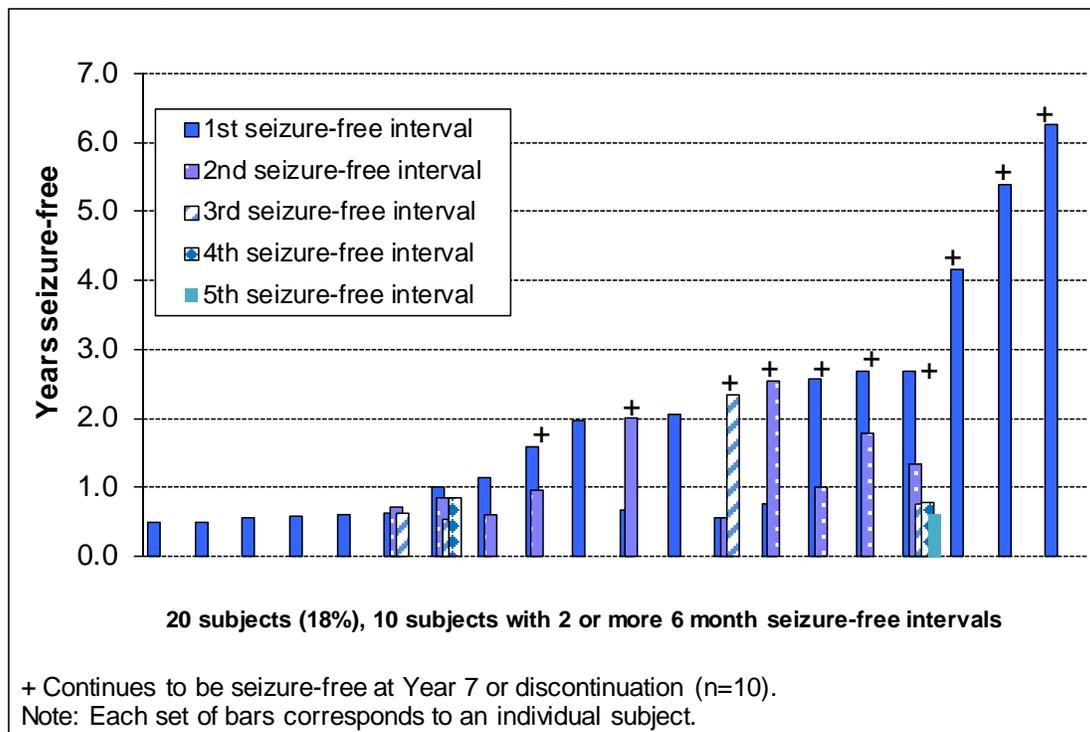


Figure 7. Subjects seizure-free for at least 6 months, by subject.

Treatment failure

A treatment failure was a subject who 1) required 3 or more doses of rescue medication within 48 hours, 3 times during the Blinded phase; or 2) had 3 episodes of convulsive status epilepticus during the Blinded phase. There were no treatment failures in the active or control groups in the Blinded phase and the difference in treatment failures between groups was not statistically significant (p=1.0, Fisher’s exact test).

Additional study measures

Seizure types and severity

Subjects recorded descriptions of their seizures and dates of occurrence. The seizure descriptions were categorized into the following types: simple partial, complex partial, partial to generalized, generalized, and other. In addition, subjects were asked at baseline to identify which of their seizure types they considered to be the most severe. They were counted in each seizure type category if they experienced that particular seizure type during the Baseline phase. Table 8 summarizes the most severe seizure types at baseline.

Table 8. Most severe seizure type at baseline

Seizure Type	Active		Control	
	n	%	n	%
Complex partial	22	51.2%	17	44.7%
Simple partial	5	11.6%	1	2.6%
Partial to generalized	15	34.9%	20	52.6%
Primary generalized	1	2.3%	0	0.0%
Total	43	100%	38	100%

Table 9 shows median seizure reductions from baseline during the Blinded phase and through Year 7 of long-term follow-up by seizure type (simple partial seizures, complex partial seizures, partial to generalized seizures, and most severe seizures). The most severe seizure type showed a statistically significant difference between active and control groups during the Blinded phase ($p=0.048$). As shown in Table 10, when the outlier subject was removed from the analysis, the complex partial seizure types also showed a statistically significant difference between groups during the Blinded phase ($p=0.041$). Only results for simple partial and complex partial seizure types are shown in Table 10 as this subject did not experience other seizure types.

Table 9. Median total seizure frequency percent change from baseline by seizure type – Blinded phase through Year 7

Time period	n	Median	25th percentile	75th percentile	Wilcoxon p-value ^a
Simple partial seizures					
Blinded Phase - Active	37	-39.9%	-65.8%	-4.3%	0.701
Blinded Phase - Control	32	-38.5%	-74.0%	11.5%	
Year 1	61	-47.3%	-100.0%	-12.2%	<0.001
Year 2	50	-73.0%	-100.0%	-41.3%	<0.001
Year 3	45	-68.5%	-100.0%	-25.3%	<0.001
Year 4	47	-76.7%	-100.0%	-8.1%	<0.001
Year 5	40	-86.0%	-100.0%	-53.6%	<0.001
Year 6	37	-97.9%	-100.0%	-60.2%	<0.001
Year 7	32	-92.2%	-100.0%	-66.4%	<0.001
Complex partial seizures					
Blinded Phase - Active	48	-36.3%	-65.5%	10.2%	0.065
Blinded Phase - Control	49	-12.1%	-41.2%	16.1%	
Year 1	90	-47.5%	-84.8%	-11.1%	<0.001
Year 2	73	-55.9%	-84.3%	-7.7%	<0.001
Year 3	69	-58.0%	-90.5%	-23.0%	<0.001
Year 4	71	-70.4%	-95.1%	-25.4%	<0.001
Year 5	54	-80.8%	-100.0%	-36.5%	<0.001
Year 6	58	-75.4%	-98.2%	-44.7%	<0.001
Year 7	44	-77.8%	-91.6%	-25.9%	<0.001
Partial to generalized seizures					
Blinded Phase - Active	19	-48.2%	-100.0%	-0.5%	0.647
Blinded Phase - Control	21	-24.7%	-66.7%	15.7%	
Year 1	37	-29.8%	-93.8%	24.7%	0.069
Year 2	28	-46.8%	-100.0%	1.8%	0.001
Year 3	25	-61.9%	-100.0%	-9.7%	0.002
Year 4	22	-43.2%	-81.4%	33.7%	0.439
Year 5	19	-82.4%	-100.0%	-30.9%	0.100
Year 6	22	-62.0%	-91.8%	11.7%	0.439
Year 7	20	-71.1%	-100.0%	-29.4%	0.006
Self-reported most severe seizures					
Blinded Phase - Active	43	-39.6%	-82.7%	-7.1%	0.048
Blinded Phase - Control	38	-20.4%	-50.0%	29.3%	
Year 1	74	-39.2%	-90.3%	-8.3%	<0.001
Year 2	62	-58.4%	-87.6%	-10.8%	<0.001
Year 3	55	-61.9%	-92.1%	-18.5%	<0.001
Year 4	55	-47.5%	-86.1%	-13.5%	<0.001
Year 5	42	-75.4%	-100.0%	-42.4%	<0.001
Year 6	44	-63.7%	-91.5%	-14.7%	0.005

Time period	n	Median	25th percentile	75th percentile	Wilcoxon p-value ^a
Year 7	30	-71.1%	-100.0%	-25.5%	<0.001

^a Blinded phase p-values are the comparison between Active and Control; Year 1-7 p-values are comparison to zero. The p-values are from post-hoc analyses and no imputation was applied for missing data.

Table 10. Median total seizure frequency percent change from baseline by seizure type – Blinded phase, outlier subject removed ^a

Time period	n	Median	25th percentile	75th percentile	Wilcoxon p-value
Simple partial seizures					
Blinded Phase - Active	36	-39.3%	-65.9%	-2.2%	0.713
Blinded Phase - Control	32	-38.5%	-74.0%	11.5%	
Complex partial seizures					
Blinded Phase - Active	47	-36.3%	-65.8%	9.5%	0.041
Blinded Phase - Control	49	-12.1%	-41.2%	16.1%	

^a Only results for simple partial and complex partial seizures types are shown as this subject did not experience other seizure types.

Liverpool seizure severity scale

Table 11 summarizes the Liverpool seizure severity scale scores at baseline and the change from baseline in the Blinded phase by treatment group and at visits Year 1 through Year 7. Only subjects that had a test at baseline and at the respective follow-up period were included. No statistically significant difference was noted between the active and control groups during the Blinded phase. A significant improvement over baseline is observed at the Year 1 through Year 7 visits.

Table 11. Liverpool Seizure Severity – Blinded phase through Year 7

Time period	n	Baseline mean \pm std	Change mean \pm std	t-test p-value ^a
Blinded Phase - Active	53	48.7 \pm 17.9	-8.2 \pm 17.8	0.699
Blinded Phase - Control	53	50.5 \pm 18.1	-6.8 \pm 19.6	
Year 1	103	48.9 \pm 18.0	-13.4 \pm 21.4	<0.001
Year 2	99	49.0 \pm 18.2	-12.4 \pm 20.7	<0.001
Year 3	93	48.1 \pm 17.9	-14.6 \pm 20.2	<0.001
Year 4	89	48.3 \pm 18.0	-17.3 \pm 23.0	<0.001
Year 5	81	49.3 \pm 17.9	-18.3 \pm 24.4	<0.001
Year 6	75	49.6 \pm 17.9	-15.2 \pm 20.3	<0.001
Year 7	67	49.0 \pm 18.6	-18.1 \pm 23.5	<0.001

^a Blinded phase p-values are the comparison between Active and Control; Year 1-7 p-values are comparison to zero. The p-values are from post-hoc analyses and no imputation was applied for missing data.

Patient programmer use

Subjects were provided a patient programmer at the week 4 randomization visit. Subjects were instructed to start a new stimulation cycle at the time they were experiencing a seizure. Both the control and active groups used the patient programmer. Subjects were not included in this analysis if they were missing programming interrogation data where counters were reset, or if they did not receive the patient programmer at the week 4 visit due to center error. The active group had a slightly lower median number of activations (13) over the entire Blinded phase compared to the control group (16) (active n=49, control n=48). However, the results were not statistically significantly different (p=0.837, Wilcoxon test).

Quality of life measures

Quality of life was measured with the QOLIE-31. The QOLIE-31 scores are summarized in Table 12 for the Blinded and Long-term follow-up phases. Only subjects who had results both at baseline and follow-up were included in the analysis. Changes from baseline to Month 4 between active and control groups were not statistically significantly different. However, a significant improvement over baseline is observed at the Year 1 through Year 7 visits.

A change in 5 points in the QOLIE-31 score is considered clinically meaningful. The percentage of subjects experiencing at least a 5-point change from baseline in QOLIE-31 score is shown in Table 13. At the end of the Blinded phase, 48% of subjects in the active group had at least a 5-point improvement compared to 32% of subjects in the control group. Seven years after device implant, 43% of subjects had at least a 5-point improvement in their QOLIE-31 score.

The percentage of subjects reported to be satisfied or greatly satisfied with the results of their therapy was 74% (74/100) at Year 1 and 84% (54/64) at Year 7.

Table 12. QOLIE-31 score – Blinded phase through Year 7

Time period	n	Baseline mean \pm std	Change mean \pm std	Median change	Wilcoxon p-value ^a
Blinded Phase - Active	52	41.8 \pm 8.6	2.5 \pm 8.7	4.4	0.555
Blinded Phase - Control	53	43.4 \pm 9.4	2.8 \pm 8.0	2.4	
Year 1	102	42.5 \pm 9.1	5.0 \pm 9.2	4.1	<0.001
Year 2	98	42.4 \pm 9.0	4.8 \pm 9.3	3.2	<0.001
Year 3	92	42.6 \pm 9.2	5.7 \pm 9.1	3.5	<0.001
Year 4	88	42.9 \pm 9.2	6.2 \pm 10.2	3.8	<0.001
Year 5	80	42.2 \pm 9.1	6.1 \pm 10.1	4.5	<0.001
Year 6	74	42.3 \pm 8.9	3.9 \pm 8.6	2.5	<0.001
Year 7	67	42.6 \pm 9.1	4.9 \pm 11.1	3.3	<0.001

^a Blinded phase p-values are the comparison between Active and Control; Year 1-7 p-values are comparison to zero. The p-values are from post-hoc analyses and no imputation was applied for missing data.

Table 13. QOLIE-31 score responder rate – Blinded phase through Year 7

Time period	n	Percent of subjects with 5-point change from baseline in the QOLIE-31 score
Blinded Phase - Active	52	48.1%
Blinded Phase - Control	53	32.1%
Year 1	102	46.1%
Year 2	98	38.8%
Year 3	92	43.5%
Year 4	88	45.5%
Year 5	80	47.5%
Year 6	74	37.8%
Year 7	67	43.3%

Neuropsychological results

Neuropsychological testing results are presented in the “Safety results” section.

Healthcare resource utilization

Table 14 summarizes the hospitalizations that occurred during the Blinded phase by treatment group and over time with both groups combined. The hospitalizations included epilepsy-related

and device-related visits. The Blinded phase analysis included all randomized subjects. Although the active group had fewer visits, the difference between groups was not statistically significant ($p=0.105$, Wilcoxon test).

Table 14. Healthcare resource utilization ^a

Group or Visit	n	Normalized annual hospitalizations (mean \pm std) ^b
Blinded Phase - Active	54	4.2 (0.08 \pm 0.56)
Blinded Phase - Control	55	20.2 (0.37 \pm 1.17)
Implant through Year 1 ^c	110	46.4 (0.42 \pm 0.90)
Year 1-2	105	6.5 (0.06 \pm 0.33)
Year 2-3	102	14.0 (0.14 \pm 0.55)
Year 3-4	98	9.6 (0.10 \pm 0.34)
Year 4-5	92	15.2 (0.17 \pm 0.51)
Year 5-6	83	4.6 (0.06 \pm 0.25)
Year 6-7	80	6.4 (0.08 \pm 0.28)

^a The p-value for the active vs. control group in the Blinded phase is not statistically significant.

^b Results were normalized to a 365.25-day year, thus utilizations are not whole integer numbers. Annual hospitalizations are the total number of hospitalizations per year for the entire group of subjects during the interval. Mean is the mean annual number of hospitalizations per subject.

^c Implant through year 1 includes Operative and Blinded phases.

Rescue medication use

Rescue medication use was allowed during the course of the study. For the Baseline and Blinded phases, 22% of subjects in each group used a rescue medication at least one time. The annual rate of rescue medication use (mean \pm standard deviation) during the Blinded phase was 3.5 ± 8.1 in the active group and 8.3 ± 23.8 in the control group, although over 75% of all subjects did not have a use (75th percentile was 0). Differences between the groups in Blinded phase rescue medication use were not statistically different ($p=0.866$, Wilcoxon test).

Subgroup comparisons

A comparison of seizure frequency for several subgroups was performed, including analyses by seizure onset location, by previous VNS device implant, by previous epilepsy surgery, and by medication status. None of these subgroup analyses were powered for statistical significance. Caution should be used when interpreting these results as the sample sizes are small and the variability is large.

Seizure onset location

A post-hoc analysis was conducted to compare seizure frequency reduction by seizure onset location.

Table 15 shows the median seizure frequency percent change from baseline for the Blinded and Long-term follow-up phases, by seizure onset location (temporal lobe seizures, frontal lobe seizures, and other seizure onset locations). A subject could be included in more than one subgroup category if the subject experienced seizures originating from more than one onset location. The differences observed between the active and control groups were statistically significant for temporal lobe seizures ($p=0.025$), but did not achieve statistical significance for frontal lobe seizures ($p=0.873$) nor for seizures originating outside the temporal and frontal lobes

($p=0.683$). However, improvements over baseline were observed for all subgroups, with statistically significant improvements after the Blinded phase.

Table 15. Median total seizure frequency percent change from baseline by seizure onset location – Blinded phase through Year 7

Time period	n	Median	25th percentile	75th percentile	Wilcoxon p-value ^a
Temporal lobe					
Blinded Phase - Active	33	-43.9%	-67.7%	-24.1%	0.025
Blinded Phase - Control	29	-21.8%	-42.8%	13.6%	
Year 1	59	-44.2%	-78.8%	-16.1%	<0.001
Year 2	47	-61.2%	-78.9%	-29.1%	<0.001
Year 3	45	-58.0%	-76.4%	-33.2%	<0.001
Year 4	44	-69.7%	-83.1%	-23.7%	<0.001
Year 5	33	-75.6%	-100.0%	-54.1%	<0.001
Year 6	38	-81.0%	-91.8%	-61.9%	<0.001
Year 7	35	-77.5%	-92.9%	-54.6%	<0.001
Frontal lobe					
Blinded Phase - Active	14	-15.0%	-35.3%	14.1%	0.873
Blinded Phase - Control	14	-19.1%	-52.4%	-4.5%	
Year 1	25	-52.6%	-78.8%	-17.0%	0.001
Year 2	20	-47.2%	-80.9%	-8.5%	0.005
Year 3	14	-52.1%	-67.3%	-18.5%	0.002
Year 4	19	-73.7%	-95.4%	-33.9%	<0.001
Year 5	17	-58.8%	-96.4%	-41.7%	0.005
Year 6	15	-69.1%	-86.5%	-42.5%	<0.001
Year 7	9	-85.6%	-92.2%	-54.8%	0.129
Other lobe					
Blinded Phase - Active	13	-35.0%	-36.7%	-0.8%	0.683
Blinded Phase - Control	14	-10.5%	-42.9%	5.1%	
Year 1	22	-33.9%	-60.4%	2.8%	0.012
Year 2	21	-54.3%	-75.0%	-13.2%	0.002
Year 3	21	-57.4%	-84.6%	-27.5%	<0.001
Year 4	18	-39.3%	-84.4%	-12.8%	0.081
Year 5	13	-68.0%	-78.3%	-36.5%	0.124
Year 6	15	-63.4%	-91.9%	31.3%	0.247
Year 7	11	-39.3%	-100.0%	21.8%	0.320

^a Blinded phase p-values are the comparison between Active and Control; Year 1-7 p-values are comparison to zero. The p-values are from post-hoc analyses and no imputation was applied for missing data.

Previous vagus nerve stimulation device implant

A post-hoc analysis was conducted to compare seizure frequency reduction for subjects with a previously implanted VNS device.

Table 16 shows the median total seizure frequency percent change from baseline during the Blinded and Long-term follow-up phases for subjects grouped by history of VNS. The differences observed between the active and control groups did not achieve statistical significance for either those with previous VNS ($p=0.158$) or without previous VNS ($p=0.516$). However, improvements over baseline were observed for both subgroups, with statistically significant improvements after the Blinded phase.

Table 16. Median total seizure frequency percent change from baseline by VNS subgroup – Blinded phase through Year 7

Time period	n	Median	25th percentile	75th percentile	Wilcoxon p-value ^a
Previous VNS					
Blinded Phase - Active	21	-35.1%	-53.9%	2.0%	0.158
Blinded Phase - Control	27	-14.1%	-42.9%	7.5%	
Year 1	45	-39.6%	-73.8%	-6.2%	<0.001
Year 2	33	-48.8%	-75.0%	-26.3%	<0.001
Year 3	32	-58.5%	-84.2%	-37.3%	<0.001
Year 4	36	-50.3%	-82.8%	-26.6%	<0.001
Year 5	25	-69.4%	-86.0%	-41.7%	<0.001
Year 6	26	-74.7%	-86.5%	-51.1%	0.001
Year 7	21	-74.7%	-88.4%	-53.7%	0.047
No previous VNS					
Blinded Phase - Active	33	-35.0%	-53.9%	-14.5%	0.516
Blinded Phase - Control	27	-22.9%	-58.8%	13.6%	
Year 1	54	-44.9%	-78.8%	-13.4%	<0.001
Year 2	49	-60.8%	-82.3%	-25.6%	<0.001
Year 3	43	-51.6%	-74.8%	-27.5%	<0.001
Year 4	40	-72.6%	-85.1%	-24.1%	<0.001
Year 5	34	-69.4%	-98.9%	-41.8%	<0.001
Year 6	38	-74.9%	-91.8%	-44.2%	<0.001
Year 7	29	-77.5%	-95.1%	-39.3%	<0.001

^a Blinded phase p-values are the comparison between Active and Control; Year 1-7 p-values are comparison to zero. The p-values are from post-hoc analyses and no imputation was applied for missing data.

Previous epilepsy surgery

Table 17 shows the median total seizure frequency percent change from baseline results during the Blinded and Long-term follow-up phases, with subjects grouped by history of previous epilepsy surgery (eg, resection). The differences observed between the active and control groups did not achieve statistical significance for either those with previous epilepsy surgery ($p=0.481$) or without previous epilepsy surgery ($p=0.295$). However, improvements over baseline were observed for both subgroups, with statistically significant improvements after the Blinded phase. For the subgroup with previous epilepsy surgery, improvements were not statistically significant at Year 7.

Table 17. Median total seizure frequency percent change from baseline by epilepsy surgery subgroup– Blinded phase through year 7

Time period	n	Median	25th percentile	75th percentile	Wilcoxon p-value ^a
Previous epilepsy surgery					
Blinded Phase - Active	11	-22.9%	-36.6%	2.0%	0.481
Blinded Phase - Control	16	-12.8%	-29.9%	9.1%	
Year 1	24	-53.4%	-75.4%	-17.9%	<0.001
Year 2	15	-55.9%	-75.8%	-17.0%	0.008
Year 3	18	-47.4%	-82.7%	-27.5%	0.001
Year 4	19	-48.6%	-73.7%	-3.9%	0.002
Year 5	14	-67.1%	-86.0%	-41.7%	<0.001
Year 6	15	-77.1%	-86.5%	-52.9%	<0.001
Year 7	10	-69.0%	-80.3%	-27.1%	0.084
No previous epilepsy surgery					

Time period	n	Median	25th percentile	75th percentile	Wilcoxon p-value ^a
Blinded Phase - Active	43	-36.2%	-59.6%	-14.5%	0.295
Blinded Phase - Control	38	-22.3%	-56.4%	7.5%	
Year 1	75	-39.7%	-77.4%	-8.3%	<0.001
Year 2	67	-55.4%	-79.5%	-25.6%	<0.001
Year 3	57	-57.4%	-78.9%	-32.1%	<0.001
Year 4	57	-72.7%	-85.4%	-26.7%	<0.001
Year 5	45	-70.4%	-96.4%	-41.8%	<0.001
Year 6	49	-72.8%	-91.4%	-44.2%	<0.001
Year 7	40	-76.4%	-94.0%	-44.8%	<0.001

^a Blinded phase p-values are the comparison between Active and Control; Year 1-7 p-values are comparison to zero. The p-values are from post-hoc analyses and no imputation was applied for missing data.

Medication status

A post-hoc analysis was conducted to compare seizure frequency reduction by medication status using the following categories for AED usage:

- **No change in AED burden** – subject is on the same medications at the same doses
- **Increase in AED burden** – subject is on an increased number or increased dosage of AEDs
- **Decrease in AED burden** – subject is on a decreased number or decreased dosage of AEDs
- **Combination** – one or more AEDs were increased or added while one or more were decreased or discontinued

AED usage was determined based on changes from the previous annual visit. For Year 1, AED usage was assessed relative to baseline. [Figure 8](#) shows seizure reduction by AED usage category.

[Figure 9](#) shows the effects of adding a new medication (as compared to baseline) on total seizure reduction. Subjects in the “AED added” category had at least one new medication added after implant, while those in the “no AED added” category had no medications added through Year 7. Overall, subjects with increases in AED burden and additions of new AEDs had results consistent with those subjects without such changes, indicating that the long term results were not driven by increases in AED burden or additions of new AEDs.

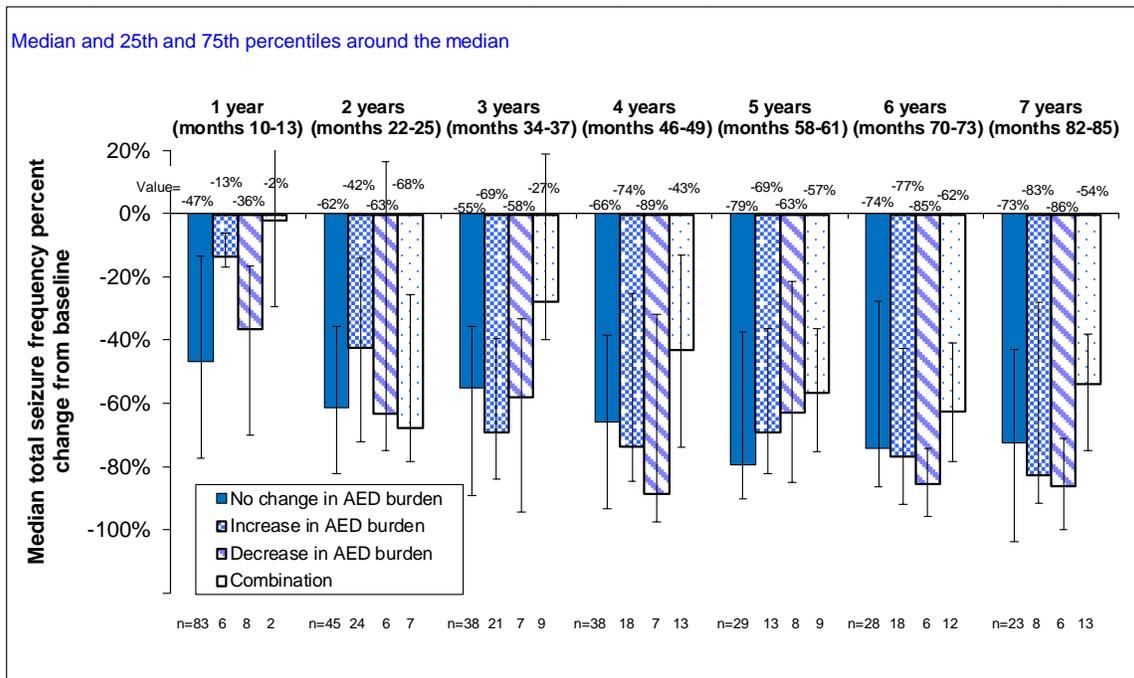


Figure 8. AED usage and median total seizure frequency percent change from baseline – Year 1 through Year 7.

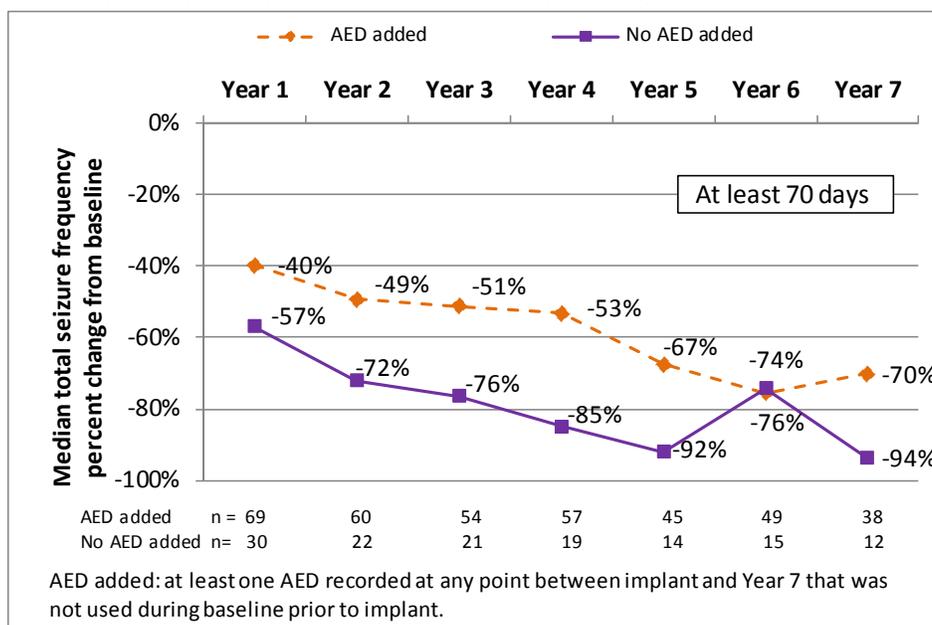


Figure 9. New AED use and median total seizure frequency percent change from baseline – Year 1 through Year 7.

Safety results

The SANTÉ study evaluated the safety of bilateral stimulation of the ANT for the treatment of epilepsy in 110 implanted subjects with a combined 713 device-years of experience. Data from

the study, including the open label period, were used to assess overall safety in which all subjects active in the study were followed for a minimum of 7 years after device implantation.

Adverse events overview

Table 18 presents an overview of adverse events (AEs). As of the database cutoff, there were 2,845 adverse events reported in 110 subjects. Serious adverse events (SAEs) accounted for 5.9% of events and device-related SAEs were 1.7% of all events. A serious device-related adverse event was reported in 34.5% (38/110) of subjects. There were no unanticipated adverse device effects.

Table 18: Adverse event summary by cause – total postimplant

Event Type	No. of events (% of events)	Subjects (%) with an Event (n=110) ^a	Number of serious events/ number of total events (% of total events)	Subjects (%) with SAE (n=110) ^a
Device	394 (13.8%)	101 (91.8%)	47/2845 (1.7%)	38 (34.5%)
Non-Device	2451 (86.2%)	110 (100.0%)	121/2845 (4.3%)	55 (50.0%)
Total	2845	110 (100.0%)	168/2845 (5.9%)	73 (66.4%)

^a Column may not add to total as subjects may have experienced more than 1 type of event.

Due to the long duration of this study, an overview of the adverse events that occurred from implant to Year 1 and from implant to Year 7 is also provided.

During the first year after device implant (Operative through the Unblinded phases), 822 adverse events were reported in 109 subjects as shown in Table 19. The majority of events (70.8%) were not device-related. Serious adverse events accounted for 6.8% of all first year events and device-related SAEs accounted for 4.1% of all first year events. Overall, 25.5% (28/110) of subjects had a serious device-related adverse event in the first year after device implant.

Table 19. Adverse event summary by cause – implant to Year 1

Event Type	No. of events (% of events)	Subjects with an Event (n=110) ^a	Number of serious events/ number of total events (% of total events)	Subjects (%) with SAE (n=110) ^a
Device	240 (29.2%)	93 (84.5%)	34/822 (4.1%)	28 (25.5%)
Non-Device	582 (70.8%)	107 (97.3%)	22/822 (2.7%)	20 (18.2%)
Total	822	109 (99.1%)	56/822 (6.8%)	40 (36.4%)

^a Column may not add to total as subjects may have experienced more than 1 type of event.

During the first 7 years after device implant (Operative phase through the Long-term follow-up phase Year 7 visit), 2,566 adverse events were reported in 110 subjects as shown in Table 20. The majority of events (85.5%) were not device-related. Serious adverse events accounted for 6.2% of events and device-related SAEs accounted for 1.7% of events. Overall, 32.7% (36/110) of subjects had a serious device-related adverse event in the first 7 years after device implant.

Table 20. Adverse event summary by cause – implant to Year 7

Event Type	No. of events (% of events)	Subjects with an Event (n=110) ^a	Number of serious events/ number of total events (% of total events)	Subjects (%) with SAE (n=110) ^a
Device	371 (14.5%)	100 (90.9%)	44/2566 (1.7%)	36 (32.7%)
Non-Device	2195 (85.5%)	110 (100.0%)	114/2566 (4.4%)	54 (49.1%)
Total	2566	110 (100.0%)	158/2566 (6.2%)	71 (64.5%)

^a Column may not add to total as subjects may have experienced more than 1 type of event.

Significant adverse events

Deaths/SUDEP

There were 7 deaths in the study, with no death directly attributed by the investigator to the implant or therapy. One death occurred in the Baseline phase prior to device implant, one in the Unblinded phase, and 5 during the Long-term follow-up phase. Of the 7 deaths, four were attributed to definite (2 subjects), probable (1), or possible (1: drowning) SUDEP. Non-SUDEP deaths were attributed to completed suicide, cardiorespiratory arrest, and liver cancer.

Table 21 shows the SUDEP rates inclusive of definite or probable SUDEP determinations for the SANTÉ study and for the subjects who participated in the pilot studies. One probable SUDEP is not included in this table since it occurred during the Baseline phase prior to device implant.

Table 21. Sudden unexplained death in epilepsy rate

Source of Data	# of SUDEP ^a	# of device years	SUDEP rate/1000 years	95% Poisson Confidence Interval
SANTÉ	2	713 years	2.8 /1000 years	[0.34, 10.13]
Pilot Follow-up ^b	0	76 years	0 /1000 years	[0, 48.54]
Total	2	789 years	2.5 /1000 years	[0.31, 9.16]

^a One probable SUDEP occurred during the Baseline phase prior to device implant and is not included.

^b Combined data from 3 pilot centers participating in the Brain Stimulation for Epilepsy Long Term Follow-up study and 2 pilot centers not participating in the follow-up study.

Intracranial hemorrhage

Intracranial hemorrhage events include those coded to MedDRA Preferred Terms of cerebral haemorrhage, haemorrhage intracranial, intraventricular haemorrhage, subdural hematoma, and post procedural haemorrhage. Eight intracranial hemorrhage events were reported in 8 of the 110 implanted subjects (7.3%). Six of the 8 events were categorized as device-related, corresponding to a device-related rate of 5.5%.

Of the 8 intracranial hemorrhage events, there was one SAE resulting in clinical manifestations reported in 1 subject (0.9%). This event was not device-related and was attributed to a head injury after 2 seizure-related falls. No surgical intervention was required and the event resolved without sequelae. The event occurred in the Long-term follow-up phase and was not related to a device implant or explant procedure.

Seven non-serious adverse events related to intracranial hemorrhage were reported in 7 subjects. None of these events resulted in clinical manifestations.

- Four of the events occurred during the Operative phase and were radiologically detected after the initial implant procedure. Three of these 4 events were detected on the protocol-required postoperative MRI, and 1 was detected on a CT scan performed after a subject had worsening of seizures the day of implant. These 4 events resolved without sequelae.
- Three of the events occurred during the Long-term follow-up phase. One was noted on a postoperative MRI following device explant. This event resolved without sequelae. A second event was discovered on a CT scan that was performed after the subject experienced a seizure-related fall that occurred the same day following a complete system explant. The third event was discovered on postoperative CT scan following a complete system explant. The second and third events were both asymptomatic and subjects did not have imaging to confirm resolution at the time of discontinuation from the study.

Device-related infection

A total of 13 SAEs of implant site infection were reported in 12 subjects (10.9%). Serious adverse events of implant site infection occurred at the neurostimulator pocket (6), lead-extension tract (5), and burr hole site (2). None of the infections were in the brain parenchyma. One event was mild in severity, 4 were moderate, and 8 were severe.

All implant site infections were treated with oral or intravenous antibiotics with or without wound drainage or debridement.

Nine subjects (8.2%) required partial or complete system explant. The device components were subsequently replaced in 3 of the 9 explanted subjects.

Display of adverse events**Adverse events in the Operative phase**

Table 22 summarizes the 29 SAEs that occurred in 23 subjects (20.9%) during the Operative phase. Of the 29 events, 25 were device-related in 22 subjects (20.0%). The most frequent serious adverse events during the Operative phase were lead(s) not in target (8.2%) and implant site infection (3.6%). Fourteen leads were replaced in 9 subjects due to the lead not being placed within the targeted area as required by the protocol. The majority of subjects with a lead not within target were in the first half of implanted subjects (7/55). The incidence of lead not within target decreased in the last half of implanted subjects (2/55). Four subjects had a SAE of implant site infection, 3 requiring partial or complete system explant. No serious adverse events related to intracranial hemorrhage occurred in the Operative phase.

Table 23 lists the device-related adverse events that occurred in $\geq 2.5\%$ of subjects during the Operative phase.

Table 24 lists all the adverse events that occurred in $\geq 2.5\%$ of subjects during the Operative phase.

Table 22. Serious adverse events during the Operative phase

Preferred Term	No. of SAEs	Subjects (%) with SAE (n=110) ^a
Lead(s) not within target	12	9 (8.2%)
Implant site infection	4	4 (3.6%)
Post procedural pain	2	2 (1.8%)
Postoperative fever	2	2 (1.8%)
Vomiting	2	2 (1.8%)
Complex partial seizures	1	1 (0.9%)
Partial seizures with secondary generalisation	1	1 (0.9%)
Pyrexia	1	1 (0.9%)
Status epilepticus	1	1 (0.9%)
Set screws not adequately secured	1	1 (0.9%)
Urosepsis	1	1 (0.9%)
Wound drainage	1	1 (0.9%)
Total	29	23 (20.9%)

^a Column may not add to total as subjects may have experienced more than 1 type of event.

Table 23. Device-related events occurring in $\geq 2.5\%$ of subjects during the Operative phase

Preferred Term	Subjects (%) with an Event (n=110)
Lead(s) not within target	9 (8.2%)
Implant site pain	8 (7.3%)
Post procedural pain	7 (6.4%)
Implant site infection	5 (4.5%)
Postoperative fever	5 (4.5%)
Hypoaesthesia	3 (2.7%)
Procedural complication	3 (2.7%)
Vomiting	3 (2.7%)

Table 24. Adverse events occurring in $\geq 2.5\%$ of subjects during the Operative phase

Preferred Term	Subjects (%) with an Event (n=110)
Lead(s) not within target	9 (8.2%)
Implant site pain	8 (7.3%)
Headache	7 (6.4%)
Post procedural pain	7 (6.4%)
Anticonvulsant toxicity	5 (4.5%)
Implant site infection	5 (4.5%)
Postoperative fever	5 (4.5%)
Head injury	4 (3.6%)
Contusion	3 (2.7%)
Drug toxicity	3 (2.7%)
Hypoaesthesia	3 (2.7%)
Procedural complication	3 (2.7%)
Simple partial seizures	3 (2.7%)
Vomiting	3 (2.7%)

The following events each occurred in 2 subjects: agitation, depression, dermatitis contact, documented hypersensitivity to administered drug, excoriation, implant site inflammation, incision site complication, injury, memory impairment, nasopharyngitis, pain in extremity, paraesthesia, pruritus, status epilepticus, tinnitus, and tremor.

The following events each occurred in 1 subject: anticonvulsant drug level decreased, anxiety, arthralgia, arthropod bite, asthenia, blister, blood magnesium decreased, blood pressure increased, cerumen impaction, chest wall pain, chills, complex partial seizures, constipation, coordination abnormal, decreased appetite, déjà vu, dizziness, dural tear, dyspnea, ecchymosis, extension fracture, face oedema, fatigue, gait disturbance, gastroenteritis viral, haemorrhage intracranial, hypoacusis, hyponatraemia, implant site effusion, implant site oedema, implant site scar, implant site swelling, incision site haemorrhage, influenza, insomnia, intraventricular haemorrhage, irritability, laceration, lead fracture, lead migration/dislodgment, musculoskeletal stiffness, nasal congestion, nausea, neck pain, onychomycosis, partial seizures with secondary generalization, peroneal muscular atrophy, pharyngolaryngeal pain, post procedural complication, post procedural drainage, post procedural haemorrhage, pyrexia, seasonal allergy, sensory disturbance, set screws not adequately secured, shoulder pain, sinusitis, skin infection,

skin laceration, subdural haematoma, syncope vasovagal, tachycardia, thermal burn, urosepsis, visual disturbance, vocal cord disorder, wound dehiscence, and wound drainage.

Adverse events in the Blinded phase

Table 25 lists the serious adverse events by treatment group that occurred during the Blinded phase. A total of 8 SAEs were reported: 2 in the active group and 6 in the control group. There were no statistically significant differences between groups in the rates of any individual serious adverse event.

Table 26 lists the device-related adverse events that occurred in $\geq 2.5\%$ of subjects (in one or both treatment groups) during the Blinded phase.

Table 27 presents adverse events occurring in $\geq 2.5\%$ of subjects (in one or both treatment groups) during the Blinded phase. Statistically significant differences between active and control groups were noted for depression and memory impairment ($p < 0.05$). Depression and memory impairment are discussed in the “Neuropsychological tests and adverse events” section.

Table 25. Serious adverse events by treatment group during the Blinded phase

Preferred Term	Active (n=54)	Control (n=55)
	Subjects (%) with SAE	Subjects (%) with SAE
Implant site infection	.	2 (3.6%)
Complex partial seizures	.	1 (1.8%)
Depression	1 (1.9%)	.
Partial seizures with secondary generalisation	.	1 (1.8%)
Anxiety	.	1 (1.8%)
Muscle contractions involuntary	.	1 (1.8%)
Status epilepticus	1 (1.9%)	.
Total	2 (3.7%)	6 (10.9%)

Table 26. Device-related events occurring in $\geq 2.5\%$ of subjects in either the active or control group during the Blinded phase

Preferred Term	Active (n=54)	Control (n=55)
	Subjects (%) with an Event	Subjects (%) with an Event
Paraesthesia	5 (9.3%)	1 (1.8%)
Implant site pain	3 (5.6%)	3 (5.5%)
Confusional state	3 (5.6%)	.
Memory impairment	3 (5.6%)	.
Anxiety	2 (3.7%)	.
Dizziness	2 (3.7%)	.
Implant site infection	1 (1.9%)	2 (3.6%)

Table 27. Adverse events occurring in $\geq 2.5\%$ of subjects in either the active or control group during the Blinded phase

Preferred Term	Active		Control		Difference ^a	Fisher's Exact p-value
	No. of subjects with event	% of subjects (n=54)	No. of subjects with event	% of subjects (n=55)		
Depression	8	14.8%	1	1.8%	13.0%	0.016
Memory impairment	7	13.0%	1	1.8%	11.1%	0.032
Anxiety	5	9.3%	1	1.8%	7.4%	0.113
Confusional state	4	7.4%	.	.	7.4%	0.057

Preferred Term	Active		Control		Difference ^a	Fisher's Exact p-value
	No. of subjects with event	% of subjects (n=54)	No. of subjects with event	% of subjects (n=55)		
Paraesthesia	5	9.3%	2	3.6%	5.6%	0.271
Influenza	3	5.6%	.	.	5.6%	0.118
Partial seizures with secondary generalisation	5	9.3%	3	5.5%	3.8%	0.489
Simple partial seizures	3	5.6%	1	1.8%	3.7%	0.363
Back pain	2	3.7%	.	.	3.7%	0.243
Tremor	2	3.7%	.	.	3.7%	0.243
Complex partial seizures	5	9.3%	4	7.3%	2.0%	0.742
Pharyngolaryngeal pain	2	3.7%	1	1.8%	1.9%	0.618
Implant site pain	3	5.6%	3	5.5%	0.1%	1.000
Anticonvulsant toxicity	3	5.6%	4	7.3%	-1.7%	1.000
Dizziness	3	5.6%	4	7.3%	-1.7%	1.000
Headache	2	3.7%	3	5.5%	-1.8%	1.000
Implant site infection	1	1.9%	2	3.6%	-1.8%	1.000
Excoriation	1	1.9%	3	5.5%	-3.6%	0.618
Dermatitis contact	.	.	2	3.6%	-3.6%	0.495
Hypoesthesia oral	.	.	2	3.6%	-3.6%	0.495
Sinusitis	.	.	2	3.6%	-3.6%	0.495
Somnolence	.	.	2	3.6%	-3.6%	0.495
Contusion	1	1.9%	4	7.3%	-5.4%	0.363
Nasopharyngitis	1	1.9%	5	9.1%	-7.2%	0.206
Upper respiratory tract infection	.	.	4	7.3%	-7.3%	0.118
Injury	1	1.9%	7	12.7%	-10.9%	0.060

^a Positive = more frequent in the active group; negative = more frequent in the control group. Table ordered by difference between groups.

Adverse events, total postimplant

Table 28 summarizes the device-related adverse events reported in $\geq 2.5\%$ of subjects by time period. The most frequent device-related adverse events were implant site pain (31.8%), paraesthesia (23.6%), therapeutic product ineffective (14.5%), and implant site infection (13.6%).

Table 29 lists device-related serious adverse events by year. The most frequent device-related serious adverse events were implant site infection (10.9%) and lead(s) not within target (8.2%), with all others reported in 1.8% of subjects or fewer.

A full listing of adverse events by system organ class is provided in “Adverse events by system organ class, by time period” on page 79 by time period.

Table 28. Device-related adverse events occurring in ≥2.5% of subjects by time period

Time Period ^a	Operative Phase (1 month) n=110 years=10		Implant to Year 1 (13 months) n=110 years=111		Implant to Year 7 (85 months) n=110 years=611		Total Postimplant ^b n=110 years=713	
	No. of subjects with event	% of subjects with event	No. of subjects with event	% of subjects with event	No. of subjects with event	% of subjects with event	No. of subjects with event	% of subjects with event
Preferred Term								
Implant site pain	8	7.3%	21	19.1%	34	30.9%	35	31.8%
Paraesthesia	1	0.9%	21	19.1%	26	23.6%	26	23.6%
Therapeutic product ineffective	14	12.7%	16	14.5%
Implant site infection	5	4.5%	10	9.1%	14	12.7%	15	13.6%
Sensory disturbance	1	0.9%	8	7.3%	10	9.1%	10	9.1%
Lead(s) not within target	9	8.2%	9	8.2%	9	8.2%	9	8.2%
Implant site inflammation	2	1.8%	5	4.5%	8	7.3%	9	8.2%
Memory impairment	.	.	6	5.5%	8	7.3%	8	7.3%
Post procedural pain	7	6.4%	7	6.4%	7	6.4%	7	6.4%
Dizziness	.	.	5	4.5%	7	6.4%	7	6.4%
Neurostimulator migration	.	.	3	2.7%	6	5.5%	6	5.5%
Postoperative fever	5	4.5%	5	4.5%	5	4.5%	6	5.5%
Extension fracture	1	0.9%	5	4.5%	5	4.5%	6	5.5%
Hypoaesthesia	3	2.7%	5	4.5%	5	4.5%	5	4.5%
Headache	2	1.8%	4	3.6%	5	4.5%	5	4.5%
Implant site effusion	1	0.9%	3	2.7%	5	4.5%	5	4.5%
Anxiety	.	.	3	2.7%	5	4.5%	5	4.5%
Confusional state	.	.	4	3.6%	4	3.6%	4	3.6%
Complex partial seizures	.	.	2	1.8%	4	3.6%	4	3.6%
Incision site complication	2	1.8%	3	2.7%	3	2.7%	4	3.6%
Implant site erosion	2	1.8%	4	3.6%
Procedural complication	3	2.7%	3	2.7%	3	2.7%	3	2.7%
Vomiting	3	2.7%	3	2.7%	3	2.7%	3	2.7%
Agitation	1	0.9%	3	2.7%	3	2.7%	3	2.7%
Extension migration/dislodgment	.	.	3	2.7%	3	2.7%	3	2.7%
Simple partial seizures	.	.	3	2.7%	3	2.7%	3	2.7%
Thinking abnormal	.	.	3	2.7%	3	2.7%	3	2.7%
Depression	.	.	2	1.8%	3	2.7%	3	2.7%
High impedance	.	.	2	1.8%	3	2.7%	3	2.7%
Panic attack	.	.	2	1.8%	3	2.7%	3	2.7%
Partial seizures with secondary generalisation	.	.	2	1.8%	3	2.7%	3	2.7%
Lead fracture	1	0.9%	2	1.8%	2	1.8%	3	2.7%

^a 'months' is the number of scheduled months in the interval for each subject. 'n' is the number of subjects entering the interval. 'years' is the number of total device years in the interval.

^b Total postimplant includes the Operative phase.

Table 29. Device-related serious adverse events by year

Time Interval ^a	Implant to Yr 1 (13 mo) n=110 yrs=111		Yr 1-2 (12 mo) n=105 yrs=95		Yr 2-3 (12 mo) n=102 years=92		Yr 3-4 (12 mo) n=97 yrs=88		Yr 4-5 (12 mo) n=92 yrs=77		Yr 5-6 (12 mo) n=82 yrs=76		Yr 6-7 (12 mo) n=80 yrs=71		Yr 7-8 (12 mo) n=73 yrs=51		Yr 8-9 (12 mo) n=42 yrs=31		Yr 9 and after n=28 yrs=20		Total Postimplant ^b n=110 yrs=713	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Implant site infection	8	7.3%	.	.	1	1.0%	.	.	2	2.2%	1	3.6%	12	10.9%
Lead(s) not within target	9	8.2%	9	8.2%
Post procedural pain	2	1.8%	2	1.8%
Postoperative fever	2	1.8%	2	1.8%
Vomiting	2	1.8%	2	1.8%
Therapeutic product ineffective	2	2.0%	2	1.8%
Muscle contractions involuntary	1	0.9%	1	0.9%
Partial seizures with secondary generalisation	1	0.9%	1	0.9%
Pyrexia	1	0.9%	1	0.9%
Set screws not adequately secured	1	0.9%	1	0.9%
Status epilepticus	1	0.9%	1	0.9%
Tension	1	0.9%	1	0.9%
Unresponsive to verbal stimuli	1	0.9%	1	0.9%
Wound drainage	1	0.9%	1	0.9%
Implant site inflammation	.	.	1	1.0%	1	0.9%
Extension fracture	1	1.0%	1	0.9%
Implant site pain	1	1.1%	1	0.9%
Convulsion	1	1.3%	1	0.9%
Implant site erosion	1	2.4%	.	.	.	1	0.9%
Incision site complication	1	2.4%	.	.	.	1	0.9%
Total ^c	28	25.5%	1	1.0%	4	3.9%	0	0.0%	3	3.3%	0	0.0%	1	1.3%	0	0.0%	1	2.4%	1	3.6%	38	34.5%

^a ‘mo’ designates the number of scheduled months in the interval for each subject. ‘yr’ is the abbreviation for ‘year’. ‘yrs’ designates the number of total device years in the interval. ‘n’ designates the number of subjects entering the interval. ‘N’ designates the number of subjects who experienced each event.

^b Row subtotals may not equal row sum, as subjects may have experienced an event in more than 1 year.

^c Column total may not equal column sum, as subjects may have experienced more than 1 event in the same time period.

Epilepsy-related adverse events

Status epilepticus

Status epilepticus was reported in 7 subjects (6.4%). The majority (4 of the 7 events) were nonconvulsive in nature. Six of the 7 subjects required hospitalization for the event and were considered serious adverse events. Three of the 7 events were reported in subjects who were not receiving stimulation at the time of the event. Two events occurred in the Operative phase, 1 in the Blinded phase (active subject), 1 in the Unblinded phase, and 3 in the Long-term follow-up phase. One serious event occurred after stimulation was turned on in a control subject on the Month 4 visit. The stimulation amplitude was reduced to 0 volts and the event resolved within 6 days. The voltage was increased to 1 V approximately 2 weeks after onset of the event without incident. No subject experienced more than 1 episode of status epilepticus.

Seizures as adverse events

Seizures were recorded as adverse events if they were status epilepticus (included in the previous section), a new seizure type, required hospitalization, or at the discretion of the investigator (eg, increased frequency or worsening of a seizure). The MedDRA Preferred Terms of epilepsy and convulsion were used when the seizure type was not reported. [Table 30](#) presents seizure events by seizure type. A total of 180 seizure events were reported in 78 subjects (70.9%). There were 7 SAEs of complex partial seizures in 7 subjects (6.4%), 15 SAEs of partial seizures with secondary generalisation in 11 subjects (10.0%), 3 SAEs of simple partial seizures in 3 subjects (2.7%), 3 SAEs of convulsion in 3 subjects (2.7%), 4 SAEs of epilepsy in 4 subjects (3.6%), and no SAEs of grand mal convulsion (0.0%).

Table 30. Seizures as adverse events

Preferred Term	Events (serious)	Subjects (%) with SAE ^a	Subjects (%) with an Event ^a
Complex partial seizures	62 (7)	7 (6.4%)	38 (34.5%)
Partial seizures with secondary generalisation	54 (15)	11 (10.0%)	34 (30.9%)
Simple partial seizures	36 (3)	3 (2.7%)	31 (28.2%)
Convulsion	14 (3)	3 (2.7%)	11 (10.0%)
Epilepsy	8 (4)	4 (3.6%)	7 (6.4%)
Grand mal convulsion	6	0 (0%)	4 (3.6%)
Total	180 (32)	22 (20.0%)	78 (70.9%)

^a Column may not add to total as subjects may have experienced more than 1 type of event.

Seizure events reported during the first week of stimulation

Five subjects reported adverse events of increased, worsening, or new seizures during the first week of stimulation. Three of these were subjects in the active group. One subject had a new type of complex partial seizure upon initiation of stimulation (outlier subject described in the “Analysis methods” section). Another subject experienced a new simple partial seizure starting 5 days after stimulation was turned on. There was no intervention and the subject continued to report seizures of this type (the subject experienced 5 other seizures of this type through Month 103 of the study). A third subject had a longer and more intense aura as part of their simple partial seizure starting the day that stimulation was turned on which resolved with programming. Two control group subjects experienced adverse events related to seizures during the first week of stimulation. One subject experienced a serious adverse event of status epilepticus and is described in the “Status epilepticus” section. A second subject had a longer than normal simple

partial seizure on the day that stimulation was turned on which resolved the same day with no intervention.

Epilepsy-related injury

Seventy-two (65.5%) subjects experienced 344 epilepsy-related injury events in the study, with 4 subjects (3.6%) experiencing serious adverse events related to epilepsy-related injury.

Table 31 summarizes the Blinded phase injury events that occurred as a direct result of a seizure for all randomized subjects. None of the events were serious. Epilepsy-related injury occurred more frequently in the control group (25.5%) than in the active group (7.4%).

Table 31: Epilepsy-related injury in the Blinded phase

Preferred Term	Active (n=54)	Control (n=55)	Total Fisher's Exact p-value
	Subjects (%) with an Event	Subjects (%) with an Event	
Injury	1 (1.9%)	6 (10.9%)	0.019
Contusion	1 (1.9%)	4 (7.3%)	
Excoriation	0.0%	2 (3.6%)	
Laceration	1 (1.9%)	0.0%	
Mouth injury	1 (1.9%)	0.0%	
Coccydynia	0.0%	1 (1.8%)	
Face injury	0.0%	1 (1.8%)	
Head injury	0.0%	1 (1.8%)	
Joint sprain	0.0%	1 (1.8%)	
Oedema	0.0%	1 (1.8%)	
Periorbital haematoma	0.0%	1 (1.8%)	
Total	4 (7.4%)	14 (25.5%)	

Neuropsychological tests and adverse events

Neuropsychological tests

Table 32 summarizes changes between baseline and Month 4 by treatment group for neuropsychological testing, for randomized subjects with assessments at baseline and Month 4. There was no statistically significant difference between groups at the end of the Blinded phase, including test scores for visual memory, verbal memory, and depression. The baseline scores for both groups indicate mild impairment especially in verbal and visual memory, verbal fluency, and aspects of executive functioning such as cognitive flexibility. At baseline, subjects self-reported levels of executive dysfunction and apathy approached clinically significant impairment. On a group basis, the impairment observed at baseline was not aggravated by treatment.

Table 33 summarizes the changes between baseline and Years 1 and 7 for those subjects with assessments at baseline and the respective follow-up time point. Improvements over baseline were seen at these follow-up periods, with the most improvement observed in visual attention, executive function, and subjective cognitive function. None of the domains showed a consistent worsening during follow-up.

Table 32. Neuropsychological results – Blinded phase

Test	Active Group				Control group				Wilcoxon p-value
	N	Baseline mean ± std	Month 4 mean ± std	Change mean ± std	N	Baseline mean ± std	Month 4 mean ± std	Change mean ± std	
Visual motor speed									
D-KEFS Trailmaking Motor Speed (ss)	54	9.5 ± 3.4	9.3 ± 2.9	-0.2 ± 2.0	46	8.7 ± 3.6	9.1 ± 3.1	0.4 ± 2.5	0.182
General verbal ability									
WASI Vocabulary (T)	54	42.5 ± 10.1	41.4 ± 11.7	-1.1 ± 7.0	43	41.3 ± 10.5	40.1 ± 9.8	-1.1 ± 6.4	0.786
General visuospatial ability									
WASI Matrix Reasoning (T)	53	50.9 ± 9.9	49.7 ± 10.8	-1.2 ± 7.7	43	49.5 ± 9.4	49.8 ± 10.8	0.3 ± 8.9	0.566
Verbal memory									
CVLT Trials 1-5 Total (T)	54	40.6 ± 12.1	40.4 ± 11.6	-0.2 ± 8.6	46	41.1 ± 13.0	39.8 ± 12.4	-1.3 ± 9.2	0.537
CVLT Long Delay Free Recall (z)	54	-1.4 ± 1.5	-1.4 ± 1.4	-0.1 ± 0.9	46	-1.6 ± 1.5	-1.5 ± 1.5	0.1 ± 1.2	0.232
CVLT Recognition Hits (z)	54	-1.1 ± 1.6	-1.1 ± 1.4	0.0 ± 1.4	46	-1.4 ± 1.6	-1.5 ± 1.6	-0.1 ± 1.5	0.845
CVLT Discriminability (z)	54	-1.0 ± 1.5	-0.9 ± 1.4	0.1 ± 1.1	46	-0.9 ± 1.2	-1.1 ± 1.4	-0.2 ± 1.2	0.154
Visual memory									
BVMT-R Total Recall (T)	54	37.4 ± 12.8	37.2 ± 12.9	-0.2 ± 11.0	46	33.8 ± 12.3	35.7 ± 13.2	1.9 ± 11.4	0.317
BVMT-R Delayed Recall (T)	54	39.8 ± 14.8	38.4 ± 14.5	-1.3 ± 14.1	46	34.7 ± 14.4	37.1 ± 12.6	2.4 ± 13.7	0.156
BVMT-R Recognition Hits (z)	54	5.4 ± 0.9	5.4 ± 0.9	0.0 ± 0.9	46	5.4 ± 0.9	5.5 ± 0.6	0.1 ± 0.9	0.378
BVMT-R False Alarms (z)	54	0.4 ± 1.1	0.2 ± 0.5	-0.2 ± 1.1	46	0.3 ± 1.0	0.2 ± 0.5	-0.1 ± 1.1	0.797
Language									
D-KEFS Verbal Fluency: Category Fluency (ss)	54	5.8 ± 4.7	5.2 ± 4.0	-0.7 ± 2.8	46	5.4 ± 3.4	4.8 ± 3.4	-0.6 ± 2.8	0.922
D-KEFS Verbal Fluency: Letter Fluency (ss)	54	6.8 ± 3.8	6.4 ± 3.4	-0.3 ± 2.2	46	6.2 ± 3.3	6.0 ± 3.2	-0.2 ± 1.8	0.780
Design fluency									
D-KEFS Design Fluency – Total Correct (ss)	54	8.5 ± 2.9	9.0 ± 3.6	0.5 ± 2.5	46	8.6 ± 3.5	9.6 ± 4.0	1.0 ± 2.7	0.379
Executive function									
D-KEFS Trailmaking Number-letter switching (ss)	53	7.0 ± 4.3	7.7 ± 4.3	0.7 ± 2.4	46	7.5 ± 4.2	8.0 ± 4.0	0.6 ± 2.4	0.595
D-KEFS Inhibition/Switching (ss)	52	6.2 ± 4.4	6.8 ± 4.7	0.6 ± 2.3	46	6.6 ± 4.5	6.5 ± 4.2	-0.1 ± 2.4	0.109
D-KEFS Tower Test Total (ss)	54	8.4 ± 3.4	10.1 ± 3.3	1.7 ± 2.8	46	8.6 ± 3.3	10.5 ± 3.3	1.9 ± 2.5	0.813
D-KEFS Verbal Fluency: Category Switching (ss)	53	6.4 ± 3.8	5.8 ± 3.7	-0.6 ± 2.7	46	6.7 ± 3.5	6.2 ± 3.2	-0.5 ± 3.0	0.573
Subjective cognitive function									
POMS Confusion/Bewilderment (T) ^a	54	60.8 ± 11.1	60.2 ± 10.2	-0.7 ± 9.1	45	58.9 ± 12.2	56.8 ± 9.6	-2.1 ± 9.9	0.841
FrsBe Executive Dysfunction (T) ^a	53	66.0 ± 17.1	64.1 ± 13.7	-1.9 ± 12.8	46	68.0 ± 18.8	64.8 ± 17.4	-3.2 ± 13.8	0.571
FrsBe Total (T) ^a	53	66.5 ± 18.3	62.7 ± 13.9	-3.8 ± 12.8	46	67.3 ± 18.5	63.5 ± 18.8	-3.8 ± 10.5	0.785
Depression and apathy									
POMS Depression (T) ^a	54	57.2 ± 12.4	57.9 ± 12.3	0.7 ± 9.3	45	54.6 ± 10.6	54.2 ± 10.0	-0.5 ± 7.4	0.396

Test	Active Group				Control group				Wilcoxon p-value
	N	Baseline mean ± std	Month 4 mean ± std	Change mean ± std	N	Baseline mean ± std	Month 4 mean ± std	Change mean ± std	
FrSBe Apathy (T) ^a	53	67.4 ± 16.9	63.5 ± 14.4	-3.9 ± 13.7	46	67.8 ± 15.8	63.6 ± 17.7	-4.2 ± 10.1	0.641
Subjective behavioral disturbance									
FrSBe Disinhibition (T) ^a	53	57.4 ± 15.4	53.5 ± 14.1	-3.9 ± 11.2	46	56.6 ± 17.7	53.8 ± 15.5	-2.8 ± 12.2	0.978
Subjective fatigue and energy									
POMS Fatigue (T) ^a	54	54.6 ± 10.7	53.6 ± 9.3	-1.0 ± 10.6	45	53.9 ± 11.0	51.7 ± 8.5	-2.2 ± 8.6	0.472
POMS Vigor (T) ^a	54	43.4 ± 7.8	43.8 ± 8.2	0.3 ± 7.6	45	43.8 ± 8.3	43.3 ± 7.9	-0.6 ± 7.6	0.850
Anxiety									
POMS Tension (T) ^a	54	60.0 ± 11.1	58.3 ± 10.7	-1.7 ± 12.1	45	57.3 ± 11.4	54.4 ± 10.2	-2.8 ± 9.3	0.795
Visual attention									
D-KEFS Trailmaking Visual Scanning (ss)	54	8.4 ± 3.3	8.8 ± 3.0	0.4 ± 2.5	46	7.8 ± 4.0	7.8 ± 4.2	0.0 ± 2.3	0.689
D-KEFS Trailmaking Letter Sequencing (ss)	54	7.4 ± 3.9	8.2 ± 4.2	0.8 ± 2.9	46	7.6 ± 4.3	8.3 ± 4.2	0.7 ± 1.8	0.980
D-KEFS Trailmaking Number Sequencing (ss)	54	7.3 ± 3.3	8.4 ± 4.0	1.1 ± 2.9	46	7.9 ± 4.2	8.5 ± 3.8	0.5 ± 2.4	0.509
Processing speed									
D-KEFS Color-Word interference Color Naming (ss)	54	6.0 ± 4.1	6.2 ± 4.4	0.3 ± 2.2	46	7.6 ± 3.6	7.7 ± 3.6	0.1 ± 2.0	0.737
D-KEFS Color-Word interference Word Reading (ss)	54	6.0 ± 3.9	6.3 ± 4.2	0.3 ± 2.3	46	6.9 ± 3.5	6.8 ± 3.7	-0.1 ± 2.1	0.432

^a Higher values (positive change) indicate improvement with the exception of the footnoted tests where lower values (negative change) indicate improvement.

Abbreviations: Brief Visual Memory Test-revised (BVM-T-R), California Verbal Learning Test (CVLT), Delis-Kaplan Executive Function System (D-KEFS), Frontal Systems Behavior Scale (FrSBe), Profile of Mood States (POMS), Wechsler Abbreviated Scale of Intelligence (WASI).

Scoring:

- Scaled scores (ss) have mean = 10 and standard deviation = 3.
- T-scores have mean = 50 and standard deviation = 10.
- z-scores have mean = 0 and standard deviation = 1.

Table 33. Neuropsychological results – Year 1 and Year 7

Test	Change at year 1			Change at year 7		
	N	mean ± std	Wilcoxon p-value	N	mean ± std	Wilcoxon p-value
Visual motor speed						
D-KEFS Trailmaking Motor Speed (ss)	105	0.5 ± 2.5	0.040	67	0.6 ± 2.9	0.104
Verbal memory						
CVLT Trials 1-5 Total (T)	105	0.8 ± 10.4	0.267	66	0.2 ± 10.9	0.758
CVLT Long Delay Free Recall (z)	105	0.2 ± 1.1	0.360	66	0.2 ± 1.2	0.347
CVLT Recognition Hits (z)	105	0.1 ± 1.7	0.501	66	0.1 ± 1.8	0.707
CVLT Discriminability (z)	105	0.1 ± 1.2	0.247	66	-0.1 ± 1.3	0.423
Visuospatial memory						
BVMT-R Total Recall (T)	105	1.7 ± 10.4	0.135	66	2.9 ± 10.1	0.012
BVMT-R Delayed Recall (T)	105	0.7 ± 11.5	0.462	66	0.4 ± 12.3	0.624
BVMT-R Recognition Hits (z)	104	0.1 ± 0.9	0.255	65	-0.1 ± 0.9	0.272
BVMT-R False Alarms (z)	104	0.0 ± 1.0	0.713	65	0.0 ± 1.1	0.603
Language						
D-KEFS Verbal Fluency: Category Fluency (ss)	105	-0.4 ± 2.9	0.174	66	-0.3 ± 3.4	0.408
D-KEFS Verbal Fluency: Letter Fluency (ss)	105	0.0 ± 2.2	0.747	66	0.6 ± 2.3	0.053
Design fluency						
D-KEFS Design Fluency – Total Correct (ss)	105	1.0 ± 2.5	<0.001	66	1.8 ± 2.8	<0.001
Executive function						

Test	Change at year 1			Change at year 7		
	N	mean ± std	Wilcoxon p-value	N	mean ± std	Wilcoxon p-value
D-KEFS Trailmaking Number-letter switching (ss)	104	1.3 ± 2.4	<0.001	67	1.1 ± 3.7	0.019
D-KEFS Inhibition/Switching (ss)	101	0.6 ± 2.6	0.004	64	1.1 ± 3.6	0.015
D-KEFS Tower Test Total (ss)	105	2.6 ± 3.2	<0.001	65	4.1 ± 3.3	<0.001
D-KEFS Verbal Fluency: Category Switching (ss)	103	-0.3 ± 3.3	0.343	65	-0.5 ± 3.6	0.325
Subjective cognitive function						
POMS Confusion/Bewilderment (T) ^a	105	0.1 ± 10.0	0.895	66	0.0 ± 11.0	0.876
FrSBe Executive Dysfunction (T) ^a	105	-5.0 ± 12.1	<0.001	66	-2.4 ± 16.7	0.299
FrsBe Total (T) ^a	105	-4.4 ± 11.1	<0.001	66	-2.9 ± 16.6	0.178
Depression and apathy						
POMS Depression (T) ^a	105	0.5 ± 10.9	0.864	66	0.1 ± 11.6	0.964
FrSBe Apathy (T) ^a	105	-3.9 ± 12.1	0.001	66	-2.7 ± 15.2	0.130
Subjective behavioral disturbance						
FrSBe Disinhibition (T) ^a	105	-1.9 ± 11.5	0.029	66	-1.7 ± 15.8	0.336
Subjective fatigue and energy						
POMS Fatigue (T) ^a	105	-2.4 ± 10.6	0.059	66	-1.6 ± 10.7	0.245
POMS Vigor (T) ^a	105	-0.9 ± 7.8	0.140	66	0.6 ± 8.7	0.521
Anxiety						
POMS Tension (T) ^a	105	-2.5 ± 11.0	0.002	66	-2.3 ± 11.8	0.226
Visual attention						
D-KEFS Trailmaking Visual Scanning (ss)	105	0.6 ± 2.4	0.007	67	0.1 ± 3.4	0.663
D-KEFS Trailmaking Letter Sequencing (ss)	105	1.4 ± 3.1	<0.001	67	1.5 ± 3.3	<0.001
D-KEFS Trailmaking Number Sequencing (ss)	105	1.7 ± 2.7	<0.001	67	1.7 ± 3.1	<0.001
Processing speed						
D-KEFS Color-Word interference Color Naming (ss)	105	-0.1 ± 2.5	0.619	66	0.3 ± 2.9	0.395
D-KEFS Color-Word interference Word Reading (ss)	105	0.1 ± 2.3	0.551	66	0.1 ± 3.1	0.453

^a Higher values (positive change) indicate improvement with the exception of the footnoted tests where lower values (negative change) indicate improvement.

Depression

A total of 46.4% of the implanted subjects had a prior medical history of depression. Over half (54.9%, 28/51) of subjects with a prior history of depression reported a postimplant depression event, compared to 25.4% (15/59) of subjects without a prior history of depression.

Forty-six depression events were reported in 43 subjects (39.1%). Of these 43 subjects, 65.1% (28/43) had a prior history of depression. One subject (0.9%) in the study experienced a serious adverse event of depression that occurred in the Blinded phase. This subject had a prior history of depression. Three events in 3 subjects were device-related events. None of these events were considered serious. All 3 of the device-related events resolved, in an average of 61 days.

During the Blinded phase, spontaneously self-reported worsening or new onset depression occurred in 14.8% (8/54) of the active subjects and 1.8% (1/55) of the control subjects (p=0.016). Of the 8 events in the active group subjects, one event was serious and required inpatient hospitalization on 2 separate occasions. All of the events were mild or moderate in severity; none were severe. Six of the 8 subjects had a prior medical history of depression that was reported as worsened during the Blinded phase. There were 2 de novo depression events. One of the two de novo depression events was determined by the investigator to be related to stimulation and resolved after programming. Depression resolved in 4 subjects and was ongoing in 4 subjects as of the database cutoff. Three of the 4 ongoing events were in subjects with pre-existing depression. Five of the 8 subjects had >35% reduction in seizure frequency by the end of

the Blinded phase; 4 of the 8 were responders (>50% reduction in seizure frequency). No subject discontinued from the study due to depression.

Suicidality

Suicidality events include those coded to MedDRA Preferred Terms of completed suicide, suicide attempt, depression suicidal, suicidal ideation, and intentional self-injury. Twelve subjects (10.9%) reported 15 suicidality events. Nine of the 15 events were serious in 7 subjects (6.4%). The serious adverse events were completed suicide (1), suicide attempt (4), depression suicidal (1), and suicidal ideation (3). The completed suicide occurred in 1 subject who was not receiving stimulation at the time of the event; the neurostimulator battery was depleted and the subject was being scheduled for a replacement procedure. The subject's seizure frequency had not increased following battery depletion. This subject had previously been a responder (at least 50% seizure reduction) at the last 2 annual visits prior to the battery depletion event. Of the 7 subjects reporting suicidality SAEs, 6 had a medical history of depression or suicide attempt.

Memory impairment

A total of 33.6% of the implanted subjects had a prior medical history of memory impairment. Approximately one-third (35.1%, 13/37) of subjects with a prior history of memory impairment reported a memory impairment event, compared to 28.8% (21/73) of subjects without a prior history of memory impairment.

Thirty-seven memory impairment events were reported in 34 subjects (30.9%). Of these 34 subjects, 38.2% (13/34) had a prior history of memory impairment. Eight events in 8 subjects (7.3%) were device-related. Seven of the 8 events resolved, in an average of 43 days. None of the memory impairment events were considered serious.

During the Blinded phase, spontaneously self-reported worsening or new onset memory impairment occurred in 13.0% (7/54) of the active subjects and 1.8% (1/55) of the control subjects (p=0.032). Of the 7 events in the active group subjects, none were serious. Four of the events were mild and 3 were moderate in severity; none were severe. Two of the 7 subjects had a prior medical history of memory impairment that was reported as worsened during the Blinded phase. Although 6 of the 7 events started the day of randomization, only 3 of the 7 events were determined by the investigator to be stimulation-related. Memory impairment resolved in all subjects, 5 without intervention. Of the 3 events related to programming/stimulation, 1 of the events resolved with reprogramming, and the other 2 events resolved with no intervention. No subject discontinued from the study due to memory impairment.

Device modifications

Device modifications were categorized as replacements, revisions, or explants. [Table 34](#) presents an overview of device modifications by system component (or complete system).

Table 34. Device replacements, revisions, or explants

Component(s) modified	Number of components (Number of subjects)		
	Replacement	Revision	Explant
Complete system ^a	5 (5)	1 (1)	29 (29)
Neurostimulator	233 (84)	6 (6)	2 (2)
Leads	17 (12)	3 (2)	0 (0)
Extensions	26 (10)	3 (3)	2 (1)

^a Neurostimulator, leads, and extensions. Complete system revisions are not included in the counts for each individual component.

Complete system

The complete system was replaced in 5 subjects due to implant site infection (2), tension (1), implant site erosion (1), and extension fracture and therapy ineffectiveness (1). The tension event was described as intermittent tense feelings related to stimulation.

The complete system was revised in 1 subject who had an infection and erosion at the implant site.

The most common causes of the complete system being explanted and not replaced in 29 subjects were therapy ineffectiveness (12), implant site infection (6), anxiety (2), and SUDEP (2, explanted posthumously). Other causes were 1 each of the following: involuntary muscle contractions, elective medical device removal, discomfort, cognitive disorder, psychotic disorder, meningitis, and undesirable change in stimulation.

Table 35 summarizes the reasons for complete system replacement, revision, or explant.

Table 35. Reason for complete system modification

Reason	Number of complete systems		
	Replacement	Revision	Explant
Therapy ineffectiveness	0	0	12
Implant site infection	2	0	6
Anxiety	0	0	2
SUDEP	0	0	2
Cognitive disorder	0	0	1
Discomfort	0	0	1
Elective medical device removal	0	0	1
Extension fracture/ therapy ineffectiveness ^a	1	0	0
Implant site erosion	1	0	0
Implant site infection/erosion ^b	0	1	0
Involuntary muscle contractions	0	0	1
Meningitis	0	0	1
Psychotic disorder	0	0	1
Tension	1	0	0
Undesirable change in stimulation	0	0	1
Total	5	1	29

^a One subject underwent replacement of the extensions due to extension fracture and replacement of the leads secondary to therapy ineffectiveness; the neurostimulator was replaced at the time of extension replacement so as to prolong time to another procedure; thus, the entire system was replaced in one procedure.

^b One subject underwent revision of the leads and extensions due to implant site infection and revision of the neurostimulator due to implant site erosion in one procedure.

Neurostimulator

The neurostimulator was replaced 233 times in 84 subjects with 219 of the replacements due to normal battery depletion. Two subjects had undergone a neurostimulator replacement secondary to paresthesia and two subjects due to a Medtronic device recall. One subject had the neurostimulator replaced as a result of implant site pain and 1 replacement was due to implant site infection. There were 8 subjects with instances where the neurostimulator was replaced because of 2 separate events. These include normal battery depletion and neurostimulator migration (2), normal battery depletion and high impedance (2), and 1 each of the following:

normal battery depletion and implant site pain, normal battery depletion and discomfort, normal battery depletion and sensory disturbance, and implant site scar with elective neurostimulator replacement.

The neurostimulator was revised in 6 subjects. The most common events resulting in a revision were neurostimulator migration (2) and set screws not adequately secured (2). One subject underwent revision due to accidental injury and 1 subject had the neurostimulator revised as a result of insufficient coupling of the device secondary to excessive depth of the neurostimulator pocket.

The neurostimulator was explanted and not replaced in 2 subjects. One was explanted posthumously and the other was explanted due to therapy ineffectiveness.

Table 36 summarizes the reasons for neurostimulator replacement, revision, or explant.

Table 36. Reason for neurostimulator modification

Reason	Number of neurostimulators		
	Replacement	Revision	Explant
Normal battery depletion	219	0	0
Medtronic device recall	2	0	0
Normal battery depletion/ high impedance ^a	2	0	0
Normal battery depletion/ neurostimulator migration ^a	2	0	0
Neurostimulator migration	0	2	0
Paresthesia	2	0	0
Set screws not adequately secured	0	2	0
Accidental injury	0	1	0
Death	0	0	1
Implant site infection	1	0	0
Implant site pain	1	0	0
Implant site scar/ elective neurostimulator replacement ^a	1	0	0
Normal battery depletion/ discomfort ^a	1	0	0
Normal battery depletion/ implant site pain ^a	1	0	0
Normal battery depletion/ sensory disturbance ^a	1	0	0
Insufficient coupling of the device	0	1	0
Therapy ineffectiveness	0	0	1
Total	233	6	2

^aThere were 8 instances in which the neurostimulator was replaced because of 2 separate events.

A Kaplan-Meier survival analysis was conducted to the first battery replacement. Subjects who did not have a neurostimulator replacement were censored at their last follow-up visit to date. The results of this analysis showed that half of the subjects in the study (ie, median survival from battery replacement) needed a neurostimulator replacement after 35.4 months (3.0 years). A second Kaplan-Meier survival analysis was conducted for all battery replacements, and half of the total neurostimulators were replaced after 25.8 months (2.2 years). Of the remaining 69 subjects active in the study (as of the database cutoff), 2 subjects have not yet undergone a battery replacement.

Lead

There were a total of 20 lead modifications that were reported in 14 subjects. Fourteen leads were replaced in 9 subjects due to the lead not being placed within the targeted area; the 14 leads were replaced in 11 surgical procedures. Other events that led to lead replacement included

unilateral lead fracture (2 subjects) and unilateral lead migration/dislodgement (1). One subject had undergone a bilateral lead revision secondary to high impedances and one subject had a unilateral lead revised due to a postimplant procedural complication.

Table 37 summarizes the reasons for lead replacement, revision, or explant.

Table 37. Reason for lead modification

Reason	Number of leads		
	Replacement	Revision	Explant
Lead not in target area	14	0	0
High impedance	0	2	0
Unilateral lead fracture	2	0	0
Postimplant procedural complications	0	1	0
Unilateral lead migration/dislodgement	1	0	0
Total	17	3	0

Extension

There were 31 extension modifications that were reported in 14 subjects. Sixteen extensions were replaced in 5 subjects as a result of extension fracture. Five of these were due to fractures that occurred in two subjects during an initial implant or replacement procedure. Two subjects underwent bilateral extension replacement due to implant site pain. Other events that resulted in bilateral extension replacements include involuntary muscle contractions, implant site infection, and extension migration/dislodgment. Three unilateral extension revisions were reported in 3 subjects. Two revisions were secondary to extension migration/dislodgment and one was the result of an implant site infection. Two extensions were explanted posthumously in one subject.

Table 38 summarizes the reasons for extension replacement, revision, or explant.

Table 38. Reason for extension modification

Reason	Number of extensions		
	Replacement	Revision	Explant
Extension fracture	16	0	0
Extension migration/ dislodgment	2	2	0
Implant site pain	4	0	0
Implant site infection	2	1	0
Death	0	0	2
Involuntary muscle contraction	2	0	0
Total	26	3	2

Programming parameters

The stimulation parameters used in the active group during the Blinded phase of the SANTÉ study were the following:

- Amplitude: 5.0 V
- Pulse width: 90 μ s
- Rate: 145 Hz
- Cycling on interval: 1 minute
- Cycling off interval: 5 minutes

During the Unblinded phase, either voltage increases to 7.5 V or rate increases to 185 Hz were allowed, but not both. In the Long-term follow-up phase, there were no programming

restrictions, parameters were changed at the discretion of the investigator. Table 39 summarizes the programming parameters at the Year 2 through Year 7 visits. Subjects were excluded from the amplitude parameters if therapy was delivered to only one hemisphere. Subjects were excluded from the cycling interval parameters (cycling on interval and cycling off interval) if cycling was disabled (ie, continuous stimulation was used). Caution should be exercised when interpreting this data. The study design was intended to limit variability in programming during the Blinded and Unblinded phases and a prospective evaluation of the impact of unlimited programming changes was not included. In some subjects, multiple programming parameters were adjusted concurrently, making it difficult to assess the impact of any one parameter. Lastly, while some subjects had improved seizure reduction temporally related to stimulation changes, others seemed to respond to a cumulative effect of stimulation.

Table 39: Programming parameters – Year 2 through Year 7

Parameter	Year	n	Mean	Standard Deviation	Minimum	25th percentile	Median	75th percentile	Maximum
Amplitude (V)	2	97	6.5	1.6	2.75	5.0	7.2	7.5	10.0
	3	93	6.3	2.0	0	5.0	7.5	7.5	10.0
	4	87	6.6	1.6	0	5.5	7.5	7.5	9.5
	5	79	6.6	1.9	0	5.0	7.5	7.5	10.0
	6	74	6.6	1.6	1.00	5.6	7.5	7.5	9.5
Pulse width (µs)	2	99	94.2	12.9	60	90	90	90	150
	3	93	98.1	23.9	60	90	90	90	210
	4	87	97.2	17.1	60	90	90	90	150
	5	79	99.1	17.6	60	90	90	120	150
	6	74	99.3	17.9	90	90	90	90	150
Rate (Hz)	2	99	156.5	25.8	70	145	145	185	185
	3	93	152.6	35.7	3	145	145	185	240
	4	87	160.0	21.0	100	145	145	185	200
	5	79	162.8	20.1	140	145	145	185	200
	6	74	163.8	20.4	130	145	147.5	185	200
Cycling on interval (min)	2	98	1.0	0.4	0.250	1	1	1	4
	3	88	1.0	0.4	0.002	1	1	1	4
	4	83	1.1	1.1	0.500	1	1	1	10
	5	79	1.2	1.0	0.017	1	1	1	6
	6	71	1.2	0.8	0.333	1	1	1	5
Cycling off interval (min)	2	98	3.4	1.7	0.083	2	3	5	5
	3	87	3.3	1.7	0.170	2	3	5	5
	4	83	3.2	1.6	0.500	2	3	5	5
	5	79	3.1	1.6	0.033	2	3	5	5
	6	71	4.0	6.9	0.333	2	3	5	60
7	56	3.6	2.2	0.330	2	3	5	15	

Conclusions

Effectiveness conclusions

The SANTÉ study demonstrated that anterior thalamic deep brain stimulation is more effective than sham stimulation at reducing the frequency of seizures in subjects with epilepsy characterized by partial onset seizures that are refractory to at least 3 antiepileptic medications.

The primary objective of the study was met with post-hoc removal of the outlier, demonstrating a reduction in total seizure frequency that was greater in the active group compared with the control group during the Blinded phase of the study. The GEE model showed a least-squares means difference in seizure frequency reduction between groups of 17% ($p=0.045$). With the same dataset, the median total seizure frequency percent change from baseline over the entire Blinded phase was -35.0% for the active group compared with -21.1% for the control group.

None of the secondary endpoints reached statistically significant differences between groups during the Blinded phase. However, the results showed a significant difference between groups in subjects' prospectively-defined most severe seizures, and in an analysis with the outlier removed, a significant difference in complex partial seizures.

The effectiveness of the treatment is further supported with long-term data demonstrating sustained improvements in seizure reduction over time with a median total seizure reduction of 75% and a responder rate of 74% at 7 years after device implant. A total of 20 (18%) subjects were seizure-free for at least 6 consecutive months during the study. While differences in quality of life between treatment groups were not found during the Blinded phase, there were statistically significant improvements over baseline in quality of life at the end of the first year that were sustained through 7 years after device implant. Long-term, almost half of the subjects experienced clinically meaningful changes in their quality of life.

Safety conclusions

This study evaluated the safety of bilateral stimulation of the ANT for epilepsy in 110 implanted subjects with a combined 713 device-years of experience. Data from the study, including the open label period, were used to assess overall safety in which all active subjects were followed for a minimum of 7 years after device implantation. There were no unanticipated adverse device effects. Seven deaths occurred in the study; none of them were determined to be related to the device.

The SUDEP rate was determined based on the SANTÉ study experience and on previous pilot studies of ANT DBS for epilepsy. Based on this experience, the rate of SUDEP was 2.5 per 1000 person-years and is lower than the rate reported for surgical candidates for epilepsy of 9.3 per 1000 person-years.²

Serious device-related adverse events were reported in 38 subjects (34.5%). The most frequent device-related serious adverse events were implant site infection (10.9%; 8.2% requiring explant) and lead(s) not in target (8.2%), with all others reported in 1.8% or fewer subjects. The majority of the device-related SAEs occurred during the Operative phase. One subject experienced a serious adverse event related to intracranial hemorrhage which resolved without surgical intervention.

During the Blinded phase, depression and memory impairment were reported in a significantly higher percentage of subjects in the active group as compared to the control group. None of the memory impairment events were serious; one of the depression events was serious in a subject reporting pre-existing depression. For the entire study follow-up period, no subjects discontinued due to depression or memory impairment events. Neuropsychological test results remained stable

² Dasheiff RM. Sudden unexpected death in epilepsy: a series from an epilepsy surgery program and speculation on the relationship to sudden cardiac death. *J Clin Neurophysiol* 1991;8:216-222.

at the end of the Blinded phase and long term through 7 years, including tests for cognition and mood.

When considering the total post-implant experience (713 device-years), 8 subjects experienced 8 intracranial hemorrhage events, 3 which occurred following a device explant procedure. One of the intracranial hemorrhage events was symptomatic. Nine subjects required at least one additional surgery to replace a lead implanted outside of the targeted area as required by the protocol. There were 7 subjects who experienced status epilepticus. Five subjects reported increased, worsening, or new seizures during the first week of stimulation. Suicidality events were reported by 12 subjects (7 subjects with SAEs), depression events were reported by 43 subjects (1 subject with SAE), and memory impairment events were reported by 34 subjects (none were serious).

Subject discontinuations after device implant through at least 7 years of follow-up included 12% due to an adverse event of therapeutic product ineffective, 5% due to implant site infection, 5% due to withdrawn consent, 5% due to death, and 5% due to other adverse events related to the device or therapy.

The safety profile for the Medtronic DBS System for Epilepsy is stable long term and has been well characterized with risks identified and quantified through a minimum of 7 years of postimplant follow-up.

Risk benefit analysis

The benefits of ANT DBS therapy outweigh the risks. The SANTÉ study demonstrated that anterior thalamic deep brain stimulation is more effective than sham stimulation at reducing the frequency of seizures in a medically refractory patient population. The safety profile of ANT DBS has been well characterized and is stable long term in a study with an extensive follow-up period. A review of the published literature indicates that risks associated with DBS for epilepsy are consistent with those associated with refractory epilepsy, other approved implanted brain stimulation device therapies for epilepsy, and approved DBS devices.

The data support the safety and effectiveness of bilateral stimulation of the ANT as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years and older diagnosed with epilepsy, characterized by partial-onset seizures, who are refractory to at least 3 antiepileptic medications and who average six or more seizures per month in the 3 months prior to implant of the DBS system (with no more than 30 days between seizures).

Limitations

Additional factors to be considered in determining probable risks and benefits for the Medtronic DBS System for Epilepsy in the primary analysis is an effect with the surgical procedure, an effect of lead implantation, regression to the mean, or a placebo effect.

In addition, though the open-label, long-term data demonstrated sustained improvements in seizure reduction, the interpretation of open-label data is limited by selection bias, expectation bias, and confounders such as antiepileptic drug and stimulation changes. Sensitivity analyses for long-term effectiveness were conducted to assess the potential impact of missing data including LOCF and Worst case analyses; in addition, an analysis of long-term effectiveness by medication status was performed to evaluate the impact of changes in antiepileptic medications. The open-label portion could not assess the magnitude of the placebo response, regression to the mean, or

the effect of changes in medications, stimulation settings or other treatments on decreasing seizure frequency.

Individualization of treatment

Best results are achieved when the patient is fully informed about the therapy risks and benefits, surgical procedure, follow-up requirements, and self-care responsibilities. Medtronic DBS for Epilepsy is appropriate for patients who meet the following criteria:

- Patients should have partial onset seizures with or without secondary generalization
- Patients should be 18 years of age or older
- Patients should be refractory to 3 or more antiepileptic medications
- Patients should average 6 or more seizures per month over the 3 most recent months prior to implant of the DBS system with no more than 30 days between seizures
- Patients should be suitable candidates for stereotactic neurosurgery

Use extreme care with lead implantation in patients with heightened risk of intracranial hemorrhage. Physicians should consider underlying factors, such as previous neurological injury or prescribed medications (anticoagulants), that may predispose a patient to the risk of bleeding.

Physicians should be aware that the risks associated with initial surgery may increase with clinical conditions such as:

- Stroke or neurological disorders other than epilepsy
- Cardiovascular disease
- Renal or hepatic failure
- Diabetes mellitus

To help ensure maximum benefits from the neurostimulation system, long-term, post-surgical management of patients is recommended.

Stimulation parameters should be adjusted such that maximal symptom suppression is achieved with minimal side effects. The effect of therapy may not be immediately apparent upon initiation of stimulation. If seizure frequency increases when stimulation is initiated, adjustment of stimulation parameters may alleviate this effect. Patients should be informed of the risks of higher parameters as noted in the appropriate information for prescribers booklet.

Use in specific populations

The safety and effectiveness of this therapy has not been established for the following:

- Patients without partial-onset seizures
- Patients who are pregnant or nursing
- Patients under the age of 18 years
- Patients with coagulopathies

Appendix A: Adverse events by system organ class and time period

Table 40 on page 79 summarizes adverse events categorized by system organ class and time period.

Table 40. Adverse events by system organ class, by time period

	Time Period ^a	Operative Phase (1 month) n=110 years=10	Blinded Phase (3 months) n=109 years=26	Implant to Year 1 (13 months) n=110 years=111	Implant to Year 7 (85 months) n=110 years=611	Total Postimplant ^b n=110 years=713
SOC	Preferred Term	Subjects (%) with an Event				
Infections and infestations	Nasopharyngitis	2 (1.8%)	6 (5.5%)	22 (20.0%)	46 (41.8%)	49 (44.5%)
	Upper respiratory tract infection	.	4 (3.7%)	15 (13.6%)	34 (30.9%)	35 (31.8%)
	Sinusitis	1 (0.9%)	2 (1.8%)	8 (7.3%)	23 (20.9%)	23 (20.9%)
	Urinary tract infection	.	1 (0.9%)	4 (3.6%)	21 (19.1%)	23 (20.9%)
	Influenza	1 (0.9%)	3 (2.8%)	7 (6.4%)	17 (15.5%)	17 (15.5%)
	Implant site infection	5 (4.5%)	3 (2.8%)	10 (9.1%)	15 (13.6%)	16 (14.5%)
	Bronchitis	.	.	5 (4.5%)	12 (10.9%)	15 (13.6%)
	Cellulitis	.	.	1 (0.9%)	10 (9.1%)	11 (10.0%)
	Gastroenteritis viral	1 (0.9%)	.	1 (0.9%)	10 (9.1%)	10 (9.1%)
	Ear infection	.	.	.	9 (8.2%)	10 (9.1%)
	Vaginal mycosis	.	.	2 (1.8%)	7 (6.4%)	8 (7.3%)
	Tooth infection	.	.	3 (2.7%)	7 (6.4%)	7 (6.4%)
	Gastroenteritis	.	.	2 (1.8%)	6 (5.5%)	7 (6.4%)
	Pharyngitis streptococcal	.	.	.	6 (5.5%)	7 (6.4%)
	Otitis media	.	.	4 (3.6%)	6 (5.5%)	6 (5.5%)
	Pneumonia	.	.	2 (1.8%)	5 (4.5%)	5 (4.5%)
	Dental caries	.	1 (0.9%)	2 (1.8%)	4 (3.6%)	4 (3.6%)
	Viral infection	.	.	2 (1.8%)	4 (3.6%)	4 (3.6%)
	Onychomycosis	1 (0.9%)	.	1 (0.9%)	4 (3.6%)	4 (3.6%)
	Eye infection	.	.	.	4 (3.6%)	4 (3.6%)
	Infection	.	.	.	4 (3.6%)	4 (3.6%)
	Gingival infection	.	.	1 (0.9%)	3 (2.7%)	4 (3.6%)
	Tooth abscess	.	.	1 (0.9%)	3 (2.7%)	4 (3.6%)
	Respiratory tract infection	.	.	1 (0.9%)	2 (1.8%)	4 (3.6%)
	Localised infection	.	.	2 (1.8%)	3 (2.7%)	3 (2.7%)
	Skin infection	1 (0.9%)	.	1 (0.9%)	3 (2.7%)	3 (2.7%)
	Lower respiratory tract infection	.	.	1 (0.9%)	3 (2.7%)	3 (2.7%)
	Vaginal infection	.	.	1 (0.9%)	3 (2.7%)	3 (2.7%)
	Bronchitis acute	.	.	.	3 (2.7%)	3 (2.7%)
	Fungal infection	.	.	.	3 (2.7%)	3 (2.7%)
	Kidney infection	.	.	.	3 (2.7%)	3 (2.7%)
	Viral upper respiratory tract infection	.	.	.	2 (1.8%)	3 (2.7%)
	Tinea cruris	.	.	.	1 (0.9%)	3 (2.7%)
Hordeolum	.	1 (0.9%)	2 (1.8%)	2 (1.8%)	2 (1.8%)	

	Time Period ^a	Operative Phase (1 month) n=110 years=10	Blinded Phase (3 months) n=109 years=26	Implant to Year 1 (13 months) n=110 years=111	Implant to Year 7 (85 months) n=110 years=611	Total Postimplant ^b n=110 years=713
SOC	Preferred Term	Subjects (%) with an Event				
	Cystitis	.	1 (0.9%)	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Folliculitis	.	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Tinea pedis	.	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Abscess	.	.	.	2 (1.8%)	2 (1.8%)
	Body tinea	.	.	.	2 (1.8%)	2 (1.8%)
	Pharyngitis	.	.	.	2 (1.8%)	2 (1.8%)
	Sialoadenitis	.	.	.	2 (1.8%)	2 (1.8%)
	Tonsillitis	.	.	.	2 (1.8%)	2 (1.8%)
	Vaginitis bacterial	.	.	.	1 (0.9%)	2 (1.8%)
	Urosepsis	1 (0.9%)	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Catheter related infection	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Herpes simplex	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Infected insect bite	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Meningitis	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Otitis externa	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Abscess neck	.	.	.	1 (0.9%)	1 (0.9%)
	Chlamydial infection	.	.	.	1 (0.9%)	1 (0.9%)
	Diverticulitis	.	.	.	1 (0.9%)	1 (0.9%)
	Gastric infection	.	.	.	1 (0.9%)	1 (0.9%)
	Hepatitis C	.	.	.	1 (0.9%)	1 (0.9%)
	Herpes virus infection	.	.	.	1 (0.9%)	1 (0.9%)
	Herpes zoster	.	.	.	1 (0.9%)	1 (0.9%)
	Herpes zoster ophthalmic	.	.	.	1 (0.9%)	1 (0.9%)
	Infectious mononucleosis	.	.	.	1 (0.9%)	1 (0.9%)
	Lobar pneumonia	.	.	.	1 (0.9%)	1 (0.9%)
	Lyme disease	.	.	.	1 (0.9%)	1 (0.9%)
	Orchitis	.	.	.	1 (0.9%)	1 (0.9%)
	Pneumonia primary atypical	.	.	.	1 (0.9%)	1 (0.9%)
	Pulpitis dental	.	.	.	1 (0.9%)	1 (0.9%)
	Rash pustular	.	.	.	1 (0.9%)	1 (0.9%)
	Rhinovirus infection	.	.	.	1 (0.9%)	1 (0.9%)
	Breast cellulitis	1 (0.9%)
	Cellulitis staphylococcal	1 (0.9%)
	Condyloma acuminatum	1 (0.9%)
	Furuncle	1 (0.9%)
	Implant site cellulitis	1 (0.9%)
	Prostate infection	1 (0.9%)
	Staphylococcal infection	1 (0.9%)
	Trichomoniasis	1 (0.9%)

Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTÉ) Clinical Summary

Time Period ^a		Operative Phase (1 month) n=110 years=10	Blinded Phase (3 months) n=109 years=26	Implant to Year 1 (13 months) n=110 years=111	Implant to Year 7 (85 months) n=110 years=611	Total Postimplant ^b n=110 years=713
SOC	Preferred Term	Subjects (%) with an Event				
	Viral pharyngitis	1 (0.9%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Skin papilloma	.	1 (0.9%)	3 (2.7%)	6 (5.5%)	6 (5.5%)
	Basal cell carcinoma	.	.	.	2 (1.8%)	3 (2.7%)
	Seborrhoeic keratosis	.	.	.	1 (0.9%)	2 (1.8%)
	Acrochordon	.	.	.	1 (0.9%)	1 (0.9%)
	Fibroadenoma	.	.	.	1 (0.9%)	1 (0.9%)
	Haemangioma	.	.	.	1 (0.9%)	1 (0.9%)
	Multiple myeloma	.	.	.	1 (0.9%)	1 (0.9%)
	Nasal neoplasm benign	.	.	.	1 (0.9%)	1 (0.9%)
	Neoplasm malignant	.	.	.	1 (0.9%)	1 (0.9%)
	Thyroid adenoma	.	.	.	1 (0.9%)	1 (0.9%)
	Benign breast neoplasm	1 (0.9%)
	Lipoma	1 (0.9%)
	Blood and lymphatic system disorders	Anaemia	.	.	.	5 (4.5%)
Lymphadenopathy		.	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
Febrile neutropenia		.	.	.	1 (0.9%)	1 (0.9%)
Thrombocytopenia		.	.	.	1 (0.9%)	1 (0.9%)
Immune system disorders	Seasonal allergy	1 (0.9%)	2 (1.8%)	3 (2.7%)	8 (7.3%)	8 (7.3%)
	Hypersensitivity	.	1 (0.9%)	3 (2.7%)	8 (7.3%)	8 (7.3%)
	Immune system disorder	.	.	.	1 (0.9%)	1 (0.9%)
Endocrine disorders	Hypothyroidism	.	.	1 (0.9%)	4 (3.6%)	4 (3.6%)
	Goitre	.	.	.	2 (1.8%)	2 (1.8%)
	Thyroid disorder	.	.	.	2 (1.8%)	2 (1.8%)
Metabolism and nutrition disorders	Hyponatraemia	1 (0.9%)	.	3 (2.7%)	7 (6.4%)	7 (6.4%)
	Hypokalaemia	.	.	.	6 (5.5%)	6 (5.5%)
	Hyperlipidaemia	.	.	.	5 (4.5%)	5 (4.5%)
	Vitamin D deficiency	.	.	.	3 (2.7%)	5 (4.5%)
	Dehydration	.	.	.	4 (3.6%)	4 (3.6%)
	Hypercholesterolaemia	.	.	.	4 (3.6%)	4 (3.6%)
	Diabetes mellitus	.	1 (0.9%)	1 (0.9%)	3 (2.7%)	3 (2.7%)
	Decreased appetite	1 (0.9%)	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Diabetes mellitus insulin-dependent	.	.	.	1 (0.9%)	1 (0.9%)
	Diabetic ketoacidosis	.	.	.	1 (0.9%)	1 (0.9%)
	Fluid retention	1 (0.9%)
Hyperglycaemia	1 (0.9%)	
Psychiatric disorders	Depression	2 (1.8%)	9 (8.3%)	22 (20.0%)	41 (37.3%)	43 (39.1%)
	Anxiety	1 (0.9%)	6 (5.5%)	8 (7.3%)	20 (18.2%)	21 (19.1%)
	Insomnia	1 (0.9%)	1 (0.9%)	5 (4.5%)	16 (14.5%)	17 (15.5%)
	Suicidal ideation	.	1 (0.9%)	1 (0.9%)	6 (5.5%)	7 (6.4%)
	Confusional state	.	4 (3.7%)	5 (4.5%)	6 (5.5%)	6 (5.5%)
	Agitation	2 (1.8%)	.	4 (3.6%)	4 (3.6%)	5 (4.5%)
	Deja vu	1 (0.9%)	.	4 (3.6%)	4 (3.6%)	4 (3.6%)
	Psychotic disorder	.	1 (0.9%)	1 (0.9%)	4 (3.6%)	4 (3.6%)
	Thinking abnormal	.	1 (0.9%)	3 (2.7%)	3 (2.7%)	3 (2.7%)
	Hallucination	.	1 (0.9%)	2 (1.8%)	3 (2.7%)	3 (2.7%)

	Time Period ^a	Operative Phase (1 month) n=110 years=10	Blinded Phase (3 months) n=109 years=26	Implant to Year 1 (13 months) n=110 years=111	Implant to Year 7 (85 months) n=110 years=611	Total Postimplant ^b n=110 years=713
SOC	Preferred Term	Subjects (%) with an Event				
	Panic attack	.	.	2 (1.8%)	3 (2.7%)	3 (2.7%)
	Stress	.	.	2 (1.8%)	3 (2.7%)	3 (2.7%)
	Irritability	1 (0.9%)	.	1 (0.9%)	3 (2.7%)	3 (2.7%)
	Conversion disorder	.	.	1 (0.9%)	3 (2.7%)	3 (2.7%)
	Sleep disorder	.	2 (1.8%)	2 (1.8%)	2 (1.8%)	3 (2.7%)
	Suicide attempt	.	.	.	2 (1.8%)	3 (2.7%)
	Initial insomnia	.	.	2 (1.8%)	2 (1.8%)	2 (1.8%)
	Nervousness	.	.	2 (1.8%)	2 (1.8%)	2 (1.8%)
	Anger	.	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Bruxism	.	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Depression suicidal	.	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Delusion	.	.	.	2 (1.8%)	2 (1.8%)
	Mental disorder	.	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Disorientation	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Emotional disorder	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Hallucination, visual	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Obsessive-compulsive disorder	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Tension	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Abnormal dreams	.	.	.	1 (0.9%)	1 (0.9%)
	Aggression	.	.	.	1 (0.9%)	1 (0.9%)
	Alcohol withdrawal syndrome	.	.	.	1 (0.9%)	1 (0.9%)
	Cognitive deterioration	.	.	.	1 (0.9%)	1 (0.9%)
	Completed suicide	.	.	.	1 (0.9%)	1 (0.9%)
	Dysphemia	.	.	.	1 (0.9%)	1 (0.9%)
	Epileptic psychosis	.	.	.	1 (0.9%)	1 (0.9%)
	Flashback	.	.	.	1 (0.9%)	1 (0.9%)
	Homicidal ideation	.	.	.	1 (0.9%)	1 (0.9%)
	Intentional self-injury	.	.	.	1 (0.9%)	1 (0.9%)
	Libido decreased	.	.	.	1 (0.9%)	1 (0.9%)
Mood swings	.	.	.	1 (0.9%)	1 (0.9%)	
Obsessive thoughts	.	.	.	1 (0.9%)	1 (0.9%)	
Self injurious behaviour	.	.	.	1 (0.9%)	1 (0.9%)	
Psychomotor agitation	1 (0.9%)	
Nervous system disorders	Headache	7 (6.4%)	5 (4.6%)	23 (20.9%)	38 (34.5%)	39 (35.5%)
	Complex partial seizures	1 (0.9%)	9 (8.3%)	15 (13.6%)	37 (33.6%)	38 (34.5%)
	Memory impairment	2 (1.8%)	8 (7.3%)	23 (20.9%)	33 (30.0%)	34 (30.9%)
	Partial seizures with secondary generalisation	1 (0.9%)	8 (7.3%)	18 (16.4%)	32 (29.1%)	34 (30.9%)
	Simple partial seizures	3 (2.7%)	4 (3.7%)	14 (12.7%)	31 (28.2%)	31 (28.2%)
	Paraesthesia	2 (1.8%)	7 (6.4%)	21 (19.1%)	27 (24.5%)	27 (24.5%)
	Dizziness	1 (0.9%)	7 (6.4%)	10 (9.1%)	17 (15.5%)	17 (15.5%)
	Sensory disturbance	1 (0.9%)	2 (1.8%)	9 (8.2%)	13 (11.8%)	13 (11.8%)

	Time Period ^a	Operative Phase (1 month) n=110 years=10	Blinded Phase (3 months) n=109 years=26	Implant to Year 1 (13 months) n=110 years=111	Implant to Year 7 (85 months) n=110 years=611	Total Postimplant ^b n=110 years=713
SOC	Preferred Term	Subjects (%) with an Event				
	Tremor	2 (1.8%)	2 (1.8%)	4 (3.6%)	11 (10.0%)	12 (10.9%)
	Convulsion	.	1 (0.9%)	2 (1.8%)	9 (8.2%)	11 (10.0%)
	Hypoaesthesia	3 (2.7%)	1 (0.9%)	6 (5.5%)	9 (8.2%)	10 (9.1%)
	Migraine	.	.	.	7 (6.4%)	8 (7.3%)
	Status epilepticus	2 (1.8%)	1 (0.9%)	4 (3.6%)	7 (6.4%)	7 (6.4%)
	Epilepsy	.	.	.	6 (5.5%)	7 (6.4%)
	Somnolence	.	2 (1.8%)	3 (2.7%)	6 (5.5%)	6 (5.5%)
	Coordination abnormal	1 (0.9%)	.	2 (1.8%)	5 (4.5%)	5 (4.5%)
	Dyskinesia	.	.	1 (0.9%)	5 (4.5%)	5 (4.5%)
	Neuropathy peripheral	.	.	1 (0.9%)	4 (3.6%)	5 (4.5%)
	Grand mal convulsion	.	.	3 (2.7%)	4 (3.6%)	4 (3.6%)
	Carpal tunnel syndrome	.	.	.	4 (3.6%)	4 (3.6%)
	Restless legs syndrome	.	2 (1.8%)	2 (1.8%)	3 (2.7%)	3 (2.7%)
	Burning sensation	.	.	1 (0.9%)	3 (2.7%)	3 (2.7%)
	Disturbance in attention	.	.	1 (0.9%)	3 (2.7%)	3 (2.7%)
	Lethargy	.	.	1 (0.9%)	3 (2.7%)	3 (2.7%)
	Sciatica	.	.	1 (0.9%)	3 (2.7%)	3 (2.7%)
	Balance disorder	.	.	.	3 (2.7%)	3 (2.7%)
	Neuralgia	.	1 (0.9%)	1 (0.9%)	2 (1.8%)	3 (2.7%)
	Intraventricular haemorrhage	1 (0.9%)	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Nystagmus	.	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Syncope	.	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Ageusia	.	.	.	2 (1.8%)	2 (1.8%)
	Cognitive disorder	.	.	.	2 (1.8%)	2 (1.8%)
	Myoclonus	.	.	.	2 (1.8%)	2 (1.8%)
	Postictal state	.	.	.	2 (1.8%)	2 (1.8%)
	Nerve compression	.	.	.	1 (0.9%)	2 (1.8%)
	Facial palsy	.	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Muscle contractions involuntary	.	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Haemorrhage intracranial	1 (0.9%)	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Syncope vasovagal	1 (0.9%)	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Essential tremor	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Intention tremor	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Mental impairment	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Postictal headache	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Transient ischaemic attack	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Unresponsive to verbal stimuli	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Areflexia	.	.	.	1 (0.9%)	1 (0.9%)
	Cerebral haemorrhage	.	.	.	1 (0.9%)	1 (0.9%)

Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTÉ) Clinical Summary

Time Period ^a		Operative Phase (1 month) n=110 years=10	Blinded Phase (3 months) n=109 years=26	Implant to Year 1 (13 months) n=110 years=111	Implant to Year 7 (85 months) n=110 years=611	Total Postimplant ^b n=110 years=713
SOC	Preferred Term	Subjects (%) with an Event				
	Dysarthria	.	.	.	1 (0.9%)	1 (0.9%)
	Extensor plantar response	.	.	.	1 (0.9%)	1 (0.9%)
	Hydrocephalus	.	.	.	1 (0.9%)	1 (0.9%)
	Hypersomnia	.	.	.	1 (0.9%)	1 (0.9%)
	Meralgia paraesthetica	.	.	.	1 (0.9%)	1 (0.9%)
	Neuropathy	.	.	.	1 (0.9%)	1 (0.9%)
	Sinus headache	.	.	.	1 (0.9%)	1 (0.9%)
	Tension headache	.	.	.	1 (0.9%)	1 (0.9%)
	Trigeminal neuralgia	.	.	.	1 (0.9%)	1 (0.9%)
	Aphasia	1 (0.9%)
Eye disorders	Diplopia	.	1 (0.9%)	1 (0.9%)	4 (3.6%)	4 (3.6%)
	Eye pain	.	.	1 (0.9%)	4 (3.6%)	4 (3.6%)
	Visual disturbance	1 (0.9%)	1 (0.9%)	2 (1.8%)	3 (2.7%)	3 (2.7%)
	Vision blurred	.	.	2 (1.8%)	3 (2.7%)	3 (2.7%)
	Eyelid ptosis	.	.	.	3 (2.7%)	3 (2.7%)
	Eye irritation	.	.	.	2 (1.8%)	3 (2.7%)
	Eyelid disorder	.	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Cataract	.	.	.	2 (1.8%)	2 (1.8%)
	Conjunctivitis	.	.	.	2 (1.8%)	2 (1.8%)
	Blindness transient	.	.	1 (0.9%)	1 (0.9%)	2 (1.8%)
	Glaucoma	.	.	.	1 (0.9%)	2 (1.8%)
	Lacrimation increased	.	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Extraocular muscle paresis	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Blepharospasm	.	.	.	1 (0.9%)	1 (0.9%)
	Eye haemorrhage	.	.	.	1 (0.9%)	1 (0.9%)
	Eye pruritus	.	.	.	1 (0.9%)	1 (0.9%)
	Macular degeneration	.	.	.	1 (0.9%)	1 (0.9%)
	Posterior capsule opacification	.	.	.	1 (0.9%)	1 (0.9%)
	Eye disorder	1 (0.9%)
	Ocular hyperaemia	1 (0.9%)
Ear and labyrinth disorders	Ear pain	.	1 (0.9%)	2 (1.8%)	5 (4.5%)	5 (4.5%)
	Tinnitus	2 (1.8%)	.	2 (1.8%)	5 (4.5%)	5 (4.5%)
	Hypoacusis	1 (0.9%)	.	2 (1.8%)	3 (2.7%)	3 (2.7%)
	Ear discomfort	.	.	.	3 (2.7%)	3 (2.7%)
	Vertigo	.	.	.	2 (1.8%)	3 (2.7%)
	Cerumen impaction	1 (0.9%)	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Deafness	2 (1.8%)
	External ear disorder	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Deafness bilateral	.	.	.	1 (0.9%)	1 (0.9%)
	Deafness neurosensory	.	.	.	1 (0.9%)	1 (0.9%)
	Tympanic membrane perforation	.	.	.	1 (0.9%)	1 (0.9%)
	Inner ear disorder	1 (0.9%)

Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTÉ) Clinical Summary

Time Period ^a		Operative Phase (1 month) n=110 years=10	Blinded Phase (3 months) n=109 years=26	Implant to Year 1 (13 months) n=110 years=111	Implant to Year 7 (85 months) n=110 years=611	Total Postimplant ^b n=110 years=713
SOC	Preferred Term	Subjects (%) with an Event				
Cardiac disorders.	Palpitations	.	.	.	2 (1.8%)	2 (1.8%)
	Tachycardia	1 (0.9%)	.	1 (0.9%)	1 (0.9%)	2 (1.8%)
	Cardiac flutter	.	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Angina pectoris	.	.	.	1 (0.9%)	1 (0.9%)
	Cardiac failure congestive	.	.	.	1 (0.9%)	1 (0.9%)
	Cardio-respiratory arrest	.	.	.	1 (0.9%)	1 (0.9%)
	Cardiomyopathy	.	.	.	1 (0.9%)	1 (0.9%)
	Mitral valve incompetence	.	.	.	1 (0.9%)	1 (0.9%)
	Sinus bradycardia	1 (0.9%)
Vascular disorders	Hypertension	.	2 (1.8%)	3 (2.7%)	11 (10.0%)	12 (10.9%)
	Haematoma	.	.	.	2 (1.8%)	2 (1.8%)
	Varicose vein	.	.	.	2 (1.8%)	2 (1.8%)
	Hot flush	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Deep vein thrombosis	.	.	.	1 (0.9%)	1 (0.9%)
	Hypotension	.	.	.	1 (0.9%)	1 (0.9%)
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	1 (0.9%)	3 (2.8%)	5 (4.5%)	12 (10.9%)	12 (10.9%)
	Sleep apnoea syndrome	.	.	1 (0.9%)	6 (5.5%)	6 (5.5%)
	Cough	.	1 (0.9%)	2 (1.8%)	5 (4.5%)	5 (4.5%)
	Dyspnoea	1 (0.9%)	.	1 (0.9%)	4 (3.6%)	4 (3.6%)
	Nasal congestion	1 (0.9%)	1 (0.9%)	2 (1.8%)	3 (2.7%)	3 (2.7%)
	Sinus congestion	.	1 (0.9%)	1 (0.9%)	3 (2.7%)	3 (2.7%)
	Vocal cord disorder	1 (0.9%)	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Epistaxis	.	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Asthma	.	.	.	2 (1.8%)	2 (1.8%)
	Painful respiration	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Atelectasis	.	.	.	1 (0.9%)	1 (0.9%)
	Chronic obstructive pulmonary disease	.	.	.	1 (0.9%)	1 (0.9%)
	Hypoxia	.	.	.	1 (0.9%)	1 (0.9%)
	Nasal polyps	.	.	.	1 (0.9%)	1 (0.9%)
	Pleural effusion	.	.	.	1 (0.9%)	1 (0.9%)
	Pneumonia aspiration	.	.	.	1 (0.9%)	1 (0.9%)
	Pneumothorax	.	.	.	1 (0.9%)	1 (0.9%)
	Pulmonary hypertension	.	.	.	1 (0.9%)	1 (0.9%)
	Respiratory distress	.	.	.	1 (0.9%)	1 (0.9%)
	Rhinitis perennial	.	.	.	1 (0.9%)	1 (0.9%)
Tonsillar hypertrophy	.	.	.	1 (0.9%)	1 (0.9%)	
Upper respiratory tract congestion	.	.	.	1 (0.9%)	1 (0.9%)	
Gastrointestinal	Constipation	1 (0.9%)	.	2 (1.8%)	14 (12.7%)	14 (12.7%)

Time Period ^a		Operative Phase (1 month) n=110 years=10	Blinded Phase (3 months) n=109 years=26	Implant to Year 1 (13 months) n=110 years=111	Implant to Year 7 (85 months) n=110 years=611	Total Postimplant ^b n=110 years=713
SOC disorders	Preferred Term	Subjects (%) with an Event				
	Diarrhoea	.	.	.	12 (10.9%)	14 (12.7%)
	Gastrooesophageal reflux disease	.	1 (0.9%)	2 (1.8%)	10 (9.1%)	10 (9.1%)
	Haemorrhoids	.	.	1 (0.9%)	9 (8.2%)	10 (9.1%)
	Vomiting	3 (2.7%)	1 (0.9%)	4 (3.6%)	8 (7.3%)	8 (7.3%)
	Nausea	1 (0.9%)	1 (0.9%)	4 (3.6%)	8 (7.3%)	8 (7.3%)
	Abdominal pain upper	.	.	1 (0.9%)	3 (2.7%)	7 (6.4%)
	Abdominal pain	.	1 (0.9%)	2 (1.8%)	6 (5.5%)	6 (5.5%)
	Tooth fracture	.	.	.	6 (5.5%)	6 (5.5%)
	Tooth disorder	.	.	.	5 (4.5%)	6 (5.5%)
	Toothache	.	.	.	3 (2.7%)	3 (2.7%)
	Hypoesthesia oral	.	2 (1.8%)	2 (1.8%)	2 (1.8%)	2 (1.8%)
	Tooth impacted	.	1 (0.9%)	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Abdominal pain lower	.	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Hiatus hernia	.	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Dyspepsia	.	.	.	2 (1.8%)	2 (1.8%)
	Dysphagia	.	.	.	2 (1.8%)	2 (1.8%)
	Colitis ulcerative	.	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Acquired oesophageal web	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Tooth loss	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Abdominal discomfort	.	.	.	1 (0.9%)	1 (0.9%)
	Cheilitis	.	.	.	1 (0.9%)	1 (0.9%)
	Diverticulum intestinal	.	.	.	1 (0.9%)	1 (0.9%)
	Dry mouth	.	.	.	1 (0.9%)	1 (0.9%)
	Epigastric discomfort	.	.	.	1 (0.9%)	1 (0.9%)
	Food poisoning	.	.	.	1 (0.9%)	1 (0.9%)
	Gastrointestinal haemorrhage	.	.	.	1 (0.9%)	1 (0.9%)
	Gingival hyperplasia	.	.	.	1 (0.9%)	1 (0.9%)
	Haematochezia	.	.	.	1 (0.9%)	1 (0.9%)
	Inguinal hernia	.	.	.	1 (0.9%)	1 (0.9%)
	Lip blister	.	.	.	1 (0.9%)	1 (0.9%)
	Mouth ulceration	.	.	.	1 (0.9%)	1 (0.9%)
	Oral pain	.	.	.	1 (0.9%)	1 (0.9%)
Pancreatic disorder	.	.	.	1 (0.9%)	1 (0.9%)	
Pancreatitis	.	.	.	1 (0.9%)	1 (0.9%)	
Stomatitis	.	.	.	1 (0.9%)	1 (0.9%)	
Flatulence	1 (0.9%)	
Gingival disorder	1 (0.9%)	
Hepatobiliary disorders	Cholelithiasis	.	.	.	3 (2.7%)	3 (2.7%)
Skin and subcutaneous tissue disorders	Rash	.	.	.	11 (10.0%)	12 (10.9%)
	Dermatitis contact	2 (1.8%)	2 (1.8%)	4 (3.6%)	7 (6.4%)	8 (7.3%)
	Acne	.	1 (0.9%)	3 (2.7%)	6 (5.5%)	6 (5.5%)
	Pruritus	2 (1.8%)	.	2 (1.8%)	4 (3.6%)	4 (3.6%)

	Time Period ^a	Operative Phase (1 month) n=110 years=10	Blinded Phase (3 months) n=109 years=26	Implant to Year 1 (13 months) n=110 years=111	Implant to Year 7 (85 months) n=110 years=611	Total Postimplant ^b n=110 years=713
SOC	Preferred Term	Subjects (%) with an Event				
	Ecchymosis	1 (0.9%)	.	1 (0.9%)	4 (3.6%)	4 (3.6%)
	Dermatitis	.	.	1 (0.9%)	3 (2.7%)	4 (3.6%)
	Ingrowing nail	.	.	.	3 (2.7%)	3 (2.7%)
	Swelling face	.	.	1 (0.9%)	1 (0.9%)	2 (1.8%)
	Blister	1 (0.9%)	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Nail disorder	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Actinic keratosis	.	.	.	1 (0.9%)	1 (0.9%)
	Alopecia	.	.	.	1 (0.9%)	1 (0.9%)
	Blood blister	.	.	.	1 (0.9%)	1 (0.9%)
	Circumoral oedema	.	.	.	1 (0.9%)	1 (0.9%)
	Dry skin	.	.	.	1 (0.9%)	1 (0.9%)
	Eczema	.	.	.	1 (0.9%)	1 (0.9%)
	Erythema	.	.	.	1 (0.9%)	1 (0.9%)
	Heat rash	.	.	.	1 (0.9%)	1 (0.9%)
	Hyperhidrosis	.	.	.	1 (0.9%)	1 (0.9%)
	Hyperkeratosis	.	.	.	1 (0.9%)	1 (0.9%)
	Increased tendency to bruise	.	.	.	1 (0.9%)	1 (0.9%)
	Lichen planus	.	.	.	1 (0.9%)	1 (0.9%)
	Precancerous skin lesion	.	.	.	1 (0.9%)	1 (0.9%)
	Rash macular	.	.	.	1 (0.9%)	1 (0.9%)
	Seborrhoea	.	.	.	1 (0.9%)	1 (0.9%)
	Seborrhoeic dermatitis	.	.	.	1 (0.9%)	1 (0.9%)
	Skin ulcer	.	.	.	1 (0.9%)	1 (0.9%)
	Urticaria	.	.	.	1 (0.9%)	1 (0.9%)
	Dermatitis allergic	1 (0.9%)
	Pain of skin	1 (0.9%)
Musculoskeletal and connective tissue disorders	Back pain	.	2 (1.8%)	7 (6.4%)	25 (22.7%)	27 (24.5%)
	Pain in extremity	2 (1.8%)	.	3 (2.7%)	16 (14.5%)	20 (18.2%)
	Arthralgia	1 (0.9%)	.	4 (3.6%)	15 (13.6%)	16 (14.5%)
	Shoulder pain	1 (0.9%)	.	5 (4.5%)	10 (9.1%)	10 (9.1%)
	Neck pain	1 (0.9%)	.	1 (0.9%)	5 (4.5%)	7 (6.4%)
	Muscle twitching	.	1 (0.9%)	1 (0.9%)	6 (5.5%)	6 (5.5%)
	Osteoporosis	.	.	1 (0.9%)	5 (4.5%)	5 (4.5%)
	Musculoskeletal stiffness	1 (0.9%)	2 (1.8%)	3 (2.7%)	4 (3.6%)	4 (3.6%)
	Chest wall pain	1 (0.9%)	.	1 (0.9%)	4 (3.6%)	4 (3.6%)
	Osteoarthritis	.	.	.	4 (3.6%)	4 (3.6%)
	Tendonitis	.	.	.	4 (3.6%)	4 (3.6%)
	Pain in jaw	.	1 (0.9%)	1 (0.9%)	3 (2.7%)	3 (2.7%)
	Muscle spasms	.	.	.	3 (2.7%)	3 (2.7%)
	Plantar fasciitis	.	.	.	3 (2.7%)	3 (2.7%)
	Ganglion	.	.	.	2 (1.8%)	3 (2.7%)

Time Period ^a		Operative Phase (1 month) n=110 years=10	Blinded Phase (3 months) n=109 years=26	Implant to Year 1 (13 months) n=110 years=111	Implant to Year 7 (85 months) n=110 years=611	Total Postimplant ^b n=110 years=713
SOC	Preferred Term	Subjects (%) with an Event				
	Intervertebral disc protrusion	.	.	.	2 (1.8%)	3 (2.7)
	Muscle tightness	.	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Bursitis	.	.	.	2 (1.8%)	2 (1.8%)
	Osteopenia	.	.	.	2 (1.8%)	2 (1.8%)
	Musculoskeletal chest pain	.	.	.	1 (0.9%)	2 (1.8%)
	Coccydynia	.	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Exostosis	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Arthropathy	.	.	.	1 (0.9%)	1 (0.9%)
	Fibromyalgia	.	.	.	1 (0.9%)	1 (0.9%)
	Foot deformity	.	.	.	1 (0.9%)	1 (0.9%)
	Intervertebral disc degeneration	.	.	.	1 (0.9%)	1 (0.9%)
	Joint hyperextension	.	.	.	1 (0.9%)	1 (0.9%)
	Muscle contracture	.	.	.	1 (0.9%)	1 (0.9%)
	Rotator cuff syndrome	.	.	.	1 (0.9%)	1 (0.9%)
	SLE arthritis	.	.	.	1 (0.9%)	1 (0.9%)
	Spondylitis	.	.	.	1 (0.9%)	1 (0.9%)
	Temporomandibular joint syndrome	.	.	.	1 (0.9%)	1 (0.9%)
	Trismus	.	.	.	1 (0.9%)	1 (0.9%)
	Bunion	1 (0.9%)
Chondritis	1 (0.9%)	
Muscular weakness	1 (0.9%)	
Myalgia	1 (0.9%)	
Night cramps	1 (0.9%)	
Renal and urinary disorders	Nephrolithiasis	.	.	.	5 (4.5%)	6 (5.5%)
	Dysuria	.	.	.	3 (2.7%)	3 (2.7%)
	Pollakiuria	.	.	.	3 (2.7%)	3 (2.7%)
	Cystitis interstitial	.	.	.	2 (1.8%)	2 (1.8%)
	Renal failure acute	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Haematuria	.	.	.	1 (0.9%)	1 (0.9%)
	Stress incontinence	.	.	.	1 (0.9%)	1 (0.9%)
	Polyuria	1 (0.9%)
	Renal failure	1 (0.9%)
Pregnancy, puerperium and perinatal conditions	Blighted ovum	.	.	.	1 (0.9%)	1 (0.9%)
	Uterine contractions abnormal	.	.	.	1 (0.9%)	1 (0.9%)
Reproductive system and breast disorders	Benign prostatic hyperplasia	.	.	1 (0.9%)	3 (2.7%)	3 (2.7%)
	Vaginal haemorrhage	.	.	1 (0.9%)	3 (2.7%)	3 (2.7%)
	Menorrhagia	.	1 (0.9%)	2 (1.8%)	2 (1.8%)	2 (1.8%)
	Breast cyst	.	.	.	2 (1.8%)	2 (1.8%)
	Erectile dysfunction	.	.	1 (0.9%)	1 (0.9%)	2 (1.8%)
Premenstrual syndrome	.	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	

Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTÉ) Clinical Summary

Time Period ^a		Operative Phase (1 month) n=110 years=10	Blinded Phase (3 months) n=109 years=26	Implant to Year 1 (13 months) n=110 years=111	Implant to Year 7 (85 months) n=110 years=611	Total Postimplant ^b n=110 years=713
SOC	Preferred Term	Subjects (%) with an Event				
	Dysfunctional uterine bleeding	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Breast mass	.	.	.	1 (0.9%)	1 (0.9%)
	Breast tenderness	.	.	.	1 (0.9%)	1 (0.9%)
	Fibrocystic breast disease	.	.	.	1 (0.9%)	1 (0.9%)
	Ovarian cyst	.	.	.	1 (0.9%)	1 (0.9%)
	Pelvic pain	.	.	.	1 (0.9%)	1 (0.9%)
	Polycystic ovaries	.	.	.	1 (0.9%)	1 (0.9%)
	Scrotal sebaceous cysts	.	.	.	1 (0.9%)	1 (0.9%)
	Sexual dysfunction	.	.	.	1 (0.9%)	1 (0.9%)
	Vulva cyst	.	.	.	1 (0.9%)	1 (0.9%)
	Vulvovaginal dryness	.	.	.	1 (0.9%)	1 (0.9%)
	Epididymitis	1 (0.9%)
	Prostatitis	1 (0.9%)
	Testicular pain	1 (0.9%)
Vaginal discharge	1 (0.9%)	
Congenital, familial and genetic disorders	Peroneal muscular atrophy	1 (0.9%)	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Epidermal naevus	.	.	.	1 (0.9%)	1 (0.9%)
	Pigmented naevus	.	.	.	1 (0.9%)	1 (0.9%)
General disorders and administration site conditions	Implant site pain	8 (7.3%)	6 (5.5%)	21 (19.1%)	34 (30.9%)	35 (31.8%)
	Pain	.	.	3 (2.7%)	14 (12.7%)	16 (14.5%)
	Therapeutic product ineffective	.	.	.	14 (12.7%)	16 (14.5%)
	Implant site inflammation	2 (1.8%)	1 (0.9%)	5 (4.5%)	8 (7.3%)	9 (8.2%)
	Chest pain	.	1 (0.9%)	2 (1.8%)	7 (6.4%)	7 (6.4%)
	Fatigue	1 (0.9%)	.	2 (1.8%)	7 (6.4%)	7 (6.4%)
	Implant site effusion	1 (0.9%)	1 (0.9%)	3 (2.7%)	5 (4.5%)	5 (4.5%)
	Asthenia	1 (0.9%)	.	1 (0.9%)	5 (4.5%)	5 (4.5%)
	Gait disturbance	1 (0.9%)	.	1 (0.9%)	4 (3.6%)	4 (3.6%)
	Pyrexia	1 (0.9%)	.	1 (0.9%)	4 (3.6%)	4 (3.6%)
	Oedema peripheral	.	.	1 (0.9%)	2 (1.8%)	4 (3.6%)
	Implant site erosion	.	.	.	2 (1.8%)	4 (3.6%)
	Drug interaction	.	.	.	3 (2.7%)	3 (2.7%)
	Non-cardiac chest pain	.	.	.	3 (2.7%)	3 (2.7%)
	Polyp	.	.	.	3 (2.7%)	3 (2.7%)
	Implant site oedema	1 (0.9%)	1 (0.9%)	2 (1.8%)	2 (1.8%)	2 (1.8%)
	Implant site scar	1 (0.9%)	.	2 (1.8%)	2 (1.8%)	2 (1.8%)
	Chills	1 (0.9%)	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Discomfort	.	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Sudden unexplained death in epilepsy	.	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Implant site haematoma	.	.	.	2 (1.8%)	2 (1.8%)
	Cyst	.	.	.	1 (0.9%)	2 (1.8%)

Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTÉ) Clinical Summary

Time Period ^a		Operative Phase (1 month) n=110 years=10	Blinded Phase (3 months) n=109 years=26	Implant to Year 1 (13 months) n=110 years=111	Implant to Year 7 (85 months) n=110 years=611	Total Postimplant ^b n=110 years=713
SOC	Preferred Term	Subjects (%) with an Event				
	Face oedema	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Implant site fibrosis	.	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Oedema	.	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Implant site swelling	1 (0.9%)	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Facial pain	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Implant site bruising	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Implant site warmth	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Ulcer	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Chest discomfort	.	.	.	1 (0.9%)	1 (0.9%)
	Circadian rhythm sleep disorder	.	.	.	1 (0.9%)	1 (0.9%)
	Drowning	.	.	.	1 (0.9%)	1 (0.9%)
	Drug withdrawal syndrome	.	.	.	1 (0.9%)	1 (0.9%)
	Feeling hot	.	.	.	1 (0.9%)	1 (0.9%)
	Hyperthermia	.	.	.	1 (0.9%)	1 (0.9%)
	Implant site discharge	.	.	.	1 (0.9%)	1 (0.9%)
	Implant site pruritus	.	.	.	1 (0.9%)	1 (0.9%)
	Implant site rash	.	.	.	1 (0.9%)	1 (0.9%)
	Inflammation	.	.	.	1 (0.9%)	1 (0.9%)
	Implant site erythema	1 (0.9%)
Implant site paraesthesia	1 (0.9%)	
Investigations	Weight increased	.	1 (0.9%)	2 (1.8%)	5 (4.5%)	6 (5.5%)
	Blood pressure increased	1 (0.9%)	1 (0.9%)	2 (1.8%)	3 (2.7%)	3 (2.7%)
	Anticonvulsant drug level decreased	1 (0.9%)	.	1 (0.9%)	3 (2.7%)	3 (2.7%)
	Blood cholesterol increased	.	.	1 (0.9%)	3 (2.7%)	3 (2.7%)
	Blood urine present	.	.	.	2 (1.8%)	3 (2.7%)
	Weight decreased	.	1 (0.9%)	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Cardiac murmur	.	.	.	2 (1.8%)	2 (1.8%)
	Electrocardiogram abnormal	.	.	.	2 (1.8%)	2 (1.8%)
	White blood cell count decreased	.	.	.	2 (1.8%)	2 (1.8%)
	Blood magnesium decreased	1 (0.9%)	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Heart rate irregular	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Activated partial thromboplastin time prolonged	.	.	.	1 (0.9%)	1 (0.9%)
	Anticonvulsant drug level below therapeutic	.	.	.	1 (0.9%)	1 (0.9%)

Time Period ^a		Operative Phase (1 month) n=110 years=10	Blinded Phase (3 months) n=109 years=26	Implant to Year 1 (13 months) n=110 years=111	Implant to Year 7 (85 months) n=110 years=611	Total Postimplant ^b n=110 years=713
SOC	Preferred Term	Subjects (%) with an Event				
	Blood alkaline phosphatase increased	.	.	.	1 (0.9%)	1 (0.9%)
	Blood glucose increased	.	.	.	1 (0.9%)	1 (0.9%)
	Blood testosterone decreased	.	.	.	1 (0.9%)	1 (0.9%)
	Electrocardiogram T wave abnormal	.	.	.	1 (0.9%)	1 (0.9%)
	Haemoglobin decreased	.	.	.	1 (0.9%)	1 (0.9%)
	Liver function test abnormal	.	.	.	1 (0.9%)	1 (0.9%)
	Vitamin B12 decreased	.	.	.	1 (0.9%)	1 (0.9%)
Vitamin D decreased	.	.	.	1 (0.9%)	1 (0.9%)	
Injury, poisoning and procedural complications	Anticonvulsant toxicity	5 (4.5%)	7 (6.4%)	20 (18.2%)	62 (56.4%)	66 (60.0%)
	Injury	2 (1.8%)	8 (7.3%)	20 (18.2%)	46 (41.8%)	48 (43.6%)
	Skin laceration	1 (0.9%)	1 (0.9%)	7 (6.4%)	30 (27.3%)	31 (28.2%)
	Contusion	3 (2.7%)	5 (4.6%)	15 (13.6%)	27 (24.5%)	31 (28.2%)
	Drug toxicity	3 (2.7%)	2 (1.8%)	7 (6.4%)	17 (15.5%)	22 (20.0%)
	Head injury	4 (3.6%)	2 (1.8%)	9 (8.2%)	18 (16.4%)	19 (17.3%)
	Excoriation	2 (1.8%)	4 (3.7%)	8 (7.3%)	17 (15.5%)	18 (16.4%)
	Laceration	1 (0.9%)	1 (0.9%)	6 (5.5%)	16 (14.5%)	18 (16.4%)
	Joint sprain	.	1 (0.9%)	3 (2.7%)	13 (11.8%)	15 (13.6%)
	Documented hypersensitivity to administered drug	2 (1.8%)	.	5 (4.5%)	12 (10.9%)	13 (11.8%)
	Limb injury	.	1 (0.9%)	2 (1.8%)	10 (9.1%)	10 (9.1%)
	Fall	.	.	.	7 (6.4%)	10 (9.1%)
	Thermal burn	1 (0.9%)	.	5 (4.5%)	8 (7.3%)	8 (7.3%)
	Post procedural pain	7 (6.4%)	.	7 (6.4%)	7 (6.4%)	7 (6.4%)
	Mouth injury	.	1 (0.9%)	3 (2.7%)	6 (5.5%)	7 (6.4%)
	Postoperative fever	5 (4.5%)	.	5 (4.5%)	5 (4.5%)	6 (5.5%)
	Upper limb fracture	.	1 (0.9%)	1 (0.9%)	5 (4.5%)	6 (5.5%)
	Joint injury	.	.	1 (0.9%)	5 (4.5%)	5 (4.5%)
	Muscle strain	.	.	.	5 (4.5%)	5 (4.5%)
	Back injury	.	.	1 (0.9%)	4 (3.6%)	5 (4.5%)
	Tooth injury	.	.	1 (0.9%)	4 (3.6%)	5 (4.5%)
	Eye injury	.	.	.	4 (3.6%)	5 (4.5%)
	Wrist fracture	.	.	2 (1.8%)	3 (2.7%)	5 (4.5%)
	Hand fracture	.	.	.	3 (2.7%)	5 (4.5%)
	Foot fracture	.	.	.	4 (3.6%)	4 (3.6%)
	Incision site complication	2 (1.8%)	.	3 (2.7%)	3 (2.7%)	4 (3.6%)
	Procedural complication	3 (2.7%)	1 (0.9%)	3 (2.7%)	3 (2.7%)	3 (2.7%)
Arthropod bite	1 (0.9%)	.	1 (0.9%)	3 (2.7%)	3 (2.7%)	

	Time Period ^a	Operative Phase (1 month) n=110 years=10	Blinded Phase (3 months) n=109 years=26	Implant to Year 1 (13 months) n=110 years=111	Implant to Year 7 (85 months) n=110 years=611	Total Postimplant ^b n=110 years=713
SOC	Preferred Term	Subjects (%) with an Event				
	Tongue injury	.	.	1 (0.9%)	3 (2.7%)	3 (2.7%)
	Arthropod sting	.	.	.	3 (2.7%)	3 (2.7%)
	Concussion	.	.	.	3 (2.7%)	3 (2.7%)
	Skeletal injury	.	.	.	3 (2.7%)	3 (2.7%)
	Clavicle fracture	.	.	1 (0.9%)	2 (1.8%)	3 (2.7%)
	Lower limb fracture	.	.	1 (0.9%)	2 (1.8%)	3 (2.7%)
	Polytraumatism	.	.	.	2 (1.8%)	3 (2.7%)
	Ankle fracture	.	.	.	1 (0.9%)	3 (2.7%)
	Face injury	.	1 (0.9%)	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Periorbital haematoma	.	1 (0.9%)	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Post procedural complication	1 (0.9%)	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Post procedural haemorrhage	1 (0.9%)	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Wound dehiscence	1 (0.9%)	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Muscle injury	.	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Animal bite	.	.	.	2 (1.8%)	2 (1.8%)
	Burns second degree	.	.	.	2 (1.8%)	2 (1.8%)
	Epicondylitis	.	.	.	2 (1.8%)	2 (1.8%)
	Fibula fracture	.	.	.	2 (1.8%)	2 (1.8%)
	Subdural haematoma	1 (0.9%)	.	1 (0.9%)	1 (0.9%)	2 (1.8%)
	Ear abrasion	.	.	1 (0.9%)	1 (0.9%)	2 (1.8%)
	Heat exhaustion	.	.	1 (0.9%)	1 (0.9%)	2 (1.8%)
	Medical device complication	.	.	1 (0.9%)	1 (0.9%)	2 (1.8%)
	Joint dislocation	.	.	.	1 (0.9%)	2 (1.8%)
	Intra-uterine contraceptive device expelled	.	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Dural tear	1 (0.9%)	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Incision site haemorrhage	1 (0.9%)	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Neck injury	.	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Chest injury	.	.	.	1 (0.9%)	1 (0.9%)
	Closed head injury	.	.	.	1 (0.9%)	1 (0.9%)
	Corneal abrasion	.	.	.	1 (0.9%)	1 (0.9%)
	Facial bones fracture	.	.	.	1 (0.9%)	1 (0.9%)
	Forearm fracture	.	.	.	1 (0.9%)	1 (0.9%)
	Foreign body in eye	.	.	.	1 (0.9%)	1 (0.9%)
	Foreign body trauma	.	.	.	1 (0.9%)	1 (0.9%)
	Hip fracture	.	.	.	1 (0.9%)	1 (0.9%)
	Human bite	.	.	.	1 (0.9%)	1 (0.9%)
	IUCD complication	.	.	.	1 (0.9%)	1 (0.9%)
	Nerve injury	.	.	.	1 (0.9%)	1 (0.9%)
	Radius fracture	.	.	.	1 (0.9%)	1 (0.9%)
Renal injury	.	.	.	1 (0.9%)	1 (0.9%)	

Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTÉ) Clinical Summary

Time Period ^a		Operative Phase (1 month) n=110 years=10	Blinded Phase (3 months) n=109 years=26	Implant to Year 1 (13 months) n=110 years=111	Implant to Year 7 (85 months) n=110 years=611	Total Postimplant ^b n=110 years=713
SOC	Preferred Term	Subjects (%) with an Event				
	Rib fracture	.	.	.	1 (0.9%)	1 (0.9%)
	Scratch	.	.	.	1 (0.9%)	1 (0.9%)
	Sunburn	.	.	.	1 (0.9%)	1 (0.9%)
	Suture related complication	.	.	.	1 (0.9%)	1 (0.9%)
	Tendon injury	.	.	.	1 (0.9%)	1 (0.9%)
	Wound	.	.	.	1 (0.9%)	1 (0.9%)
	Ligament injury	1 (0.9%)
	Medication error	1 (0.9%)
	Skin injury	1 (0.9%)
Surgical and medical procedures	Therapeutic procedure	.	.	.	2 (1.8%)	2 (1.8%)
	Post procedural drainage	1 (0.9%)	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Wound drainage	1 (0.9%)	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Contraception	.	.	.	1 (0.9%)	1 (0.9%)
	Tendon operation	.	.	.	1 (0.9%)	1 (0.9%)
Social circumstances	Menopause	.	.	.	1 (0.9%)	1 (0.9%)
Medtronic ^c	Lead(s) not within target	9 (8.2%)	.	9 (8.2%)	9 (8.2%)	9 (8.2%)
	Neurostimulator migration	.	.	3 (2.7%)	6 (5.5%)	6 (5.5%)
	Extension fracture	1 (0.9%)	1 (0.9%)	5 (4.5%)	5 (4.5%)	6 (5.5%)
	Extension migration/dislodgment	.	.	3 (2.7%)	3 (2.7%)	3 (2.7%)
	High impedance	.	.	2 (1.8%)	3 (2.7%)	3 (2.7%)
	Lead fracture	1 (0.9%)	.	2 (1.8%)	2 (1.8%)	3 (2.7%)
	Set screws not adequately secured	1 (0.9%)	.	1 (0.9%)	2 (1.8%)	2 (1.8%)
	Recharging unable to recharge	.	.	.	2 (1.8%)	2 (1.8%)
	Low impedance	.	1 (0.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Lead migration/dislodgment	1 (0.9%)	.	1 (0.9%)	1 (0.9%)	1 (0.9%)
	Change in sensation of stimulation	.	.	.	1 (0.9%)	1 (0.9%)
Adverse Event Total ^d		83 (75.5%)	84 (77.1%)	109 (99.1%)	110 (100.0%)	110 (100.0%)

^a 'months' is defined as the number of scheduled months in the interval for each subject. 'n' is the number of subjects entering the interval. 'years' is the number of total device years in the interval.

^b Total postimplant includes the Operative phase.

^c A SOC that allowed coding of adverse events that were specific to device-related terms under investigation but did not exist in the MedDRA dictionary at the time the study was implemented.

^d Column subtotals may not equal final total, as subjects may have experienced more than 1 event type.



Medtronic

N'VISION[®] CLINICIAN PROGRAMMER 8840
with SOFTWARE 8870

Medtronic[®] DBS[™] System for Epilepsy using the Activa[®] PC
Neurostimulator

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09/15 Programmer guide for software version B

USA Rx only

CE0123
2008

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Explanation of symbols on product and package labeling for non-USA audiences.



Serial number



Caution, consult accompanying documents



Consult instructions for use



Temperature limitation



For USA audiences only



Non-ionizing electromagnetic radiation



IEC 60601-1/EN60601-1, Type BF Equipment



Conformité Européenne (European Conformity). This symbol means that the device fully complies with AIMD Directive 90/385/EEC.



System meets the applicable Canadian [C22.2-601.1-M90 (R2001)] electrical safety standard requirements.



Do not dispose of this product in the unsorted municipal waste stream. Dispose of this product according to local regulations. See <http://recycling.medtronic.com> for instructions on proper disposal of this product.



Chinese Standard (SJ/T11364-2006) Logo: Electronic Information Products Pollution Control Symbol. (The date in this logo means the environmental protection use period of the product.)



Authorized Representative in the European Community



Manufacturer

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Refer to the indications sheet for indications and related information.

Refer to the device implant manual for device description, package contents, device specifications, and instructions for use.

Refer to System Eligibility Battery Longevity reference manual for battery longevity calculations.

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Device description

The Medtronic N'Vision Model 8840 Clinician Programmer with the Medtronic Model 8870 Application Card is part of a neurostimulation system for deep brain stimulation.

This manual is intended for use with the Medtronic DBS System for Epilepsy. It is designed to provide the information needed to use the clinician-only features on the Medtronic Intercept Model 37441 Patient Programmer and to program and troubleshoot the programmable parameters for the:

- Activa PC Model 37601 Implantable Neurostimulator (INS)
- Model 37022 External Neurostimulator (ENS)

Package contents

- Application card with case
- Product literature

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Introduction

The N'Vision Model 8840 Clinician Programmer (Figure 1) with the Model 8870 Application Card is a hand-held device for programming Medtronic devices for Medtronic Neuromodulation therapies. The programmer is used to review and program device parameters using telemetry, a radio-frequency (RF) communication. The programmer is also used to set limits for the patient control devices.

If using a programmer for the first time, see the set-up instructions on the Getting Started card that is packaged with the programmer.

Programmer components

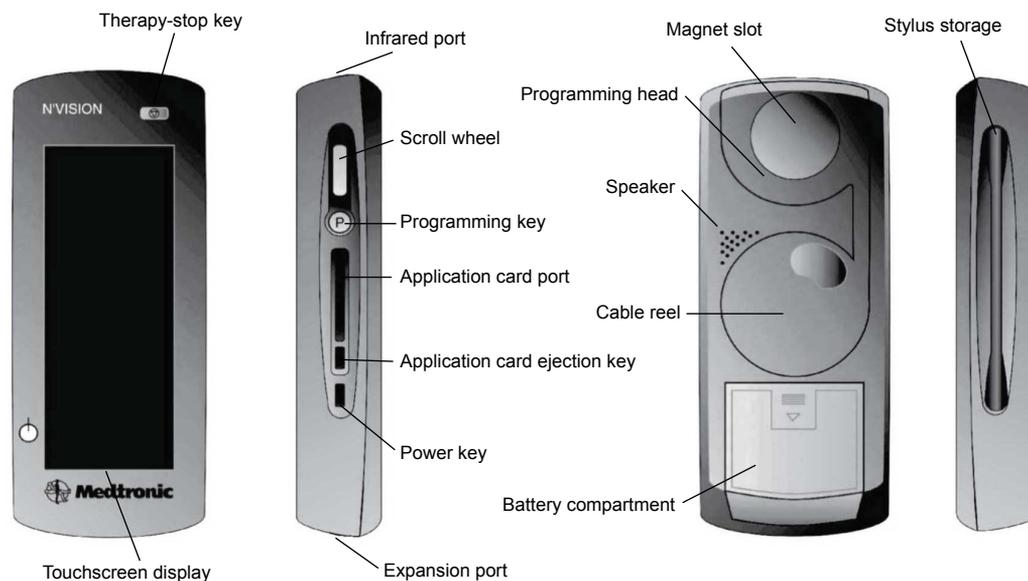


Figure 1. N'Vision clinician programmer components.

△ **Caution:** Do not use the expansion port. The expansion port is a testing port used by Medtronic personnel. Connecting any equipment to this port may damage the programmer.

- **Therapy-stop key** (⏏)—Stops all active therapy
- **Touchscreen display**—Programmer touchscreen for display and data input
- **Infrared (IR) port**—Allows communication with compatible printers or devices
- **Scroll wheel**—Turning the wheel scrolls up and down to adjust values for some functions
- **Programming key** (P)—Pressing the key initiates interrogation or programming for some functions
- **Application card port**—Slot for the application card

- **Application card ejection key**—Ejects the application card from the programmer
- **Power key** (⏻)—Turns the programmer on and off; reactivates the programmer after Stand-by mode
- **Expansion port**—Do not use; currently only used for Medtronic testing
- **Magnet slot**—Holds the Model 8529 magnet (the Model 8529 magnet is not used for all therapies and devices)
- **Programming head**—Allows the programmer to communicate with the device
- **Cable reel**—Stores a 1 meter (3.3 ft) extendable cable that connects the programming head to the programmer
- **Speaker**—Programmer speaker
- **Battery compartment**—Contains the programmer batteries
- **Stylus**—Use to enter data through the touchscreen display

Printer

The optional Model 3445 Seiko DPU Printer (Figure 2) communicates with the programmer via IR signals. The printer is available in the Medtronic Model 8527 Printer Kit.



Figure 2. Model 3445 Seiko DPU printer.

Most standard desktop printers with IR capability and protocol IrDA 1.0 compliant at data rates of 9600 and 57,600 bits per second may also be used with the programmer.

A desktop printer must have IR capability or must be fitted with a commercially available IR converter.

Note: IR functionality is only intended for communication between the N'Vision Programmer and compatible printers or compatible Medtronic patient programmers. Any other use is not certified by Medtronic.

Navigation, status, and data entry

The touchscreen display allows you to navigate through the application, read status, and enter data. When navigating or entering data, use the pointed end of the stylus to make contact with the display screen. Do not use sharp objects (eg, pencils, pens, paper clips) on the touchscreen display. Use only the stylus or your fingertip. Simultaneous screen taps cause the programmer to average the values and execute a command midway between the two points touched.

△ **Caution:** If stylus contact with the touchscreen display results in a different function, action, or therapy than expected, calibrate the touchscreen on the display.

For instructions on calibrating the display, see "To calibrate the touchscreen" on page 96.

Navigation and status

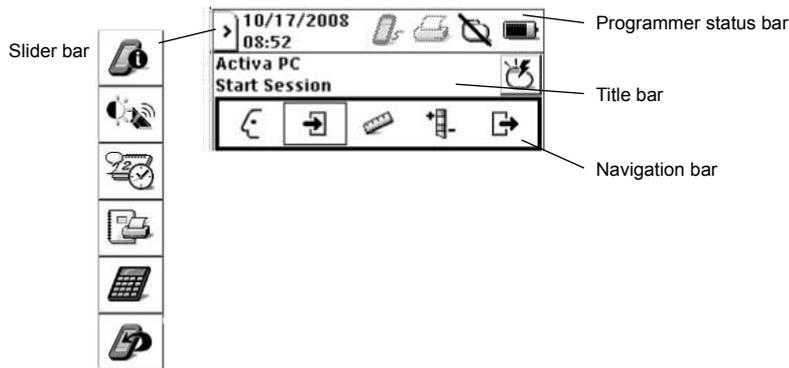


Figure 3. Navigation and status icons.

Navigation and status icons are in the following locations (Figure 3):

- **Programmer status bar**—Displays system date and time as well as status of selected functions and components
- **Slider bar**—Provides access to programmer information, system settings, and accessories
- **Title bar**—Displays application name, active screen name, and the **Neurostimulator on/off** button
- **Navigation bar**—Provides access to application menus

Note: If a value or button appears gray, that option is not available during the current function.

Programmer status bar

The programmer status bar shows the status of peripheral devices, the programming head, Demo mode, and the programmer battery.

Table 1. Programmer status bar icon descriptions

Nontelemetry communication port (Expansion port, Medtronic use only)					
	Nontelemetry communication is active		Nontelemetry communication is inactive		
Printer					
	Printing		Printing error		Printing inactive
Programming head					
	Programming head present		Programming head not present		
	Communication established between programming head and device		No communication between programming head and device		
	Magnet present on programming head		Magnet present; telemetry successful		Magnet present; telemetry not successful
Demo mode					
	Demo mode is active				
Programmer battery					
	High battery status		Medium battery status		
	Low battery status		Depleted battery status (blinking)		

Slider bar

The slider bar provides access to programmer information, operating system and touchscreen display settings, and printer and calculator functions. The slider bar can be accessed any time during a programming session by selecting the **Slider bar** button on the programmer status bar (Figure 4).

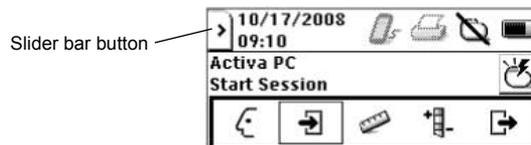


Figure 4. Slider bar button.

Table 2. Slider bar button descriptions

Button	Description
 Information	<ul style="list-style-type: none"> View the names, model numbers, and version numbers for programmer, application, and associated software and peripheral devices
 Settings	<ul style="list-style-type: none"> Adjust the display contrast Adjust the speaker volume Adjust the key click sound Calibrate the touchscreen
 Localization	<ul style="list-style-type: none"> Select the language preference Select the date format and set the date Select the decimal format Set the time format
 Session Data Manager	<ul style="list-style-type: none"> Print session reports View session reports Delete session reports
 Calculator	<ul style="list-style-type: none"> Access the calculator
 Exit application	<ul style="list-style-type: none"> Return to the Neurostimulation desktop screen to select a new application

Title bar

The title bar displays the application name and the active programmer screen. The title bar also provides access to the **Neurostimulator on/off** button (Figure 5).

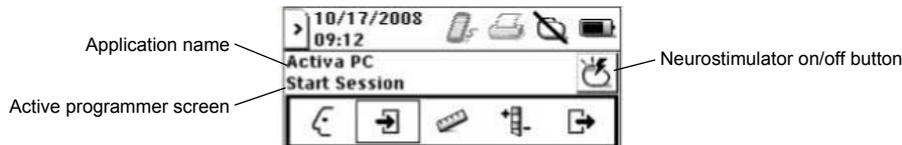


Figure 5. Title bar.

Navigation bar

The navigation bar provides access to the application menus and programming functions (Figure 6).

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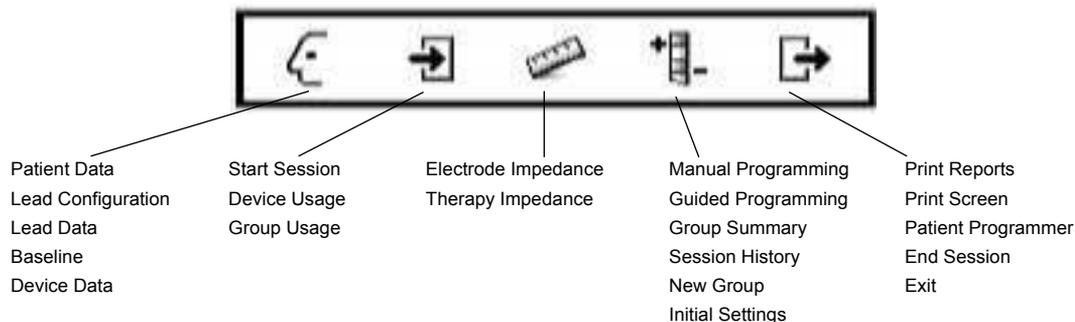


Figure 6. Navigation bar with available menu items.

Table 3. Menu descriptions

Menu	Function descriptions
 Profile	<ul style="list-style-type: none"> • Enter patient and physician information • Configure leads • Enter device and implant information • Enter baseline diagnosis information • Set neurostimulator date and time • View neurostimulator system information
 Start Session	<ul style="list-style-type: none"> • View name and date of last patient session • View initial settings • View initial neurostimulator battery status • View initial system status messages • View patient use data by groups or by days
 Measurement	<ul style="list-style-type: none"> • Perform electrode impedance measurements • Perform therapy impedance measurements
 Programming	<ul style="list-style-type: none"> • Create, add, and delete groups and programs • Program stimulation parameters • Record and select settings in Screening History. • View summary of group settings • Return all settings to initial values • View Session History and import groups
 End Session	<ul style="list-style-type: none"> • Print a copy of current screen • Select and print session reports • Program patient control limits • Program patient reminder • Program Cycling • View name of current patient session • View final group settings • View/enter clinician notes • Exit application

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Data entry

Enter data into the programmer through the touchscreen display. Most data are accepted through the following:

- **Drop-down list**—Select the arrow on the right side of a drop-down list. Select a value or entry.

- **Setting input box**—A selection of values appears when the stylus contacts a setting input box. Select a value.

- **Keyboard**—The keyboard appears when the stylus contacts an input box that requires alphanumeric input. To enter data, select each character. Four keyboards are available (Figure 7):

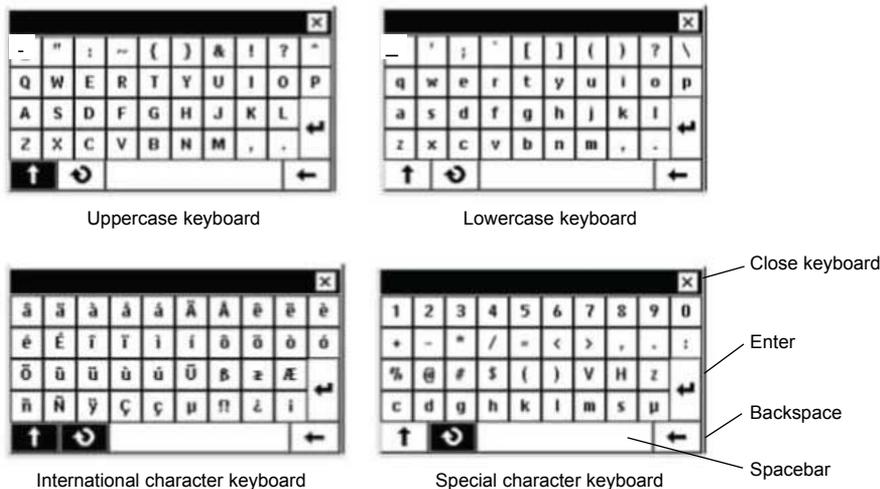


Figure 7. Programmer keyboards.

Alternate keyboards are available by selecting the following buttons:

- **Straight Arrow**  —Uppercase alpha and international characters
- **Circular Arrow**  —International and special characters

Using the programming head

After entering data into the clinician programmer, use the programming head to send the data to the device via telemetry.

Disconnecting the magnet

The magnet must be removed from the programming head before using it with any device except SynchroMed and SynchroMed EL pumps.

△ **Caution:** The Model 8529 Magnet is for use with Medtronic SynchroMed and SynchroMed EL Pumps only. Remove the magnet from the Model 8840 Clinician Programmer before approaching a patient with a different pump, a neurostimulator or another active implanted medical device (eg, pacemaker, defibrillator). If the magnet is too close to another active device, the therapy of the other device may change.

◆ **To disconnect the magnet from the programming head**

1. Unlock the magnet from the programming head by turning the magnet (Figure 8).
2. Store the magnet in the programmer carrying case.

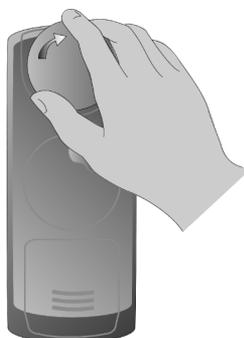


Figure 8. *Unlocking the magnet from the programming head.*

△ **Caution:** Do not place the magnet on or near computer monitors, magnetic storage disks or tapes, televisions, credit cards, or other items affected by strong magnetic fields. If the magnet is too close to these items, they may be damaged.

Extending and retracting the programming head

The programming head can be used while it is docked on the programmer or extended from the programmer.

△ **Caution:** To prevent the cable or electrical contact from being damaged, which could prevent further programming and cause unsaved data to be lost:

- do not use excessive force when extending the programming head.
- do not tangle the cable during extension or retraction.

- do not turn the cable reel counterclockwise.

◆ **To extend the programming head**

1. Press down and forward on the programming head until it snaps out of the docked position (Figure 9).



Figure 9. Extending the programming head.

2. Extend the programming head to the desired position.

◆ **To retract and dock the programming head**

1. Turn the cable reel in the direction of the arrow until the programming head rests against the programmer (Figure 10).

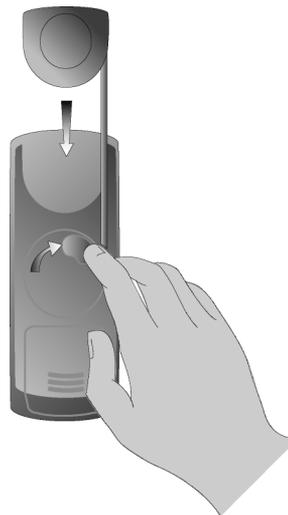


Figure 10. Retracting the programming head.

2. Gently push the programming head into place until it snaps into the docked position.

Using the programmer in Demo mode

Demo mode can be used to work with the programmer for training and demonstration purposes and to familiarize yourself with the programmer interface before a programming session. Demo mode can also be used to ensure that high-output interlocks do not apply.

Note: If Demo mode is selected, the programmer remains in Demo mode until the application is exited. Demo mode cannot be used to actually interrogate or program a device.

◆ **To access Demo mode**

1. From the **Neurostimulation Desktop** screen (Figure 14 on page 38), select the **To work in demo mode** button. The **Demo mode** screen appears.
2. Select a therapy.
3. Select a neurostimulator.
4. Select the **OK** button ().

Note: The neurostimulator icon on the programmer status bar and the Demo mode designation on the title bar show that Demo mode is active.

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Programming for intraoperative test stimulation

The Model 8840 Clinician Programmer is connected to the Model 37022 External Neurostimulator (ENS) for intraoperative test stimulation. The Model 8870 Application Card provides the software to program the ENS for these procedures.

Preparing the ENS

Refer to the ENS user manual for instructions for:

- Connecting/disconnecting the ENS to/from the Model 8840 Clinician Programmer.
- Connecting the screening cable to the ENS.
- Changing ENS batteries.

Note: Put new batteries in the ENS prior to each new test stimulation.

Refer to the appropriate cable accessory kit for instructions for connecting the cable to the extension.

Interrogating the ENS

When the ENS is interrogated, the programmer identifies the ENS model and reads the current ENS configuration (if applicable, this includes previous information stored in the device along with the associated therapy application).

Selecting a test stimulation option

New and **Follow-up** options are available from the **Test Stim selection** screen after initial interrogation (Figure 11). The **New** option erases previous test stimulation information. The **Follow-up** option retains previous test stimulation information and is used to reestablish the previously programmed settings in the ENS and continue intraoperative testing for the DBS Lead.

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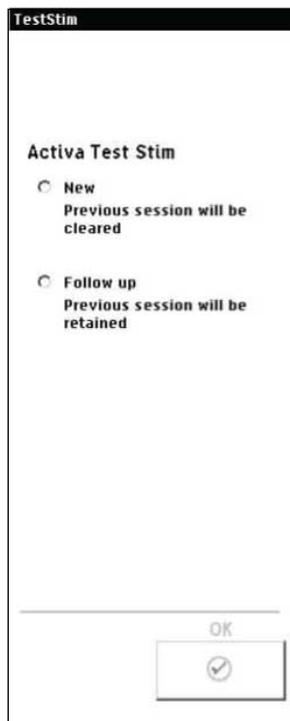


Figure 11. Test Stim selection screen for programming the ENS.

DBS intraoperative test stimulation

DBS intraoperative test stimulation is intended as an aid in lead placement and neurostimulator selection for movement disorder therapies. Test stimulation has not been evaluated for placement of leads in the anterior nucleus of the thalamus (ANT).

Refer to Table 4 for basic instructions for intraoperative test stimulation with the Model 8870 Application Card. Use the reference page numbers listed in Table 4 to find additional information in other sections of the manual.

Table 4. Intraoperative test stimulation with the ENS

Procedure:	Do this:	Refer to:
Prepare for the test stimulation process:		
1. Check the programmer.	• Ensure that the application card is properly installed.	page 38
2. Turn the programmer on.	• Turn on the programmer. • Check/replace programmer batteries.	page 39 page 94
3. Navigate to the Neurostimulation Desktop screen.	• Select the Neurostimulation application button.	page 39

Table 4. Intraoperative test stimulation with the ENS (continued)

Procedure:	Do this:	Refer to:
4. Interrogate the ENS.	<ul style="list-style-type: none"> • Connect the ENS to the programmer. • Interrogate the ENS. • If no error messages appear, continue. (If an error message appears, see the troubleshooting section.) • Confirm device and therapy application information. 	page 20 page 80
5. Select the test stimulation option.	<ul style="list-style-type: none"> • Select an option from the Test Stim selection screen. 	page 21
Configure the lead and check system performance:		
1. Follow the prompts on the Guided profile screen.	<ul style="list-style-type: none"> • Select the lead configuration. • Select the lead location and hemisphere. • Enter additional information, as desired. <p>Note: Only one lead can be screened at a time when working with the ENS.</p>	page 33
2. Check electrode impedance, if desired. Note: Perform this procedure at the beginning of the session. These measurements verify the integrity of lead/extension/connector pathways.	<ul style="list-style-type: none"> • Access the Measurement menu and select Electrode Impedance. • Select the settings and electrodes for the measurement. • Take the measurement. • Review electrode impedance measurement results. <p>Note: This procedure takes approximately 1 minute. In order to perform measurements, this procedure temporarily reprograms the stimulation settings.</p>	page 51
Set stimulation parameters:		
1. Ensure that the ENS is on.	<ul style="list-style-type: none"> • If the neurostimulator is off, select the ENS on/off button. 	page 50
2. Set electrode polarities. Note: This step is not applicable if alligator clips are used.	<ul style="list-style-type: none"> • Access the Programming menu and select Manual Programming. • Use the stylus to select negative (-), positive (+), or off electrode polarities for the selected lead. 	page 58
3. Set rate and pulse width.	<ul style="list-style-type: none"> • Select the rate input box, then select a rate. • Select the pulse width input box, then select a pulse width. 	page 59
4. Set amplitude resolution and amplitude.	<ul style="list-style-type: none"> • Select the amplitude input box, then select an amplitude resolution setting, amplitude auto increase setting, and amplitude mode. • Select an amplitude setting. The amplitude ramps to the target value. 	page 60
5. If desired, set stimulation parameters for a new program.	<ul style="list-style-type: none"> • Select the New button. • Set stimulation parameters for the new program. 	page 66
Check therapy impedance (optional):		
3. Check therapy impedance, if desired. Note: Perform this procedure at the end of the session. These measurements provide documentation that pathways are intact and the current provided is sufficient for the selected therapy.	<ul style="list-style-type: none"> • Access the Measurement menu and select Therapy Impedance. • Take the measurement. • Review impedance and stimulation current data. <p>Note: This measurement is available only when a program has been defined.</p>	page 52
Complete the test stimulation process:		

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Table 4. Intraoperative test stimulation with the ENS (continued)

Procedure:	Do this:	Refer to:
6. Exit application.	<ul style="list-style-type: none">• Access the End Session menu and select Exit.• View or print the session report from the Session Data Manager.	page 74 page 75

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Programming concepts

Programming the neurostimulator involves reviewing and modifying the information, settings, and optional features that are programmed in the neurostimulator. Information and settings may have been programmed in an earlier session or may be the default parameters that were set during manufacturing.

When changing therapy parameter settings, increase or decrease in small increments while evaluating the patient's response.

During a programming session, telemetry transfers and retrieves data to and from the neurostimulator. The data transferred and retrieved include the following:

- **Stimulation parameters**
 - **Electrode polarities**—Programmed positive (+), negative (-), or off.
 - **Case**—Positive (+) or off.
 - **Pulse width**—Duration of each pulse in microseconds (μ s).
 - **Rate**—Frequency of pulses in hertz (Hz).
 - **Amplitude**—Strength of pulse, programmed in either voltage mode (volts or V) or current mode (milliamperes or mA).
 - **Cycling**—Cycles the neurostimulator on and off at programmed intervals.
- **Optional features**
 - **SoftStart/Stop**—Allows a gradual increase in amplitude (up to the programmed value) when stimulation is turned on and a gradual decrease in amplitude (to 0.0) when stimulation is turned off.
 - **Patient Control Limits**—Sets upper and lower limits for patient adjustment of parameters.
 - **Patient Reminder**—Reminds the patient to check the neurostimulator battery status at a specific time each day.

Groups and programs

Stimulation can be applied unilaterally or bilaterally. In unilateral stimulation, targeted structures in only one side of the brain (one hemisphere) are stimulated. In bilateral stimulation, targets in both sides of the brain are stimulated (using two leads).

Stimulation pulses that will be delivered to each hemisphere are defined by programs. Each hemisphere can have two programs. A program is defined by a specific combination of pulse width, rate, and amplitude settings acting on a specific electrode combination. When using more than one program, the pulses are delivered sequentially—first a pulse from one program, then a pulse from the next program, and so on (Figure 12). In bilateral stimulation, pulses alternate between hemispheres. Pulses from different programs are never delivered simultaneously.

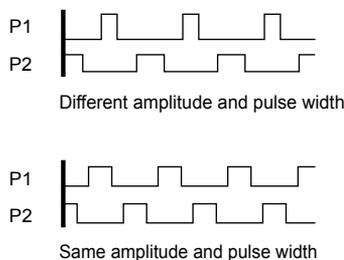


Figure 12. Using multiple programs.

Multiple programs are combined to define a group. Pulse width, amplitude, and electrode polarity are programmed separately for each program within the group, that is, each program within the group can have different values. Amplitude limits, electrode polarity, and pulse width limits are programmed separately for each hemisphere within the group. Amplitude (voltage mode or current mode), rate, rate limits, SoftStart/Stop, and Cycling are programmed for each group, that is, each program within the group will have the same values.

Groups are designated as A, B, C, or D. Programs are designated by the hemisphere and target location entered on the **Lead Configuration** screen. If the same hemisphere has more than one program, the programs are also designated as 1 or 2. A maximum of 4 groups can be programmed, with a maximum of 4 programs per group (2 programs per hemisphere).

Groups and programs are described as defined, undefined, active, or inactive to designate various states within the programming process. An undefined group or program is available as a new group or new program. Once a new group or new program is created, it is described as defined. An inactive group or program is one that is not providing therapy or stimulation. Once a group is activated, it is the group providing therapy. When a program within an active group has an amplitude greater than 0.0, it is an active program.

Amplitude modes

Stimulation amplitude can be programmed in either current (mA) mode or voltage (V) mode. Only one amplitude mode can be used within a group.

- **Current mode**—Amplitude is programmed to pulse current, allowing the pulse voltage to change according to the impedance (pulse voltage = programmed current x impedance).
- **Voltage mode**—Amplitude is programmed to pulse voltage, allowing the pulse current to change according to the impedance (pulse current = programmed voltage / impedance).

Each program in current mode will support only a single anode (+) and a single cathode (-). When changing from current mode to voltage mode, the therapy impedance measurement indicates the comparable amplitude setting in voltage mode.

Each program in voltage mode can support one or more anodes or cathodes. When changing from voltage mode to current mode and each voltage mode program has only one anode (+) and one

cathode (-), the therapy impedance measurement indicates the comparable amplitude setting in current mode. When changing from voltage mode to current mode and each voltage mode program has more than one anode (+) or cathode (-), a comparable amplitude setting in current mode cannot be determined. Electrode selection must be modified and reiteration to therapeutic effect will be necessary. Refer to "To modify amplitude mode" on page 62.

High-output interlocks

Certain combinations of high amplitude, pulse width, and rate settings are not allowed by the clinician programmer. High-output interlocks can prevent certain values from being available for programming. If you attempt to program a parameter value (or limit) that will cause the settings to exceed the high output interlock limit, the desired parameter value can only be achieved by reducing one of the other parameter values. Refer to "Error and informational messages" on page 80.

Refer to Table 5 for examples of maximum amplitudes in voltage mode at high programmed rate and pulse width combinations.

Table 5. Maximum programmable amplitude at high rate/pulse width combinations for the Activa PC Model 37601 Neurostimulator using voltage mode

No. of programs intended for use	Rate (Hz)	Pulse width (µsec)					
		60	120	180	240	330	450
1 ^a	50	10.5V	10.5V	10.5V	10.5V	10.5V	10.5V
1	70	10.5V	10.5V	10.5V	10.5V	10.5V	10.0V
1	100	10.5V	10.5V	10.5V	10.5V	10.5V	9.3V
1	125	10.5V	10.5V	10.5V	10.5V	10.15V	8.75V
1	160	10.5V	10.5V	10.5V	10.5V	9.5V	8.1V
1	180	10.5V	10.5V	10.5V	10.4V	9.15V	7.75V
1	200	10.5V	10.5V	10.5V	10.05V	8.85V	7.4V
1	220	10.5V	10.5V	10.5V	9.75V	8.55V	7.1V
1	250	10.5V	10.5V	10.3V	9.35V	8.1V	6.7V
2 ^b	25	10.5V	10.5V	10.5V	10.5V	10.5V	10.5V
2	35	10.5V	10.5V	10.5V	10.5V	10.5V	10.0V
2	50	10.5V	10.5V	10.5V	10.5V	10.5V	9.3V
2	80	10.5V	10.5V	10.5V	10.5V	9.5V	8.1V
2	100	10.5V	10.5V	10.5V	10.05V	8.85V	7.4V
2	120	10.5V	10.5V	10.45V	9.45V	8.25V	6.8V
2	125	10.5V	10.5V	10.3V	9.35V	8.1V	6.7V
2	140	10.5V	10.5V	9.85V	8.9V	7.65V	6.25V
2	160	10.5V	10.5V	9.35V	8.4V	7.15V	5.75V
2	180	10.5V	10V	8.85V	7.9V	6.65V	5.25V
2	200	10.5V	9.55V	8.4V	7.45V	6.2V	4.8V
2	220	10.5V	9.1V	7.95V	7V	5.75V	4.35V
2	250	10V	8.5V	7.35V	6.4V	5.15V	3.75V
3 or 4 ^c	10	10.5V	10.5V	10.5V	10.5V	10.5V	10.5V

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Table 5. Maximum programmable amplitude at high rate/pulse width combinations for the Activa PC Model 37601 Neurostimulator using voltage mode (continued)

No. of programs intended for use	Rate (Hz)	Pulse width (µsec)					
		60	120	180	240	330	450
3 or 4	20	10.5V	10.5V	10.5V	10.5V	10.5V	9.75V
3 or 4	40	10.5V	10.5V	10.5V	10.5V	9.5V	8.1V
3 or 4	60	10.5V	10.5V	10.45V	9.45V	8.25V	6.8V
3 or 4	80	10.5V	10.5V	9.35V	8.4V	7.15V	5.75V
3 or 4	100	10.5V	9.55V	8.4V	7.45V	6.2V	4.8V
3 or 4	120	10.2V	8.7V	7.55V	6.6V	5.35V	3.95V
3 or 4	125	10V	8.5V	7.35V	6.4V	5.15V	3.75V

^a In this instance, the lead configuration is 1X4 and only one program is defined.

^b In this instance, the lead configuration is 2X4, and one program is defined per lead/hemisphere.

^c In this instance, the lead configuration is 2X4, and a second program is in use on one or both leads or in one or both hemispheres.

Charge density

A survey of literature regarding electrical stimulation of neural tissue suggests that damage may occur above 30 microcoulombs/cm²/phase. The Medtronic DBS System for Epilepsy is capable of producing charge densities in excess of 30 microcoulombs/cm²/phase. If the maximum charge density threshold is reached, the charge density warning message appears. See the following sections for details on the charge density warning message.

Charge density depends on the delivered current:

- In voltage mode, the delivered current depends on the therapy impedance.
- In current mode, the delivered current remains constant regardless of therapy impedance.

Charge density in voltage mode

When programming parameters using voltage mode, there are two charge density thresholds to be considered:

- The first threshold is based on the default conservative 500-ohm impedance.
- The second threshold is based on the actual therapy impedance measurement.

Charge density is first calculated using the programmed settings and the default conservative impedance of 500 ohms. If parameter limits are programmed, the upper limit settings for amplitude and pulse width are always used in the charge density calculation.

The first time the programmed therapy settings result in a charge density that exceeds the default threshold (30 microcoulombs/cm²/phase), the following charge density warning appears:

Charge density may be high enough to cause tissue damage. Consult the technical manual. Select OK to continue and use the selected value.

Note: A parameter setting that exceeds the default threshold would fall in the grey area above the solid line in Figure 13 on page 30.

After the warning message appears, you can select the **Cancel** button and return to the previously selected parameter settings or select the **OK** button to continue using the new parameter settings, see the following text for details.

- Select the **Cancel** button to cancel programming the selected parameters. The warning message will appear again if new selected parameters exceed 30 microcoulombs/cm²/phase (within the same programming session).
- Select the **OK** button to continue. The system then measures the therapy impedance. This establishes the second charge density threshold.

If the selected parameters do not exceed the new threshold, then these parameters are programmed.

If the selected parameters do exceed the new threshold, then the following warning message appears where "xxx" represents the measured impedance value. This value will change depending on the measured impedance:

Charge density may be high enough to cause tissue damage. This warning is based on a measured impedance of xxx ohms. Consult the technical manual. Select OK to continue and use the selected value.

- Select the **Cancel** button to cancel programming the selected parameter values to the device. No additional charge density warning message will appear again during this programming session unless the charge density threshold is manually reactivated.
- Select the **OK** button to continue programming the selected parameters to the device. The new measured impedance value (represented by "xxx" in the message) will be used as the new warning threshold (within the same programming session).

The charge density threshold, using the measured impedance, is reactivated when the amplitude is programmed below the current threshold setting. The charge density message appears again for any future increases in parameters that result in a charge density above 30 microcoulombs/cm²/phase. The 500 ohm threshold is also reactivated in the following circumstances:

- New programming session
- Electrode programming change

Charge density in current mode

If the Medtronic DBS System is programmed with the amplitude in current mode:

- If the parameter limits are programmed, the upper limit settings for amplitude and pulse width are used.

- If the charge density exceeds 30 microcoulombs/cm²/phase, the following message appears:
Charge density may be high enough to cause tissue damage. Consult the technical manual. Select OK to continue and use the selected value.
 - Select the **Cancel** button to cancel programming the selected parameters to the device. The warning message appears again if new selected parameters exceed 30 microcoulombs/cm²/phase.
 - Select the **OK** button to continue programming the selected parameters to the device. The warning message will not appear again for the current programming session unless the warning level is specifically reactivated.

To reactivate the charge density threshold, the programmed parameters (and upper limit settings, if used) need to be decreased so that the charge density is at or below the 30 microcoulombs/cm²/phase.

Selecting **OK** when the warning message appears will continue programming the selected parameter values to the device. The warning message will not appear again for this program unless the warning level is reactivated. To reactivate the charge density warning message, the program parameters (and upper limit settings, if used) need to be decreased so that the charge density is at or below the 30 microcoulombs/cm²/phase level. The charge density message appears again for any future increases in parameters that result in a charge density above 30 microcoulombs/cm²/phase.

Charge density examples

The maximum programmable amplitude is 10.5 V (25.5 mA) and the maximum programmable pulse width in 450 μ s. The curved lines in Figure 13 represent a charge density of 30 microcoulombs/cm²/phase at impedances of 500 ohms and 1170 ohms, calculated for the electrode surface area of the DBS Model 3387 and Model 3389 Leads.

The shaded area to the right of the dashed line in Figure 13 indicates a charge density above 30 microcoulombs/cm²/phase at the example impedance of 1170 ohms.

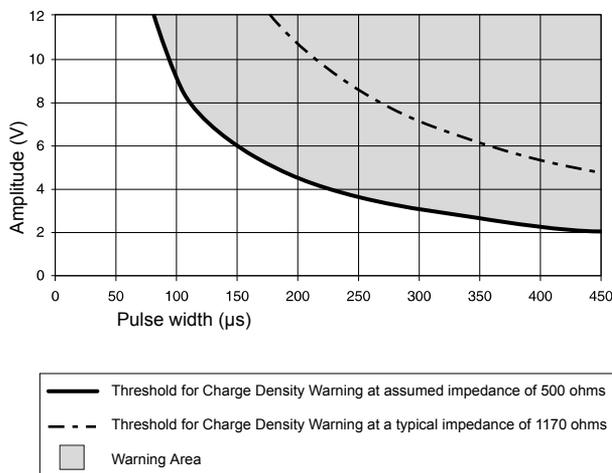


Figure 13. Impedance values and charge density warnings.

Note: The amplitude and pulse width limits were computed for an impedance of 500 ohms, an example impedance of 1170 ohms, an electrode surface area of 0.06 cm², and a charge density threshold of 30 microcoulombs/cm²/phase.

Programming warnings and cautions

△ Cautions:

- When the patient has a cochlear implant, minimize or eliminate the potential for unintended audible clicks during telemetry by keeping the external portion of the cochlear system as far from the programming head as possible or by turning off the cochlear implant during programming.
- The N'Vision Programmer is not certified for use in the presence of a flammable anaesthetic mixture with air or with oxygen or nitrous oxide. The consequences of using the N'Vision Programmer near flammable atmospheres are unknown.
- When a patient has a neurostimulator and another active implanted device (eg, pacemaker, defibrillator, neurostimulator) the radio-frequency (RF) signal used to program these devices may reset or reprogram the other device.

To verify that inadvertent programming did not occur, clinicians familiar with each device should check the programmed parameters of each device before the patient is discharged from the hospital and after each programming session of either device (or as soon as possible after these times).

Also, inform patients to contact their physician immediately if they experience symptoms that could be related to either device or to the medical condition treated by either device.

Therapy stop

Press the **Therapy-stop** key (⏏) on the programmer to turn the neurostimulator off (Figure 1 on page 10). The **Therapy-stop** key is available immediately after the **Neurostimulation Desktop** screen appears (Figure 14 on page 38) and throughout a patient session. The **Therapy-stop** key is not available while the Model 8870 application is loading or when files are being copied to the application card.

During a patient session, if the **Therapy-stop** key is pressed during the electrode impedance test, the programmer turns the neurostimulator off and returns the neurostimulator parameters to the pretest settings.

◆ *To stop therapy*

- Hold the programming head steady over the neurostimulator, then press the **Therapy-stop** key (⏏).

Stand-by mode

If the programmer receives no input for 6 minutes, Stand-by mode is activated. While in Stand-by mode, the programmer screen is blank.

Note: If the programmer is in Stand-by mode for more than 1 hour, the programmer turns off and any unsaved data is lost.

◆ *To return to programming from Stand-by mode*

- Slide and momentarily hold the **Power** key (⏻). The programmer returns to the screen that was displayed at the time Stand-by mode was activated.

Resolving pending values

During a programming session, changes to parameters that have not yet been programmed to the neurostimulator are considered pending. While you have pending values on the screen, you cannot navigate (via the navigation bar) to any other screen unless you program or clear the pending values.

Pending values are presented in two ways:

- A pending flag (▼) appears next to the changed parameter or checkbox.
- The target (pending) value appears below the current value, with an arrow pointing from the current value to the pending value.

Programming pending values – See the programming procedures in this manual for information on how to program pending values. When pending values are programmed, the following occurs:

- The pending flag disappears from the screen.
- The target (pending) value becomes the current value.

Clearing pending values – When pending values are cleared, the currently programmed values are again displayed on the screen. Clear pending values by selecting the **Clear pending** button ().

Printing screen displays

A copy of the current screen displayed on the programmer can be printed at any time during the programming session.

◆ *To print the current screen*

1. Ensure the printer is on.
2. Access the **End Session** menu () and select Print Screen.
3. Move the programmer to within 1 meter (3.3 ft) of the printer, with the printer and programmer IR ports directly facing each other.

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Programming the neurostimulator

Guided Profile and Guided Programming

Upon successful interrogation of the neurostimulator for the first time, Guided Profile will automatically appear prior to programming lead configuration. Guided Profile will not appear if lead configuration has been previously performed. Guided Profile takes the user through the **Profile** menu items: Patient Data, Lead Configuration, Lead Data, Baseline, and Device Data.

Note: Hold the programming head steady over the neurostimulator throughout the Guided Profile process.

Guided Programming is not intended for use with patients who have epilepsy. It takes the user through the screening process: electrode impedance test, screening settings selection, electrode pair screening (varying amplitude and recording effects), program selection, program review, and final amplitude programming.

Parameter settings in the SANTÉ study

Note: The use of cycling may cause a reduction in battery longevity depending on programmed settings.

The following were the Kinetra neurostimulator programming parameters used in the active group during the Blinded phase of the SANTÉ study:

- Amplitude: 5 V
- Rate: 145 Hz
- Pulse width: 90 μ sec
- Cycling on interval: 1 minute
- Cycling off interval: 5 minutes

Table 6 summarizes the programming in use at the Year 2 and Year 7 visits. Outputs equivalent to the Kinetra neurostimulator are achieved at slightly lower voltage settings on the Activa PC neurostimulator. For example, an amplitude setting of 4.45 V on the Activa PC neurostimulator provides an output that is approximately equal to that obtained with a setting of 5.0 V on the Kinetra neurostimulator. The amplitude values in Table 6 have been adjusted from Kinetra neurostimulator programming parameters to Activa PC programming parameters.

Table 6. SANTÉ study programming parameters adjusted for Activa PC – Year 2 and Year 7

	Parameter	n	Median	25th percentile	75th percentile
Year 2	Amplitude (V)	97	6.4	4.5	6.5
	Pulse width (μ sec)	99	90	90	90
	Rate (Hz)	99	145	145	185
	Cycling on interval (m)	98	1	1	1
	Cycling off interval (m)	98	3	2	5

Table 6. SANTÉ study programming parameters adjusted for Activa PC – Year 2 and Year 7 (continued)

	Parameter	n	Median	25th percentile	75th percentile
Year 7	Amplitude (V)	62	6.7	5.4	6.5
	Pulse width (µsec)	62	90	90	120
	Rate (Hz)	62	145	145	185
	Cycling on interval (m)	56	1	1	1
	Cycling off interval (m)	56	3	2	5

Basic programming steps

During the initial programming session, the focus is typically on establishing baseline stimulation parameters. Titrating to optimal therapy may take multiple programming sessions. Refer to "Parameter settings in the SANTÉ study" for stimulation parameters used in the SANTÉ clinical study. Therapeutic and side effects can be recorded on the **Clinician Notes screen** and used to determine the optimal electrodes and final stimulation parameters (refer to "Entering clinician notes" on page 49). In bilateral programming, each hemisphere is programmed separately—first one and then the other.

Table 7 presents an overview of the basic steps for a typical programming session. Use the reference page numbers listed in the table to locate detailed instructions and additional information for each step.

Note: The clinician programmer and the installed application card cannot be used to program any devices other than associated Medtronic neurostimulators and pumps. If an attempt is made to program an incompatible device, an error message appears on the programmer.

Table 7. Basic programming steps

Procedure:	Do this:	Refer to:
Prepare for the programming session:		
1. Check the programmer.	<ul style="list-style-type: none"> Ensure that the application card is properly installed. 	page 38
2. Turn the programmer on.	<ul style="list-style-type: none"> Turn on the programmer. Check/replace programmer batteries. 	page 39 page 94
3. Navigate to the Neurostimulation Desktop screen.	<ul style="list-style-type: none"> Select the Neurostimulation application button. 	page 39
4. Interrogate the neurostimulator.	<ul style="list-style-type: none"> Interrogate the neurostimulator. If no error messages appear, continue. (If an error message appears, see the troubleshooting section.) 	page 41 page 80
Configure leads:		
1. If the Guided profile screen appears, configure leads:	<ul style="list-style-type: none"> Enter the lead configuration. Enter the lead location and hemisphere. Follow the prompts on the Guided profile screen to enter additional information, as desired. 	page 43
2. Begin Manual Programming. Note: A Guided Programming option is also available on the Exit Guided profile screen. Guided Programming is not intended for use with patients who have epilepsy.	<ul style="list-style-type: none"> To program using Manual Programming, select the Manual Programming option from the Exit Guided profile screen. Proceed to the instructions under Review/modify Stimulation Parameters. When finished, proceed to the instructions under Customize Device Settings. 	page 54
Review initial programming:		

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Table 7. Basic programming steps (continued)

Procedure:	Do this:	Refer to:
1. If desired, review/update patient and device information.	<ul style="list-style-type: none"> • Access the Profile menu. • Select Patient Data to review/update patient information. • Select Lead Configuration to review/update the lead configuration. • Select Lead Data to review/update the lead information. • Select Device Data to review/update neurostimulator and implant information. • Select Device Data to set neurostimulator date and time. 	<ul style="list-style-type: none"> page 42 page 43 page 44 page 44 page 44
2. Review neurostimulation system information.	<ul style="list-style-type: none"> • Access the Start Session menu and select Start Session. • Review battery information and active program settings. • Check the Observations box for significant system events that have occurred. 	page 46
3. Review patient use data, if available.	<ul style="list-style-type: none"> • Access the Start Session menu and select Start Session to view percentage of time that therapy was turned on. • Access the Start Session menu and select Group Usage to view patient use data by group. • Access the Start Session menu and select Device Usage to view patient use data by day. 	<ul style="list-style-type: none"> page 46 page 47 page 47
4. Review data from the Seizure key.	<ul style="list-style-type: none"> • Access the Start Session menu and select Start Session. • Select the Clinician Notes button to view data from the Seizure key. 	page 49
5. If desired, enter clinician notes.	<ul style="list-style-type: none"> • Access the Start Session menu and select Start Session. • Select the Clinician Notes button. • Select anywhere in the text input box, confirm the cursor is positioned after any existing notes, then use the keyboard to enter notes. 	page 49
6. If desired, program using Manual Programming.	<ul style="list-style-type: none"> • Proceed to the instructions under Review/Modify Stimulation Parameters. • When finished, proceed to the instructions under Customize Device Settings. 	page 54
Check system performance:		
1. Ensure that the neurostimulator is on.	<ul style="list-style-type: none"> • If the neurostimulator is off, hold the programming head steady over the neurostimulator, select the Neurostimulator on button to turn the neurostimulator on. 	page 50
2. Check neurostimulator battery information.	<ul style="list-style-type: none"> • Access the Start Session menu and select Start Session. • Review the neurostimulator service life. 	page 54

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Table 7. Basic programming steps (continued)

Procedure:	Do this:	Refer to:
3. Check electrode impedance. Note: Perform this procedure at the beginning of the session. These measurements verify the integrity of lead/extension/connector pathways.	<ul style="list-style-type: none"> • Access the Measurement menu and select Electrode Impedance. • Select the hemisphere for the measurement. • Select the settings and electrodes for the measurement. • Take the measurement. • Review electrode impedance measurement results. • Repeat the electrode impedance measurement for the opposite hemisphere. <p>Note: This procedure takes approximately 1 minute. In order to perform measurements, this procedure temporarily reprograms the stimulation settings.</p>	page 51
4. Check therapy impedance, if desired. Note: Perform this procedure at the end of the session. These measurements provide documentation that pathways are intact and the current provided is sufficient for the selected therapy.	<ul style="list-style-type: none"> • Access the Measurement menu and select Therapy Impedance. • Select the group for the measurement. • Take the measurement. • Review impedance and stimulation current/voltage results. • Repeat for additional groups. 	page 52
Review/modify stimulation parameters:		
1. Select a group and a program.	<ul style="list-style-type: none"> • Access the Programming menu and select Manual Programming. • If more than one group is defined, select a group. • Activate the group (if it is not active). • Select a program tab. 	page 54
2. Review/modify electrode polarities.	<ul style="list-style-type: none"> • Use the stylus to select negative (-), positive (+), or off electrode polarities for the selected lead and case. 	page 58
3. Review/modify rate and pulse width.	<ul style="list-style-type: none"> • Select the rate input box, then select a rate. • Select the pulse width input box, then select a pulse width. 	page 59
4. Review/modify amplitude resolution and amplitude.	<ul style="list-style-type: none"> • Select the amplitude input box and select an amplitude resolution setting and, if desired, an amplitude auto increase setting. 	page 60
5. Modify amplitude mode.	<ul style="list-style-type: none"> • Check therapy impedance. • Select the amplitude input box and select an amplitude mode. 	page 62
6. If desired, review stimulation parameters for all programs in each group.	<ul style="list-style-type: none"> • Access the Programming menu and select Group Summary. • Review the stimulation parameters for all programs in the selected group. • Select other groups to review. 	page 55
7. If desired, review/modify Cycling.	<ul style="list-style-type: none"> • Access the End Session menu and select End Session. • If more than one group is defined, select a group. • Select the Cycling input box. • If needed, select the checkbox to turn the feature on. • Select Cycling ON and OFF Time values. 	page 64
Customize device settings:		
The following feature is optional and is designed to increase patient comfort and ease of use.		

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Table 7. Basic programming steps (continued)

Procedure:	Do this:	Refer to:
1. If desired, review/modify SoftStart/Stop.	<ul style="list-style-type: none"> • Access the Programming menu and select Manual Programming. • If more than one group is defined, select a group. • Activate the group (if it is not active). • Select a program tab. • Select the SoftStart/Stop input box, then select a value. 	page 65
Program the neurostimulator for patient control:		
1. Review/modify patient control limits.	<ul style="list-style-type: none"> • Access the End Session menu and select Patient Programmer. • If more than one group is defined, select a group. • Select a patient control mode. • If using Advanced Mode, select a parameter and the level of patient control. • If using View and Adjust level of control, select the Set Limits button and set parameter limits. 	page 69
2. Program patient reminder.	<ul style="list-style-type: none"> • If needed, select the checkbox to turn the feature on. • Select the patient reminder time input box, then select a time. 	page 70
3. Set Seizure mode using the Medtronic Intercept Model 37441 Patient Programmer. Note: This procedure must be done using the Medtronic Intercept Model 37441 Patient Programmer.	<ul style="list-style-type: none"> • Press the Selection keys on the patient programmer simultaneously. • Navigate to the Seizure mode set up screen. • Select Cycling Reset on or Cycling Reset off. 	page 71
Complete the programming session:		
1. Review programmed settings.	<ul style="list-style-type: none"> • Access the End Session menu and select End Session. • Review the programmed settings. • To review detailed programmed settings, access the Programming menu and select Group Summary. 	page 72
2. If desired, enter clinician notes.	<ul style="list-style-type: none"> • Select the Clinician Notes button. • Select anywhere in the text input box, then use the keyboard to enter notes. 	page 49
3. Print report.	<ul style="list-style-type: none"> • Ensure that the printer is on. • Access the End Session menu and select Print Reports. • Select the desired reports in the print now column. • Move the programmer to within 1 meter of the printer, with the printer and programmer IR ports directly facing each other. • Select the Print button. 	page 73
4. Exit application.	<ul style="list-style-type: none"> • Access the End Session menu and select Exit. • Select the OK button. 	page 74

Preparing for a programming session

Before beginning a programming session, insert the appropriate application card, turn the programmer on, check the programmer battery status, and navigate to the neurostimulation application.

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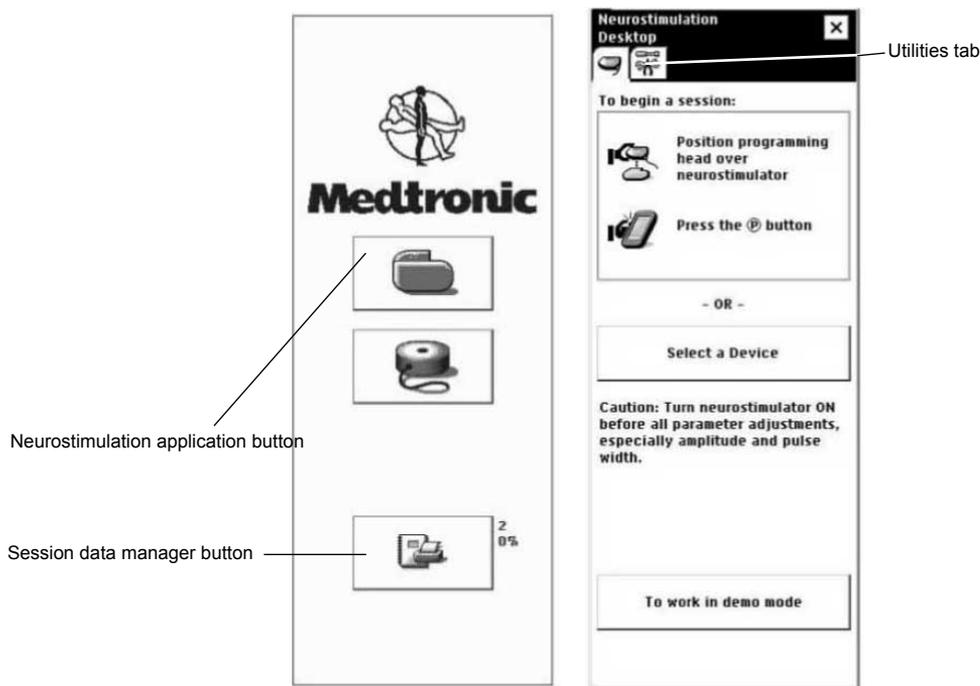


Figure 14. Application Selection and Neurostimulation Desktop screens.

Preparing for a programming session

For information on battery status, refer to "To check neurostimulator battery information" on page 54. For information on changing the programmer batteries refer to "To replace the programmer batteries" on page 94.

Before beginning a programming session, insert the appropriate application card, turn the programmer on, check the programmer battery status, and navigate to the neurostimulation application.

◆ To insert and eject the application card

1. Insert the application card (arrow and bar code side facing up and in the direction of the arrow) into the card slot until it is seated (Figure 15).
△ **Caution:** To avoid damaging the components, do not force the application card into the clinician programmer and do not insert non-Medtronic application cards.
2. To lock the application card in place, pull out the **Application card ejection** key, then flip it down and to the side so that it is flush with the opening.

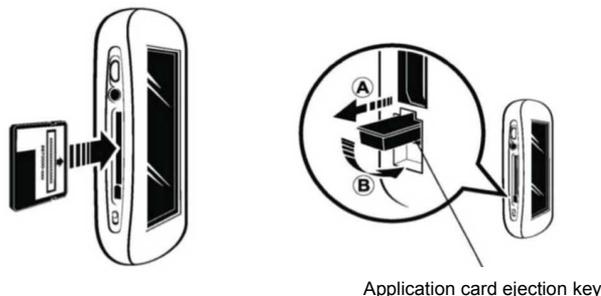


Figure 15. Inserting the application card.

3. To eject the application card, reverse the instructions in step 2, then push in the **Application card ejection key**.

Note: Do not remove the application card while the programmer is on. If the application card must be ejected, turn the programmer off, reinsert the card, then turn the programmer on.

△ **Caution:** Do not remove the application card while the application is active. If the application card is removed while the application is active, the session will automatically end and unsaved data will be lost.

◆ **To turn the programmer on or off**

- Slide and momentarily hold the **Power key** (⏻) (Figure 1 on page 10).

◆ **To check programmer battery status**

- View the battery status icon on the status bar.

Note: For information on battery status and changing the programmer batteries, see "To replace the programmer batteries" on page 94.

◆ **To navigate to the Neurostimulation Desktop screen**

1. Turn the programmer on. The **Application Selection** screen appears (Figure 14 on page 38).
2. Select the **Neurostimulation application** button (📄). The **Neurostimulation desktop** screen appears (Figure 14 on page 38).

Transferring patient information

Patient data and session data are copied from one application card to another with the Copy Patient Data feature on the **Utilities** tab. Depending on the neurostimulator implanted, the data copied include:

- Patient ID and lead configuration data.
- Session reports.

Note: Data saved on the **Clinician Notes** screen, including seizure information, will not be copied from one application card to another.

◆ **To transfer patient information**

1. Ensure the **destination** card (Application Card 1) is inserted in the programmer.
2. From the **Neurostimulation Desktop** screen (Figure 14 on page 38), select the **Utilities** tab.
3. Select the **Copy Patient Data** button (Figure 16).

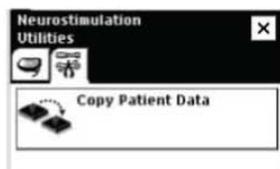


Figure 16. Utilities tab.

4. Select the checkbox for the type of data to be copied (Figure 17).
 - a. Select the Patient data checkbox to add patient ID and lead configuration information from the source card to the destination card.
 - b. Select the Session data checkbox to add patient reports stored on the source card to the destination card.

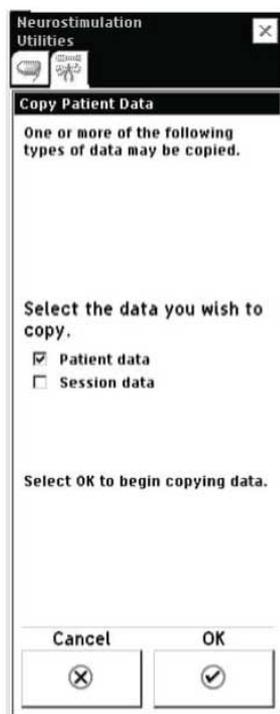


Figure 17. Copy Patient Data screen.

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5. Select the **OK** button to begin copying data.
6. When prompted, remove Application Card 1 and insert the **source** application card (Application Card 2).
7. When prompted, remove Application Card 2 and reinsert Application Card 1.
8. Repeat steps 6 and 7 when prompted.
9. The card copy will notify you when the copy is complete. The files that were copied onto the destination card can now be used in a programming session.

Interrogating the neurostimulator

Interrogating the neurostimulator begins a programming session. When the neurostimulator is interrogated, the programmer identifies the neurostimulator model and reads the current neurostimulator parameters.

△ **Cautions:**

- To use the nonsterile clinician programmer in a sterile field, place a sterile barrier between the patient and the programming head to prevent infection. Do not sterilize any part of the clinician programmer. Sterilization may damage the programmer.
- To ensure successful telemetry, hold the programming head steady over the neurostimulator until telemetry is complete. If telemetry is interrupted before programming is complete and telemetry cannot be reestablished, the session will end and any unsaved data will be lost.
- Do not attempt telemetry near equipment that may generate electromagnetic interference (EMI). If EMI disrupts programming, move the programmer away from the likely source of EMI. Examples of sources of EMI are magnetic resonance imaging (MRI), lithotripsy, computer monitors, cellular telephones, x-ray equipment, and other monitoring equipment.

◆ **To interrogate the neurostimulator**

1. Navigate to the **Neurostimulation Desktop** screen (Figure 14 on page 38).
2. Position the programming head over the neurostimulator.
Note: If the programming head is docked on the programmer, position the programmer so that the programming head is closest to the neurostimulator.
3. Hold the programming head steady over the neurostimulator, then press the **Programming** key (P) or use the stylus to select anywhere in the To Begin a Session box.
4. If the programming head is extended, a status light is visible on the back of the programming head:
 - **Green light flashing**—Telemetry is successful.
 - **Amber light flashing**—Telemetry is unsuccessful. An error message appears on the screen (see the appropriate “Telemetry Failure” message in Table 10 on page 80 for more information).

Entering patient and physician information

The programmer provides two fields for patient information, a drop-down list for patient diagnosis, two fields for physician information, and a field for physician notes. The patient and physician information is stored in the neurostimulator.

◆ To enter patient information

1. Access the **Profile** menu () and select Patient Data.
2. Enter patient name, ID number, or any other appropriate information in the patient ID fields (Figure 18).

Note: The patient session name includes the information from the first patient ID field. The patient session name will appear at the bottom of every screen and on session reports.

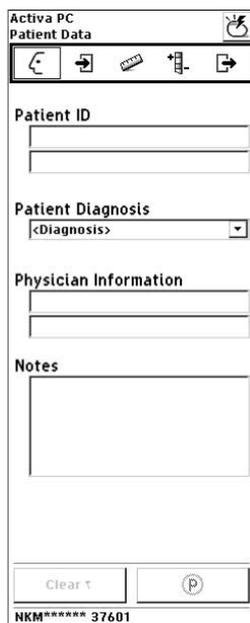


Figure 18. Patient data screen.

Note: The Patient Diagnosis drop-down list does not include epilepsy. Diagnosis information can be added on the **Clinician Notes** screen. Refer to "Entering clinician notes" on page 49 for more information.

3. Enter physician name and phone number or any other appropriate information in the physician information fields and notes field (Figure 18).
4. Hold the programming head steady over the neurostimulator, then press the **Programming (P)** key or select the **Program (P)** button on the programmer screen.

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Entering device information

The Medtronic DBS System for Epilepsy uses the Medtronic Activa PC Model 37601 Neurostimulator, a 4-electrode lead, and an 8-4 extension (allowing connection of the 4-electrode lead to the 8-contact port of the neurostimulator). The electrodes in the Activa PC Neurostimulator are numbered 0-7 on the front (left) side and 8-15 on the back (right) side. Only the first four electrodes (0-3 in the front socket and 8-11 in the back socket) in each of the neurostimulator sockets will be used (Figure 19). The Activa PC software defaults to the correct lead configuration for Medtronic DBS Therapy for Epilepsy.

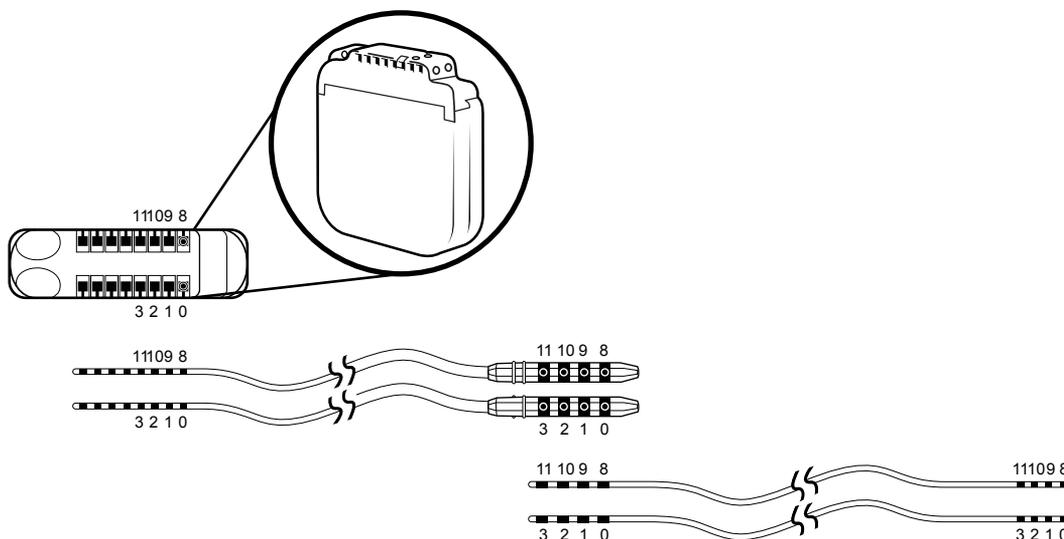


Figure 19. Medtronic DBS System for Epilepsy electrode configuration.

◆ To program lead configuration

Changing the lead configuration or numbering will delete all parameter settings and session information associated with the current lead configuration. Only physician information and notes, patient ID, and neurostimulator information will be retained.

1. Access the **Profile** menu () and select Lead Configuration.
2. Select the appropriate lead configuration from the lead configuration drop-down list (Figure 20).

Notes:

- Typically, the correct lead configuration for DBS Therapy for Epilepsy is 2x4 with Lead I located in the left hemisphere and numbered 0-3 and Lead II located in the right hemisphere and numbered 8-11. The software defaults to this lead configuration.
- For DBS Therapy for Epilepsy, it may be helpful to program the left and right lead assignments during implant when the lead-extension location can be confirmed.

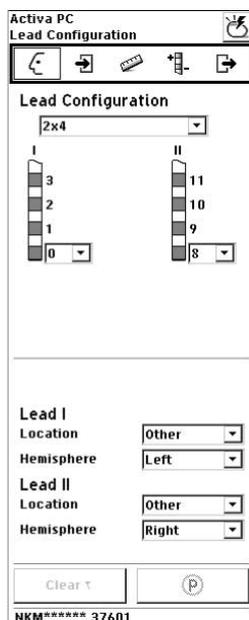


Figure 20. Lead Configuration screen.

3. If appropriate, renumber the electrodes using the electrode numbering drop-down list (if lead connection to the neurostimulator is different than pictured).
4. Select the lead location(s) and hemisphere(s) for each lead from the drop-down lists (Figure 20). Epilepsy-specific lead locations are not listed in the drop-down lists. "Other" can be used instead.

Note: The program name includes the hemisphere and location entered on the **Lead Configuration** screen. The program name will appear on the program tab.

5. Hold the programming head steady over the neurostimulator, then press the **Programming (P)** key or select the **Program (P)** button on the programmer screen.

Electrode selection may be confirmed by measuring electrode impedance before completing the programming session. Refer to "Checking system performance" on page 50 for more information.

◆ **To enter lead model number**

1. Access the **Profile** menu () and select Lead Data.
2. Enter lead model numbers in the lead model number fields.
3. Hold the programming head steady over the neurostimulator, then press the **Programming (P)** key or select the **Program (P)** button on the programmer screen.

◆ **To enter neurostimulator information**

1. Access the **Profile** menu () and select Device Data.

2. Select the date and time input field to view the current date and time stored in the neurostimulator (Figure 21). To reset the date and time use the **increase** and **decrease** buttons or use the **Match N'Vision** button.

Note: The date and time stored in the neurostimulator are used when collecting patient use data and when programming the patient reminder.

Activa PC
Device Data

Neurostimulator
Model Number 37601
Serial Number NKM*****

Date and Time
10/17/2008
09:13:48

Location
Chest Left

Implantation Date
10/17/2008

About Device...

Clear

NKM***** 37601

Figure 21. Device Data screen.

3. Select the neurostimulator implant location from the drop-down list or add another location (Figure 21).
4. Enter the date the neurostimulator was implanted by selecting the implantation date input box (Figure 21) then selecting a date.
5. Hold the programming head steady over the neurostimulator, then press the **Programming (P)** key or select the **Program (P)** button on the programmer screen.

Entering baseline diagnosis information

The baseline diagnosis screen is available from the **Profile** menu () and is not intended for use with patients who have epilepsy. Diagnosis information can be added to the **Clinician Notes** screen (refer to "Entering clinician notes" on page 49).

Reviewing patient use information

Patient use data are information about how the patient is using the neurostimulator. The neurostimulator collects patient use data between sessions. The collected data can also be viewed by group or by day.

The neurostimulator collects the data based on the date and time entered on the **Device data** screen (refer to "To enter neurostimulator information" on page 44).

Note: Patient use information can be viewed throughout the programming session by accessing the **Start Session** menu. Programming changes made during the session are not updated on the screens associated with this menu.

◆ **To review neurostimulation system information**

1. Access the **Start Session** menu () and select Start Session.
2. Review the Observations box for significant system events that have occurred (Figure 22). The observations are brief notifications (eg, Check INS clock, Stimulation off) that need to be investigated (refer to Table 9 on page 78).

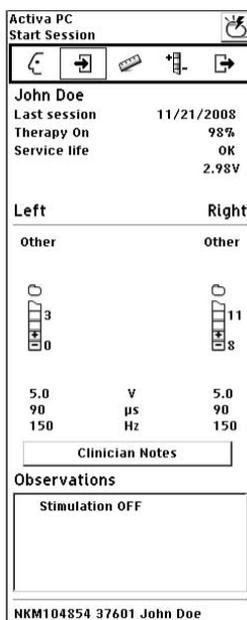


Figure 22. Start Session screen.

3. Check the Service Life and battery voltage for the neurostimulator.
4. For additional information on checking battery status, refer to "To check neurostimulator battery information" on page 54.

◆ **To review patient use data by Therapy On percentage**

1. Access the **Start Session** menu () and select Start Session.

2. View the Therapy On percentage (the percentage of neurostimulator On Time since the last follow-up session).

Note: When the Cycling feature is enabled, Cycling OFF Time is included in the Therapy On percentage. Refer to "To review/modify Cycling" on page 64.

◆ **To review the patient use data by group**

1. Access the **Start Session** menu () and select Group Usage¹.
2. Review the group use data.

◆ **To review the patient use data by day**

1. Access the **Start Session** menu () and select Device Usage.
2. Review the patient use data per day on the calendar.
3. Select a specific day on the calendar to view the patient use data in detail for that day. Events displayed include:
 - Active groups
 - Stimulation On periods
 - Periods when data may be inaccurate due to time changes

Reviewing data from the Seizure key

Data from the **Seizure** key on the patient programmer appears as two lines of text on the **Clinician Notes** screen (Figure 23). The first row displays data from the **Seizure** key when Cycling Reset was turned on. The second row displays data from the **Seizure** key when Cycling Reset was turned off. Refer to "Setting Seizure mode" on page 71 for more information about Seizure mode and the Cycling Reset feature.

Note: Reviewing data from the Seizure key was not a feature that was used in the SANTÉ study.

¹ Only available if a group is activated.

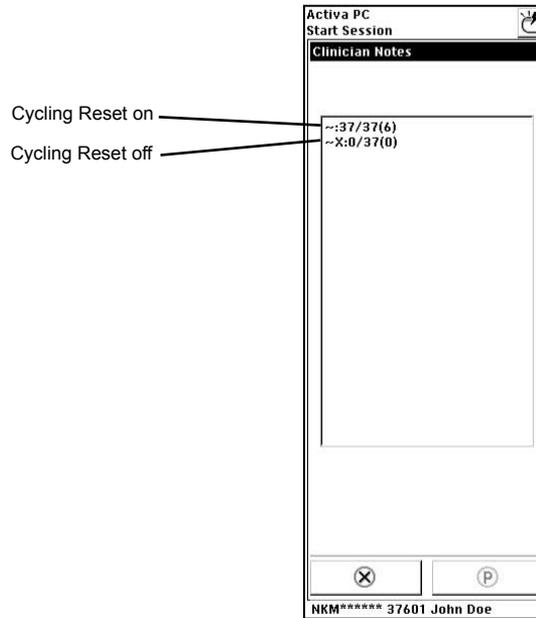


Figure 23. Data from the **Seizure** key displayed on the **Clinician Notes** screen.

The sample data from the **Seizure** key shown in Figure 24 indicates that the **Seizure** key was pressed a total of 37 times since the last programming session. It was pressed 37 times with Cycling Reset turned on, and 6 times with Cycling Reset turned on and stimulation turned off. It was pressed 0 times with Cycling Reset off, and 0 times with both Cycling Reset off and stimulation off.

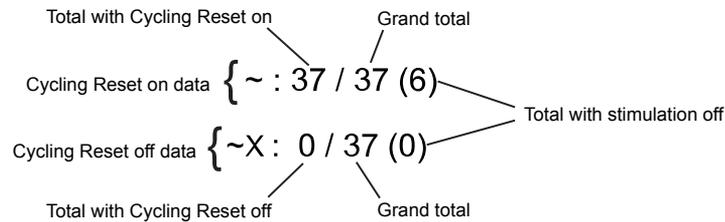


Figure 24. Sample data from the **Seizure** key.

Refer to Table 8 for a description of the data from the **Seizure** key displayed on the **Clinician Notes** screen.

Table 8. Description of data from the **Seizure** key displayed on the **Clinician Notes** screen

Text element	Definition	Description
~:	Cycling Reset on	<ul style="list-style-type: none"> This icon indicates that the data that follows was recorded when Cycling Reset was turned on.
~X:	Cycling Reset off	<ul style="list-style-type: none"> This icon indicates that the data that follows was recorded when Cycling Reset was turned off.
##	Seizure key count	<ul style="list-style-type: none"> The number before the slash indicates the number of times the Seizure key was pressed in the mode of the given row. The number after the slash indicates the total number of times the Seizure key was pressed since the last programming session.
(#)	Stimulation off count	<ul style="list-style-type: none"> The number in parentheses indicates the number of times the Seizure key was pressed in the mode of the given row while stimulation was turned off.

Compare the data from the **Seizure** key to the data recorded during the patient's last programming session. Identical numbers could indicate that the patient has not been using the **Seizure** key. You should also compare the data from the **Seizure** key to the patient's paper seizure log. When finished reviewing the data from the **Seizure** key, reset the **Seizure** key count to zero. Refer to "To reset the patient programmer seizure count to zero" on page 73 for more information.

Note: If more than one patient programmer has been used to record a seizure event since the last programming session, only the data from the patient programmer that was used last will appear.

◆ **To review use data from the Seizure key**

1. Access the **Start Session** menu () and select Start Session.
Note: The **Clinician Notes** screen may also be reached from the **End Session** menu.
2. Select the **Clinician Notes** button.
3. Review the data from the **Seizure** key on the **Clinician Notes** screen (Figure 23).
4. Select the **Cancel** button () to exit the screen.

Entering clinician notes

The data from the **Seizure** key appears on the **Clinician Notes** screen. Other data can also be recorded on the **Clinician Notes** screen. Always enter any new data after the data from the **Seizure** key and any existing notes to avoid interrupting the presentation of data.

◆ **To enter data on the Clinician Notes screen**

1. Access the **Start Session** menu and select Start Session.
Note: The **Clinician Notes** screen may also be reached from the **End Session** menu.
2. Select the **Clinician Notes** button.
3. Select anywhere in the text input box.
4. Confirm that the cursor appears after the data from the **Seizure** key and any existing notes.

5. To enter data, select each character on the keyboard.
6. Select the **Program (P)** button on the programmer screen to save the data.

Turning the neurostimulator on or off

Turning the neurostimulator on allows the neurostimulator to deliver stimulation to the patient. Before changing any parameters during a session, turn the neurostimulator on.

◆ *To turn the neurostimulator on or off*

- Select the **Neurostimulator on/off** button to turn the neurostimulator on () or off (.

Checking system performance

Recommendations when using measurement functions

The measurement functions assist in identifying problems with system components or the entire implanted system.

Measurements and diagnostic data obtained from the clinician programmer are intended to aid in your clinical management. However, as with any electronic system, internal and external factors can influence neurostimulator measurements.

- If you obtain a reading that seems inconsistent with your previous patient data, repeat the measurement.
- Use the measurement functions in combination with other clinical methods to test the system performance, including x-ray or fluoroscopy, observation of side effects, and efficacy of the therapy settings.

Before using any measurement functions, please note the following:

- **Measure electrode impedance at the beginning of each programming session.** These measurements provide information regarding the integrity of the lead/extension, connector pathways, and potential problems such as broken conductors, a short circuit, an open circuit, or problems with electrode configuration or numbering. For example, measurements that show a significant increase in impedance can indicate a broken conductor, a loose setscrew, etc. Conversely, a significant decrease in impedance can indicate shorted conductors, a breach in lead insulation, etc. Measurements taken at the beginning of the session may be useful in interpreting diagnostic data collected during previous clinic visits.
 - **Measure therapy impedance at the end of each programming session.** Measurements that are within normal limits indicate that the conduction pathways are intact.
- △ **Caution:** DO NOT rely solely on the results of impedance testing for troubleshooting. Accuracy of the data generated during impedance tests can fluctuate based on the neurostimulator that is being tested and on the programmed therapy settings. Test for possible open and short circuits by measuring

electrode impedance on all electrodes and the case. If an open or short circuit is suspected, repeat electrode impedance measurements, testing all electrodes in both unipolar and bipolar configurations.

◆ **To check electrode impedance**

During the electrode impedance test, preset rate and pulse width values are used. The preset values are displayed on the settings screen. The amplitude value can be modified for the electrode impedance test by choosing an amplitude value from the drop-down list on the **Electrode impedance settings** screen. Typically the lowest settings possible to successfully complete the test should be used. At the end of the test, the most recently programmed settings are restored.

Notes:

- The electrode impedance measurement delivers a short sequence of pulses to each possible electrode pair, one after another. This can potentially cause transient unexpected effects. The measurement can be stopped at any time using the **Therapy-Stop** key or **Cancel** button. All measurements recorded prior to selection of the **Therapy-Stop** key or **Cancel** button will be displayed on the **Electrode impedance** screen.
- If amplitude is programmed too low, the electrode impedance measurement will result in an out-of-range reading.

1. Access the **Measurement** menu () and select Electrode Impedance.
2. Select the Left (hemisphere) tab or the Right (hemisphere) tab (Figure 25).

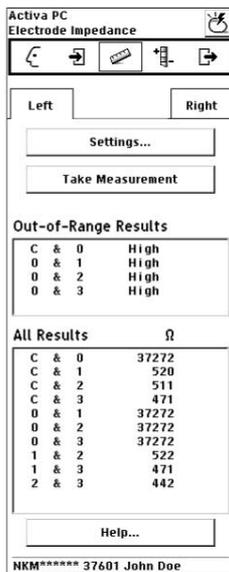


Figure 25. Electrode Impedance screen.

3. Select the **Settings** button (Figure 25).
4. Select an amplitude value from the drop-down list (Figure 26).

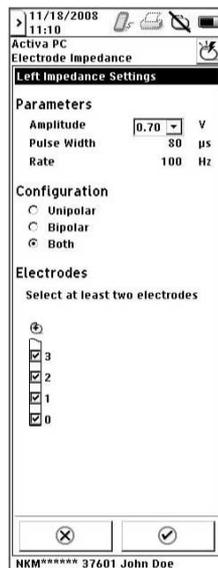


Figure 26. Electrode impedance settings screen

5. Select an electrode configuration option (Figure 26).
6. Select the electrode(s) to test.
7. Select the **OK** button (✓).
8. Position the programming head over the neurostimulator, then select the **Take measurement** button (Figure 25 on page 51).
9. Select the **OK** button (✓) and maintain the position of the programming head over the neurostimulator for the duration of the test.

Note: To stop the electrode impedance test, do one of the following:

- Select the **Cancel** button (✕).
- Push the red **Therapy-stop** key (⏏) to turn the neurostimulator off.

10. Review the electrode impedance test results.

Note: If any measurements are above the range for the selected amplitude setting, a prompt appears to repeat the high measurement at the next higher amplitude setting.

11. For additional information about electrode impedance results, select the **Help** button (Figure 25 on page 51), then select one of the options from the drop-down list.

Note: Test results can be viewed any time during the programming session by returning to the **Electrode Impedance** screen.

◆ **To check therapy impedance**

Therapy measurements are impedance and stimulation current measurements taken at the programmed settings for each program.

Notes:

- Under some conditions, such as low amplitudes (less than 0.25 V or 0.4 mA) or narrow pulse widths, a measurement cannot be obtained.
 - Using shared electrodes may affect accuracy when measuring therapy impedance.
 - The neurostimulator reports current measurement values as current delivered during the stimulation pulse instead of current averaged over the rate period. Current measured during the stimulation pulse will have higher values than current that is averaged over the rate period.
1. Access the **Measurement** menu (☰) and select Therapy Impedance.
 2. If more than one group is defined, use the **Group selection scroll** buttons to select a group (Figure 27).

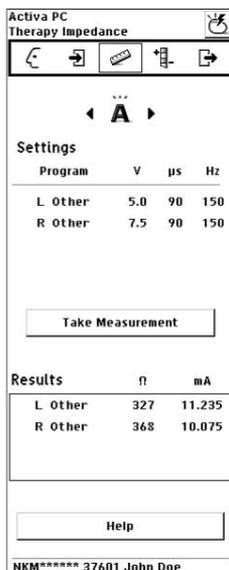


Figure 27. Therapy Impedance screen.

3. Position the programming head over the neurostimulator, then select the **Take measurement** button (Figure 25 on page 51).
4. Select the **OK** button (☑) and maintain the position of the programming head over the neurostimulator for the duration of the test.
Note: To stop the therapy impedance test, do one of the following:
 - Select the **Cancel** button (⊗).
 - Push the red **Therapy-stop** key (⏏) to turn the neurostimulator off.
5. Review the therapy impedance test results.

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6. For additional information about therapy impedance results, select the **Help** button (Figure 27), then select one of the options from the drop-down list.

Note: Test results can be viewed at any time during the programming session by returning to the **Therapy Impedance** screen.

◆ **To check neurostimulator battery information**

Upon each interrogation, the updated neurostimulator service life and the battery voltage information is displayed on the **Start Session** screen.

- Review the **Start Session** screen for the neurostimulator service life and battery voltage.
- If the neurostimulator battery status is low, the displayed service life will appear as ERI.

Note: You cannot repeat battery voltage measurement during the session. To remeasure the battery status, reinterrogate the device.

Returning to initial settings during programming

During a programming session, you can reset all parameters to values in effect at the start of the session. If you return to initial settings, however, you will lose all changes made to group and program parameters during the session.

Note: You will not be able to retrieve initial settings if you have changed the lead configuration during the session.

◆ **To return to initial settings**

1. Access the **Programming** menu () and select Initial Settings.
2. Hold the programming head steady over the neurostimulator, then select the **OK** button ().

Programming with groups and programs

To program stimulation parameters, a group must be selected and activated. Within an active group, 1 to 4 programs of stimulation (2 programs per hemisphere) may be programmed. All programs within a group must share the same amplitude mode (voltage mode or current mode). The program name that appears on the program tab includes the hemisphere and location entered on the **Lead Configuration** screen.

Note: Programming with groups and programs was not used in the SANTÉ study.

◆ **To select and activate a group**

1. Access the **Programming** menu () and select Manual Programming.

2. If more than one group is defined, use the **Group selection scroll** buttons to select a group (Figure 28).

Note: If only one group is defined, the group is automatically active and no letter or scroll buttons are displayed.

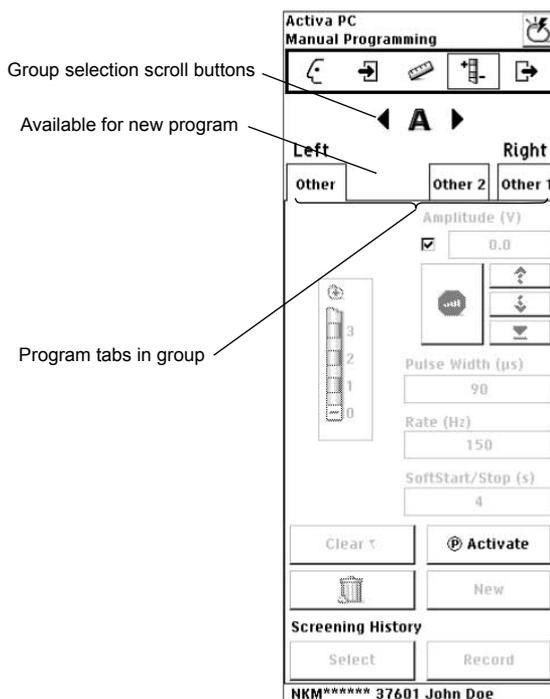


Figure 28. Programming screen.

3. To activate the group, hold the programming head steady over the neurostimulator, then press the **Programming (P)** key or select the **Activate** button on the programmer screen.

Reviewing group settings during programming

You can review stimulation parameter settings for all programs in a group on the **Group summary** screen at any time during programming. The settings on the **Group Summary** screen are updated throughout the session as programming changes are made.

Note: It is not necessary for the group to be active to view the group parameter settings.

◆ To review group settings

1. Access the **Programming** menu () and select Group Summary.

2. If more than one group is defined, use the **Group selection scroll** buttons to select a group (Figure 28).
3. Review the stimulation parameters for all programs in the selected group.
4. To review detailed settings for a specific program within a specific group, select and activate the group, then select the **Hot Link** button (Figure 29 on page 57) next to the program.

Note: The group must be active to access the **Hot Link** button.

◆ **To adjust amplitudes from the Group summary screen**

Note: Amplitude settings can also be adjusted from the program tabs (refer to "To review/modify amplitude resolution and amplitude" on page 60).

1. Access the **Programming** menu () and select Group Summary.
2. Select and activate a group (refer to "To select and activate a group" on page 54).
Note: The group must be active to adjust amplitude settings.
3. Hold the programming head steady over the neurostimulator and use the **Amplitude Adjustment** buttons (Figure 33) for the desired program.
Note: If electrode polarities have not been programmed, both **Amplitude Adjustment** buttons will be unavailable. Electrode polarities must be programmed before amplitude settings can be adjusted.
4. To temporarily make an active program inactive (temporarily set the amplitude to 0.0), hold the programming head steady over the neurostimulator and select the checkbox next to the amplitude value so the check mark is removed.

Note: To reactivate the program at the previous amplitude, hold the programming head steady over the neurostimulator and select the checkbox again.

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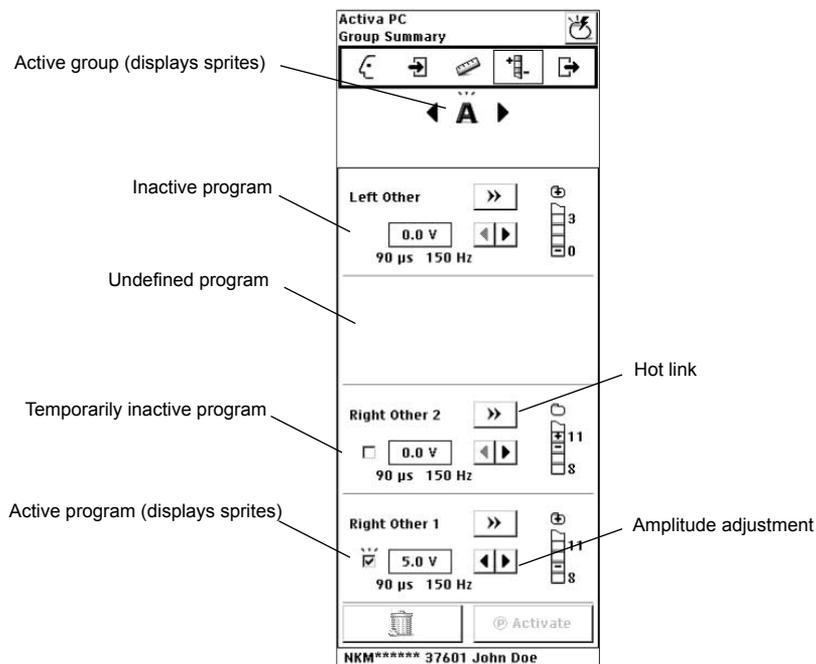


Figure 29. Group summary screen.

Reviewing/modifying stimulation parameters

Reviewing and modifying the stimulation parameters includes programming the electrode polarities, pulse width, amplitude resolution and amplitude for each program in a group. Rate is programmed for all programs in a group.

When changing therapy parameter settings, increase or decrease in small increments while evaluating the patient's response.

Note: If Cycling is enabled, the Cycling ON period restarts each time a parameter is adjusted. Refer to "To review/modify Cycling" on page 64 for more information.

△ **Caution:** Always decrease the amplitude to 0.0 before changing pulse width. After the change, slowly increase the amplitude to avoid unpleasant effects of stimulation to the patient.

Selecting and programming groups and programs – Refer to "Programming with groups and programs" on page 54 when selecting groups and programs to review/modify.

Using the scroll wheel for programming – If desired, the scroll wheel on the clinician programmer can be used to make fine adjustments when programming stimulation parameters. When a stimulation parameter value is selected with the stylus, the **Scroll wheel** icon () appears next to the selected parameter, indicating the value can be adjusted by the scroll wheel. See further instructions for using the scroll wheel in the sections on reviewing/modifying electrode polarities, pulse width and rate, and amplitude.

◆ **To review/modify electrode polarities**

The neurostimulator can be programmed in either a unipolar configuration or a bipolar configuration. When programming electrode polarity, electrodes may be programmed +, -, or off. Selecting and activating different combinations of electrodes allows therapy to be individualized for specific patient therapy needs. In current mode, only one electrode may be negative and one electrode or the case may be positive.

Note: There are no specific recommendations for polarity settings based on data from the SANTÉ study.

- Bipolar configuration:
 - In a bipolar configuration, at least one electrode is positive, one electrode is negative, and the case is off. (In current mode the configuration is limited to one negative electrode and one positive electrode.) Bipolar configurations are better suited for electrically “noisy” environments.
 - If only two neurostimulator electrodes are active, the longevity of the battery is generally longer than with unipolar configurations. However, if more than two electrodes are active, the battery longevity may be significantly shorter.
- Unipolar configuration:
 - In a unipolar configuration, at least one electrode is negative and the case is positive, the other electrodes can be either negative or off. (In current mode the configuration is limited to one negative electrode.)
 - An advantage of unipolar configurations is that lead positioning is less critical than with bipolar configurations. A disadvantage may be reduced longevity for the neurostimulator.

Notes:

- The use of cycling may cause a reduction in battery longevity depending on programmed settings.
- Activating more than the minimum number of electrodes in either unipolar or bipolar configurations spreads the stimulation over a greater area. This may reduce the battery longevity for the neurostimulator.
- An electrode may be unavailable for programming (X), if it is used by another program in the same hemisphere.
- The amplitude automatically changes to 0.0 when polarities are changed.

1. Access the **Programming** menu () and select Manual Programming.
2. Select and activate a group (refer to "To select and activate a group" on page 54).
3. Select a program tab.

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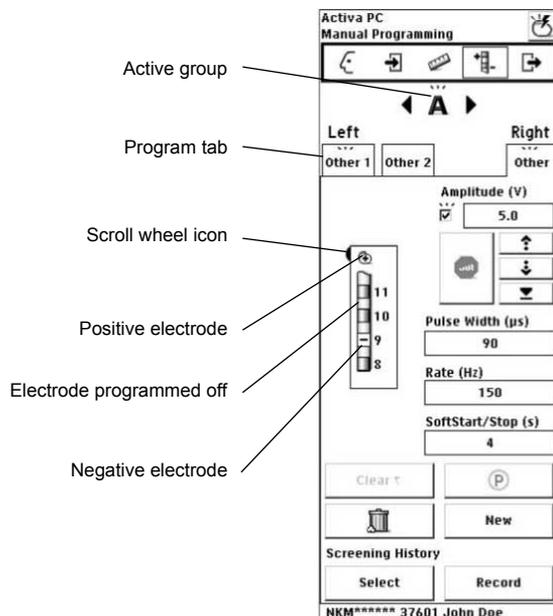


Figure 30. Programming electrode polarities.

4. Select the electrode -, +, or blank (off) options on the lead to be programmed. The **Scroll wheel** icon appears next to the selected lead input box (Figure 30).
5. If desired, turn the scroll wheel to move electrode polarity assignments up or down.
6. If desired, set other parameters on this screen (refer to "To review/modify the pulse width or rate" on page 59).

Note: When creating a new program, select electrode polarities and pulse width and rate values before programming amplitude.

7. Hold the programming head steady over the neurostimulator, then press the **Programming (P)** key or select the **Program (P)** button on the programmer screen.

◆ **To review/modify the pulse width or rate**

Pulse width is the duration of the pulses. Rate is the frequency of pulses in hertz.

Note: When using more than one program in a group, the rate is the same for all programs in the group.

1. Access the **Programming** menu () and select Manual Programming.
2. Select and activate a group (refer to "To select and activate a group" on page 54).
3. Select a program tab.
4. Select the pulse width input box or the rate input box (Figure 31).

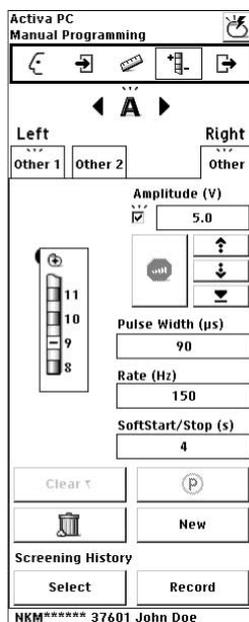


Figure 31. Programming pulse width or rate.

5. Select a target value from the list of values that appears in the value window. The actual and target values appear in the input box with an arrow pointing from the actual value to the target value.
Note: Some values may not be available due to high-output interlocks (refer to "High-output interlocks" on page 26).
6. If desired, fine tune the target value by turning the scroll wheel to increase or decrease the target.
7. Hold the programming head steady over the neurostimulator, then press the **Programming (P)** key or select the **Program (P)** button on the programmer screen.

◆ **To review/modify amplitude resolution and amplitude**

Amplitude is the strength of the pulse. Amplitude can be programmed in either voltage (V) mode or current (mA) mode, but only one mode can be used within a group. Amplitude resolution is the size of the incremental or decremental steps during the time that the amplitude is ramping (increasing or decreasing) and when the patient adjusts the amplitude setting with the patient programmer. Amplitude auto increase is the time in seconds between the steps during ramping. If amplitude auto increase is programmed off, the amplitude value will not ramp.

Notes:

- Amplitude is automatically programmed when a target value is selected. Ramping to the new value begins immediately (if auto increase is not programmed off). This differs from pulse width and rate programming, which require the clinician to press the **Programming (P)** key or select the **Program (P)** button on the programmer screen before the new values take effect.

- Amplitude values may also be modified from the **Group summary** screen (refer to "To adjust amplitudes from the Group summary screen" on page 56).

1. Access the **Programming** menu () and select Manual Programming.
2. Select and activate a group (refer to "To select and activate a group" on page 54).
3. Select a program.
4. Select the amplitude input box (Figure 32).

Note: Electrode polarities must be programmed before amplitude can be programmed.

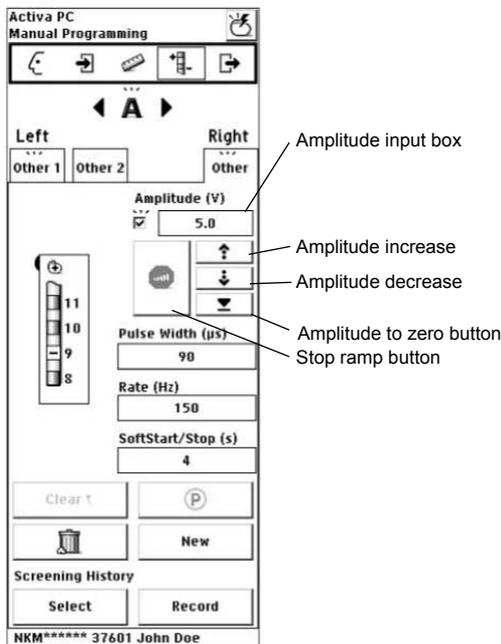


Figure 32. Programming amplitude.

5. Select the amplitude resolution, auto increase, and amplitude mode values (Figure 33).

Note: Changing the amplitude mode will clear all programs in the selected group.

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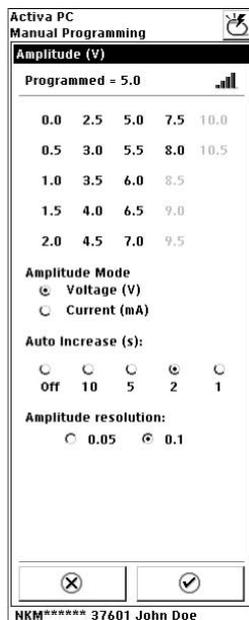


Figure 33. Selecting amplitude values.

6. To set amplitude, hold the programming head steady over the neurostimulator and select a target value from the amplitude values displayed (Figure 33).
 - a. If a value was selected for auto increase, ramping to the target value begins immediately, and the input box displays an arrow pointing from the actual value to the target value.
 - b. If auto increase is turned off, the amplitude must be programmed by selecting the **Program (P)** button on the programmer screen or **Programming (P)** key.

Notes:

- To stop the amplitude while it is ramping, select the **Stop** button or press the scroll wheel.
- To immediately set the amplitude to 0.0, hold the programming head steady over the neurostimulator and select the **Amplitude to zero** button.
- To temporarily set the amplitude to 0.0, hold the programming head steady over the neurostimulator and select the checkbox next to the amplitude value so the check mark is removed. To return to the original amplitude value, select the checkbox again.
- To go directly to the target amplitude, hold the programming head steady over the neurostimulator and select the **Program (P)** button on the programmer screen or **Programming (P)** key while the amplitude is ramping.

◆ **To modify amplitude mode**

Stimulation amplitude can be programmed in either current (mA) mode or voltage (V) mode. Only one amplitude mode can be used within a group. When changing amplitude modes, measuring the therapy impedance can indicate a comparable amplitude setting in the new mode only if a single anode (+) and cathode (-) are used. When changing from a voltage mode program with multiple anodes (+) or cathodes (-), a comparable current mode amplitude cannot be determined. Electrode selection must be modified and retitration to therapeutic effect will be necessary.

Changing the amplitude mode will reset all stimulation parameters in the selected group to default settings. Use the measured therapy voltage as the starting point for titration when changing to voltage mode and the measured therapy current as the starting titration point when changing to current mode.

1. Access the **Programming** menu () and select Manual Programming.
2. Select and activate a group (refer to "To select and activate a group" on page 54).
3. Confirm that each program uses only one anode (+) and one cathode (-).

Note: When changing amplitude modes, measuring the therapy impedance can indicate a comparable amplitude setting in the new mode only if a single anode (+) and cathode (-) are used.

4. Check the therapy impedance to determine the comparable voltage or current value (refer to "To check therapy impedance" on page 52).
5. Note the measured voltage or current (Figure 34). This value will be used in step 11.

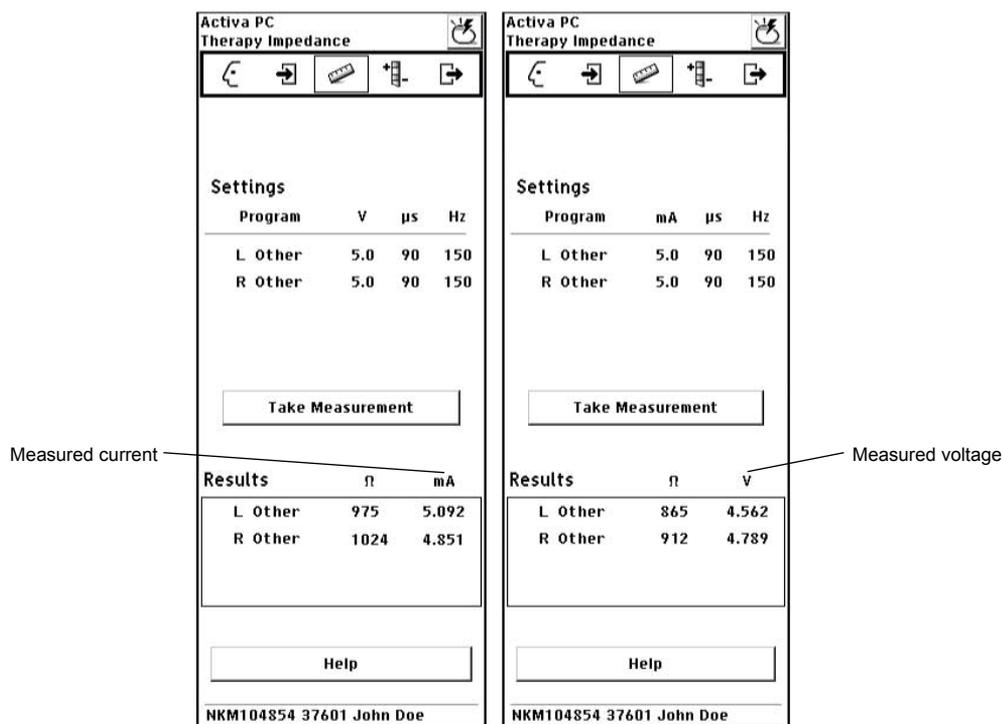


Figure 34. Therapy impedance measurements in voltage mode and current mode.

6. Access the **Programming** menu () and select Manual Programming.
7. Select a program tab in the active group.
8. Select the amplitude input box.

9. Select an amplitude mode.

Note: Only one amplitude mode can be used within a group. Changing the amplitude mode will clear all programs in the selected group.

10. Set the electrode polarities, pulse width, and rate (refer to "Reviewing/modifying stimulation parameters" on page 57).
11. Set the amplitude resolution and amplitude (refer to "To review/modify amplitude resolution and amplitude" on page 60).

Note: When using current mode, the OOR (Out Of Regulation) error message will appear if the amplitude is set too high. If OOR occurs while using current mode, switch to voltage mode.

◆ **To review/modify Cycling**

Cycling turns stimulation on and off at clinician-determined intervals (eg, 0.1 second to 24 hours). Cycling may extend battery life. During Cycling ON Time, the neurostimulator is on and is delivering stimulation. During Cycling OFF Time, the neurostimulator is on but is not delivering stimulation.

Note: The Cycling feature defaults to off. It must be enabled to program Cycling ON Time and Cycling OFF Time.

1. Access the **End session** menu () and select End Session.
2. If more than one group is defined, use the **Group selection scroll** buttons to select a group (Figure 41 on page 72).
3. Select the Cycling input box (Figure 41 on page 72).
4. Select the On radio button to enable the feature (if it is not active) (Figure 35).

Note: To disable Cycling, select the Off radio button.

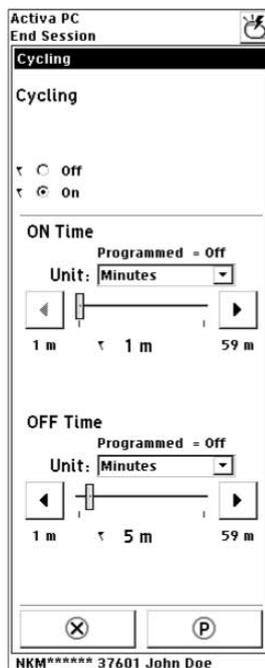


Figure 35. Programming Cycling.

5. Select units for ON Time and OFF Time (Figure 35).
6. Select the Cycling ON Time and the Cycling OFF Time.
7. Hold the programming head steady over the neurostimulator, then press the **Programming** (P) key or select the **Program** (P) button on the programmer screen.

Customizing device settings

The SoftStart/Stop feature is optional. This feature is designed to increase patient comfort and ease of use.

◆ To review/modify SoftStart/Stop

SoftStart/Stop allows a gradual increase in amplitude (up to the programmed value) as stimulation is turned on and a gradual decrease in amplitude (to 0.0) when stimulation is turned off. The slow ramping may feel more comfortable to sensitive patients.

1. Access the **Programming** menu () and select Manual Programming.
2. Select the SoftStart/Stop input box (refer to Figure 30 on page 59).
3. Select a setting, then select the **OK** button ().
4. Hold the programming head steady over the neurostimulator, then press the **Programming** (P) key or select the **Program** (P) button on the programmer screen.

Reviewing/modifying screening history

Screening history is available on the **Manual Programming** screen. It is not intended for use with patients who have epilepsy. Therapeutic effects and side effects of DBS Therapy for Epilepsy can be recorded on the **Clinician Notes** screen. Refer to "Entering clinician notes" on page 49.

Adding groups and programs

To provide additional therapy options for your patient, you may wish to add new groups or to add new programs to existing groups. You can create a new group (without programs) or import a group (with programs) from session history.

◆ *To add and activate a new group*

1. Hold the programming head steady over the neurostimulator, access the **Programming** menu (, and select New Group.

Note: Alternatively, select Group Summary, then scroll to an undefined group and select the **Create new group** button.

2. Select a program in the new group. Refer to "To select and activate a group" on page 54.
3. Select electrode polarities.
4. Hold the programming head steady over the neurostimulator, then press the **Programming** (P) key or select the **Program** (P) button on the programmer screen.

◆ *To add a second program to a hemisphere*

1. Access the **Programming** menu () and select Manual Programming.
2. Select and activate a group (refer to "To select and activate a group" on page 54).
3. Select a program.
4. Select the **New** button.

Note: A second program can only be added to a hemisphere if the electrode polarities have been programmed for the first program in that hemisphere.

5. Select electrode polarities.
6. Hold the programming head steady over the neurostimulator, then press the **Programming** (P) key or select the **Program** (P) button on the programmer screen.

Note: The rate limit is 250 Hz with only one program per hemisphere. Once either hemisphere has two programs, the rate for all programs is limited to 125 Hz.

◆ *To import a group from Session History*

1. Access the **Programming** menu () and select Session History.
2. Select a programming session date from the drop-down list (Figure 36).

3. If more than one group was defined on that date, use the **Group selection scroll** buttons to select a group (Figure 36).

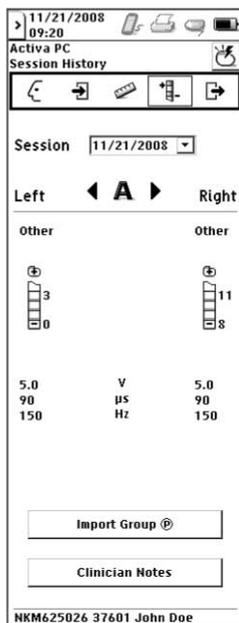


Figure 36. Importing a new group from session history.

4. Hold the programming head steady over the neurostimulator, then press the **Programming** (P) key or select the **Import Group** button on the programmer screen (Figure 36).
Note: The amplitude of the imported settings will automatically be set at 0.0 and Cycling mode will automatically be set to off.
5. A message appears naming the new group. Close the message window. The new group is added to the list of defined groups.

Deleting groups and programs

◆ *To delete a group*

1. Access the **Programming** menu () and select Group Summary.
2. Select an inactive group using the **Group selection scroll** buttons. Refer to "To select and activate a group" on page 54.
3. Select the **Delete** button ().

Notes:

- An active group cannot be deleted.
- When a group is deleted, its associated letter becomes available for creating a new group.

- When a group is deleted, all programs in the group are deleted.

◆ **To delete a program in a group**

1. Access the **Programming** menu () and select Manual Programming.
2. Select and activate a group (refer to "To select and activate a group" on page 54).
3. Select the program tab.
4. Select the **Delete** button ().
5. Hold the programming head steady over the neurostimulator and select the **OK** button ().

Programming a neurostimulator for patient control

Seizure mode and patient control limits for amplitude, pulse width, and rate can be set by the clinician and programmed to the neurostimulator before the patient leaves the clinic. The patient uses a patient programmer to record a seizure event, reset the stimulation cycle, and adjust the stimulation parameter values within the clinician-set limits.

Note: The Seizure key was not a feature that was used in the SANTÉ study.

There are two patient programmer modes: Simple Mode and Advanced Mode. If more than one group is programmed, only Advanced Mode is available.

Simple Mode allows the patient to record a seizure, reset the stimulation cycle (if programmed by the clinician), view battery status, adjust the preferences of the patient programmer, and turn stimulation on or off, but not access other stimulation settings.

Advanced Mode allows the patient to do everything that Simple Mode does and, in addition, access their stimulation settings. There are two options within Advanced Mode: (1) View and (2) View and Adjust. Selecting the View option allows the patient to only view their stimulation settings. The View and Adjust option allows the patient to also make adjustments to their stimulation settings.

Note: The patient can use the patient programmer to reset stimulation parameters to the original clinician settings. Patients can be sent home with a paper copy of their settings for reference when adjusting their therapy. Refer to "Printing session reports" on page 73 for more information.

To program the ranges in which a patient can adjust the amplitude, pulse width, or rate, you must set an upper limit value and a lower limit value for the stimulation parameter. Limits can be set for active or inactive groups. For amplitude and pulse width, program upper and lower limits individually for each hemisphere in a group. For rate, the programmed upper limit and lower limit will apply to both hemispheres and all programs in a group.

Patient control limits are tracking limits. Tracking limits automatically remain at a specified value above and below the programmed parameter value. Upper limits and lower limits change when the programmed value for amplitude, pulse width, or rate is changed with the clinician programmer. The patient is able to adjust only one parameter per group. Limits can be programmed for only that parameter. For example, if the upper limit for amplitude is +3, then the upper limit will always remain 3 greater than the amplitude value

programmed by the physician (up to the maximum allowable value). Similarly, if the lower limit for amplitude is -3, then the lower limit will be 3 less than the programmed amplitude value (down to the minimum allowable value).

◆ **To set amplitude, pulse width, or rate limits**

1. Access the **End Session** menu () and select Patient Programmer.
2. If more than one group is defined, use the **Group selection scroll** buttons to select a group.

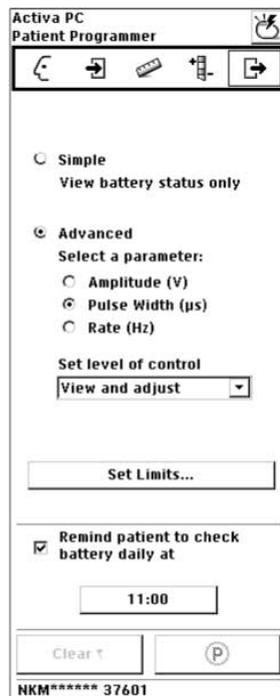


Figure 37. Programming patient control limits.

3. Select Advanced Mode (Figure 37).
4. Select a parameter.
Note: The patient is able to adjust only one parameter per group. Limits can be programmed for only that parameter.
5. Select View and Adjust from the drop-down list.
6. Select the **Set limits** button.
7. For bilateral therapy, select a hemisphere (for pulse width or amplitude limits) (Figure 38).
Note: The rate is the same for all programs in a group. Rate or rate limits cannot be programmed for individual programs.
8. If more than one program is available for that hemisphere, select the appropriate option to allow the patient to adjust settings for a specific program or for both programs (Figure 38).

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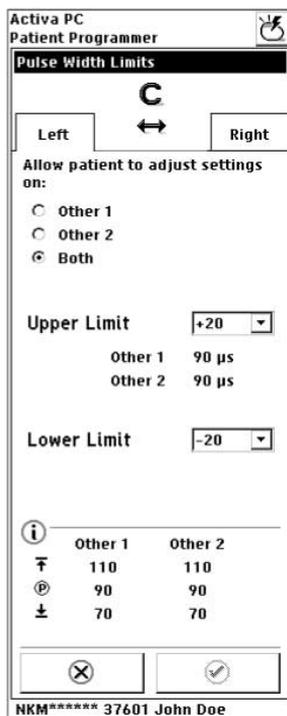


Figure 38. Programming parameter limits.

9. Select the limit value(s) using the drop-down list(s).

Note: The programmed values for each program are displayed between the Upper Limit drop-down list and the Lower Limit drop-down list. The calculated limit values (based on the tracking limits selected from the drop-down lists) are displayed in the information area at the bottom of the screen.
10. If desired, select the other hemisphere and program limit values.
11. Select the **OK** button (⏹).
12. Hold the programming head steady over the neurostimulator, then press the **Programming** (P) key or select the **Program** (P) button on the programmer screen.

◆ **To set the patient reminder**

The patient reminder is used to remind the patient to check the neurostimulator battery status at a specific time each day. If the patient has not checked the neurostimulator battery status before the programmed time, the patient programmer alerts the patient. If the patient has checked the neurostimulator battery before the programmed time, the patient programmer will not alert the patient.

Note: The patient reminder feature is initially set to off.

1. Access the **End Session** menu (⏹) and select Patient Programmer.
2. Select the checkbox next to the patient reminder to turn on the feature (if it is not active) (Figure 37 on page 69).

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3. Select the time input box.
4. Set the reminder hour and minute.
5. Hold the programming head steady over the neurostimulator, then press the **Programming (P)** key or select the **Program (P)** button on the programmer screen.

Setting Seizure mode

The patient programmer **Seizure** key records a seizure event every time it is pressed. It can be set up to reset Cycling and record a seizure event (Cycling Reset on) or to record a seizure event only (Cycling Reset off) every time it is pressed. The **Seizure mode set up** screen displays the active mode at the top of the screen. The icons at the bottom of the screen allow the user to change the setting.

Note: The **Seizure** key functions the same in both Simple Mode and Advanced Mode.

◆ To set Seizure mode using the Medtronic Intercept Model 37441 Patient Programmer

1. Press the **Power/Backlight On/Off** key to turn on the patient programmer (Figure 39).
2. Press and hold the **Selection** keys (Figure 39) at the same time until the next screen appears. The **lead connections** screen is displayed on the patient programmer.



Figure 39. Patient programmer keys

3. Press the left or right arrow on the **Navigator** key until you reach the **Seizure mode set up** screen (Figure 40).

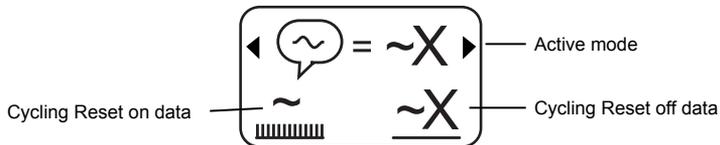


Figure 40. Seizure mode set up screen.

4. Press the appropriate **Selection** key (Figure 39) to set the Seizure mode to record a seizure event and reset Cycling (Cycling Reset on [\sim]) or to record a seizure event only (Cycling Reset off [\sim X]) each time the **Seizure** key is pressed.
5. The active mode appears at the top of the patient programmer screen.
6. Press the **Power/Backlight On/Off** key to turn off the patient programmer (Figure 39).

Completing the programming session

◆ To review programmed settings

A summary of neurostimulator settings programmed during the programming session are displayed on the **End Session** screen. Details of the settings are displayed on the **Programming** screen (Figure 28 on page 55).

1. Access the **End Session** menu (\rightarrow) and select End Session.
2. Review settings on the **End Session** screen (Figure 41).

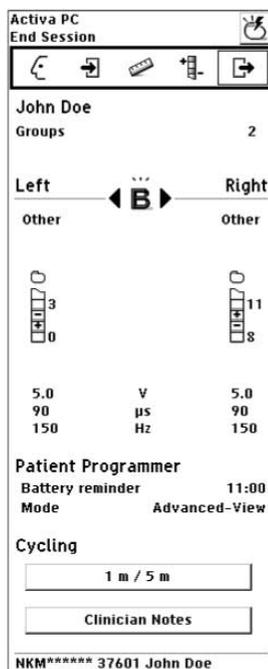


Figure 41. Reviewing programmed settings.

Notes:

- Check Cycling settings prior to exiting the application.
- Always check the patient control limit settings on the **Patient programmer** screen (in the **End Session** menu [\rightarrow]) prior to the patient leaving the office.

3. To correct settings or make changes, access the **Programming** menu ().

◆ **To reset the patient programmer seizure count to zero**

The data from the **Seizure** key in the clinician programmer and the **Seizure** key count in the patient programmer can be reset to zero upon exiting the programming session.

1. Access the **End Session** menu () and select Exit.
2. Hold the programming head steady over the neurostimulator, then select the **OK** button ().
3. Press the **Power** key to turn on the patient programmer.
4. Hold the patient programmer over the neurostimulator and press the **Check** key to confirm that the **Seizure** key count was reset to zero. If the **Seizure** key count does not change, hold the patient programmer over the neurostimulator and press the **Check** key again.

Ask the patient to wait in the clinic for a period of time after ending the programming session to monitor the patient for any immediate adverse events due to programming changes.

Printing session reports

Session reports contain the settings and patient and system information from patient sessions. You can print reports during and after patient sessions. The following reports can be selected for printing, depending on whether data exist for the report:

- **Session summary report**—neurostimulator data and history (this report is always available as indicated by the check mark by the title)
- **Measurements report**—battery information and results from the electrode impedance test and therapy impedance test
- **History report**—information on all programs in session and screening histories
- **Groups report**—group and program information
- **Device usage report**—use data since the last session
- **Patient report (for the patient)**—information on patient settings and available patient limits
- **MDT Data report**—data that can be provided to Medtronic Technical Services (this report is a separate file in the Session Data Manager)
- **All Reports**—all reports are selected for printing

◆ **To print a report during the session**

1. Ensure the printer is on.
2. Access the **End Session** menu () and select Print Reports.
3. Select the checkbox in the “Now” column next to the report on the list.
4. Move the programmer to within 1 meter (3.3 ft) of the printer, with the printer and programmer IR ports directly facing each other.

5. Select the **Print** button ().

◆ **To select a report for printing after the session**

Session summary reports and any other reports selected for printing after a patient session are saved as a single report in the Session Data Manager with the patient session name. This report or session data file is saved to the application card. You can print session reports from the Session Data Manager any time during or after the programming session.

1. Access the **End Session** menu () and select Print Reports.
2. Select the checkbox in the “Later” column next to the report on the list. The report will be available from the Session Data Manager.

Exiting the application

When you exit the application, the session settings and selected reports are saved to a session data file. Session data files are saved in the Session Data Manager.

◆ **To exit the application**

1. Access the **End Session** menu () and select Exit.
2. Hold the programming head steady over the neurostimulator, then select the **OK** button ().

Working with the Session Data Manager

As long as there is space on the application card, a new session data file is generated at the end of each programming session. Session data files are stored in the Session Data Manager.

The **Application Selection** screen displays the session data file status when the Model 8840 Clinician Programmer is turned on (Figure 42 on page 75):

- Number of files saved
- Percentage of memory used

If the percentage of memory used approaches 100% or a message that the Session Data Manager is full appears when the application is launched, delete unneeded files.

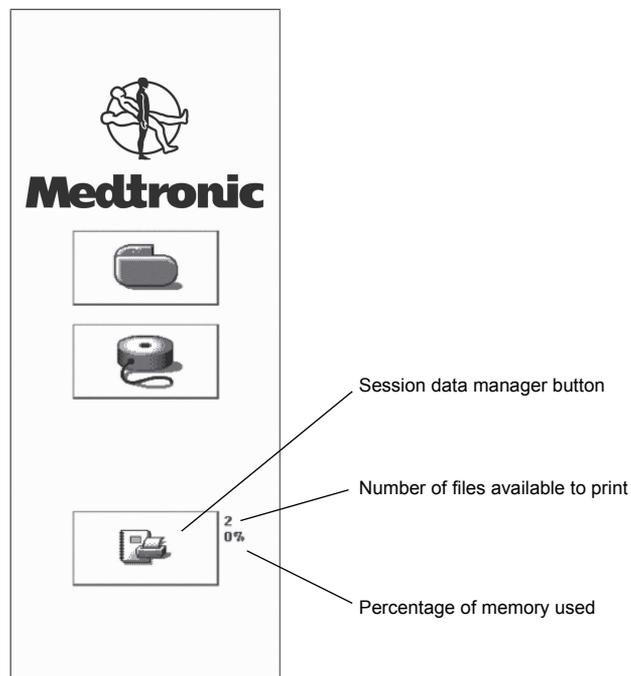


Figure 42. Application Selection screen.

◆ **To view a session report from the Session Data Manager**

1. Select the **Session Data Manager** button () from the slider bar.
2. Select a report from the **Session Data Manager** screen (Figure 43).
3. Select the **View** button ().

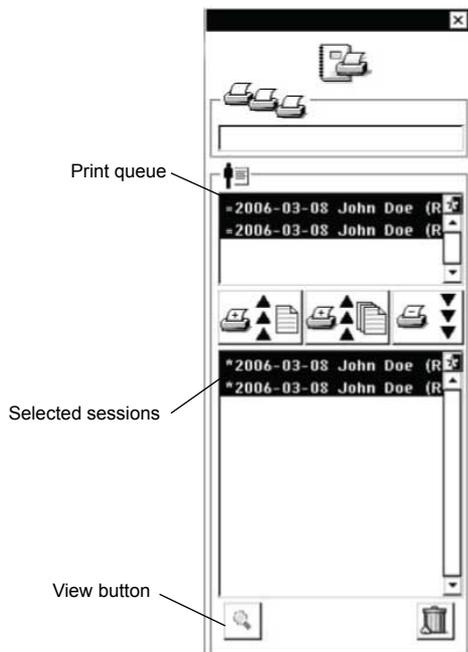


Figure 43. Session Data Manager screen.

◆ **To print a session report from the Session Data Manager**

1. Ensure that the printer is on.
2. Select the **Session Data Manager** button () from the slider bar.
3. Select the report(s).
 - a. Highlight report(s) from the session list to select one or more reports.
 - b. Select the **Select/Deselect all reports** button () to select or deselect all reports.
4. Move the programmer to within 1 meter (3.3 ft) of the printer, with the printer and programmer IR ports directly facing each other.
5. Select a print report button to move sessions into and out of the print queue:
 - a. Select the **Print Short Report** button () to print the summary report only.
 - b. Select the **Print Long Report** button () to print all reports that were selected from the **Print Reports** screen.
 - c. Select the **Remove From Print Queue** button () to move the report out of the print queue.

◆ ***To delete a session file from the Session Data Manager***

1. Select the **Session Data Manager** button (Figure 42) from the **Application Selection** screen or the slider bar.
2. Select a patient session or sessions.
3. Select the **Delete** button (.
4. Select the **Delete** button () again.

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Troubleshooting

This section covers troubleshooting and error messages relating to the Model 8840 Clinician Programmer with the Model 8870 Application Card.

Approach troubleshooting conservatively. Prior to performing invasive procedures, ensure that all noninvasive causes have been considered, and contact the appropriate Medtronic representative listed on the inside back cover of this manual.

Troubleshooting reference guide

Table 9. Quick reference troubleshooting guide

Problem	Possible solution	Refer to:
<ul style="list-style-type: none"> • The power is on, but there is no display. • The programmer cannot be operated. • Touchscreen does not respond. 	<ul style="list-style-type: none"> • Turn the programmer off, then on again. • Install new AA batteries in the programmer. Ensure the batteries are properly installed. • Calibrate touchscreen. 	<ul style="list-style-type: none"> page 39 page 94 page 96
<ul style="list-style-type: none"> • Telemetry is interrupted or not initiated. 	<ul style="list-style-type: none"> • Ensure that the application card is correctly inserted. • Check the battery status. • See the telemetry failure checklist. 	<ul style="list-style-type: none"> page 38 page 39 page 78
<ul style="list-style-type: none"> • Power to the programmer is suddenly interrupted. 	<ul style="list-style-type: none"> • Install new AA batteries in the programmer. 	<ul style="list-style-type: none"> page 94
<ul style="list-style-type: none"> • The programmer is not communicating with the printer. 	<ul style="list-style-type: none"> • Clean the IR lens. • Ensure that the programmer and printer are directly facing and within 1 meter (3.3 ft) of each other. • Contact the printer manufacturer for printer-specific troubleshooting information. 	<ul style="list-style-type: none"> page 95 page 73
<ul style="list-style-type: none"> • Telemetry cannot be established. 	<ul style="list-style-type: none"> • See the telemetry failure checklist. 	<ul style="list-style-type: none"> page 78
<ul style="list-style-type: none"> • The programmer is operating erratically. 	<ul style="list-style-type: none"> • Move away from any equipment (eg, MRI, lithotripter, computer monitor) that may be generating EMI. EMI may cause a disruption in programmer function. 	<ul style="list-style-type: none"> page 41
<ul style="list-style-type: none"> • An error message or icon appears on the display. 	<ul style="list-style-type: none"> • See instructions in the error and informational messages section. 	<ul style="list-style-type: none"> page 80

For clinician programmer maintenance questions, repairs, and returns, contact the appropriate Medtronic representative listed on the inside back cover of this manual.

Telemetry failure checklist

The most common corrections for telemetry failures are listed below. Refer to the telemetry messages described in Table 10 on page 80 for specific error message information.

- Decrease the distance between the programming head and the neurostimulator, pressing the programming head firmly over the implanted neurostimulator.
- Hold the programming head steady over the neurostimulator, then press the **Programming (P)** key or select the **Program (P)** button.

- If telemetry fails while holding the programming head steady, move the programming head around slowly near the implanted neurostimulator. Press the **Programming (P)** key or select the **Program (P)** button.
- When holding the programming head over the implanted neurostimulator, do not drape your hand over the back of the programming head. Hold the programming head at the base.
- Ensure that the programmer batteries are not depleted.
- Move away from sources of possible EMI (eg, computer monitors).

System connection check

To verify the physical connections between the lead, extension, and device (INS or ENS) you can use the patient programmer.

◆ *To verify system connections using the patient programmer*

1. Press the **Power/Backlight On/Off** key to turn on the patient programmer (Figure 44).
2. Press and hold the **Selection** keys (Figure 44) at the same time until the next screen appears. The **Lead connections** screen is displayed on the patient programmer.

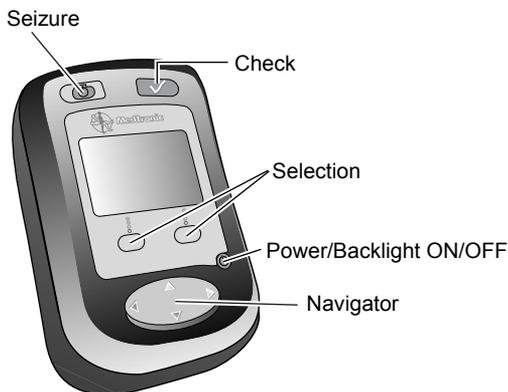


Figure 44. Patient programmer keys

3. Hold the patient programmer over the neurostimulator and press the **Check** key (Figure 44).
Note: During the system connection check, the patient programmer delivers stimulation at an amplitude of 1.5 V, a pulse width of 80 μ sec, and a rate of 100 Hz.
4. When the connection check is complete, the number of connected electrodes is displayed on the patient programmer screen.
Note: To check the impedance of these connections, use the clinician programmer (refer to "Checking system performance" on page 50). The patient programmer should not be used in conjunction with performing an MRI.

Reading serial numbers

◆ **To read the neurostimulator serial number**

1. Interrogate the neurostimulator.
2. Read the neurostimulator serial number from the bottom of any of the programmer screens.

◆ **To read the clinician programmer serial number**

- Do one of the following:
 - Remove the battery compartment cover and batteries (refer to page 94). The clinician programmer serial number is located inside the battery compartment.
 - Select the **Information** button () from the slider bar. The clinician programmer serial number is located next to the programmer icon.

Error and informational messages

The clinician programmer displays text (Table 10 below and Table 12 on page 85) and iconic (Table 11 on page 84) error and informational messages. The patient programmer displays messages that may require patients to contact their physicians (Table 13 on page 85).

Note: Before referring to Table 10, ensure that you have gone through the "Telemetry failure checklist" on page 78.

Table 10. Error and informational messages

Message	Explanation
APPLICATION CARD MISSING The application card has been removed. Exit application.	When the application card is removed the current session will end and unsaved data will be lost.
APPLICATION CARD FAILURE The application card has been corrupted. Turn the programmer off and contact Medtronic technical services.	There is a problem with the application card and it cannot be used. A new card must be obtained before a session can be started.
APPLICATION FAILURE The application has been stopped because of an error. Contact Medtronic Technical Services.	There is a problem with the application. An unrecoverable software error has occurred. Contact Medtronic with the service code.
BATTERY WARNING The programmer batteries are low. Turn the programmer off. Replace batteries now.	The programmer batteries are low and may not last an entire programming session. Replace the batteries before starting a session.
BATTERY WARNING Neurostimulator batteries are depleted. Replace batteries now. Exit application.	The ENS batteries must be replaced now for the ENS to function properly.
CHANGE IN AMPLITUDE MODE Changing Amplitude Mode will clear active program(s). Select OK to change Amplitude Mode.	Changing Amplitude Mode will delete all programs in the group.

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Table 10. Error and informational messages (continued)

Message	Explanation
CHARGE DENSITY WARNING Charge density may be high enough to cause tissue damage. Consult the technical manual. Select OK to continue and use the selected value.	The programmed amplitude or pulse width value or upper limit exceeds the charge density warning threshold and may, depending on impedance values, be high enough to cause tissue damage.
CHARGE DENSITY WARNING Charge density may be high enough to cause tissue damage. Consult the technical manual. Select OK to proceed with the new limit(s).	The selected limit exceeds the charge density warning threshold and may, depending on impedance values, be high enough to cause tissue damage.
CHARGE DENSITY WARNING Charge density may be high enough to cause tissue damage. This warning is based on a measured impedance of: Consult the technical manual. Select OK to continue and use the selected value.	The programmed amplitude or pulse width value or upper limit exceeds the charge density warning threshold calculated using the indicated measured impedance.
CONFIGURATION CHANGE Parameter and session information, including groups, programs, and limits, associated with the current configuration will be deleted. Physician information, physician notes, patient ID, and device implant information will be retained. Select OK to change configuration.	Changing lead configuration will delete all device and session information (except physician information and notes, patient ID, and neurostimulator information) associated with the current lead configuration.
CONFIGURATION CHANGE Parameter and session information, including groups, programs, and limits, associated with the current configuration will be deleted. Physician information, physician notes, all patient information, all device information, baseline diagnosis, and screening history will be retained. Select OK to change configuration.	Changing lead configuration will delete all device and session information (except screening history, physician information and notes, patient ID, and neurostimulator information) associated with the current lead configuration.
DEFAULT SETTING CHANGE Changing the default values will clear active programs. Select OK to continue.	Changing the default settings will delete all active programs associated with the current default settings.
DELETE GROUP Select OK to delete this group.	Deleting the group will delete the group and all programs associated with the group.
DELETE PROGRAM Select OK to delete this program.	Selecting OK will delete the program.
DELETE PROGRAM Before deleting program, decrease amplitude to 0.0 on all programs to prevent possible uncomfortable or unexpected stimulation.	In some cases, deleting a program can cause a slight increase in the amplitude of the remaining program(s). Reduce the amplitude to 0.0 before deleting the program to prevent any effects caused by this possible increase.
DEVICE NOT SUPPORTED Detected device is not supported by this version of application card. Contact Medtronic technical services.	This device cannot be programmed using this version of the application card.
DEVICE NOT SUPPORTED This neurostimulator was last programmed with an incompatible version of the application card. Select Cancel to exit the application and contact Medtronic technical services or select OK to clear all settings and start session.	The device was programmed using a different (newer) version of the application card. The device can be programmed using this version of the application card, but device settings will be cleared.

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Table 10. Error and informational messages (continued)

Message	Explanation
DEVICE NOT SUPPORTED The detected device is not supported by this application card. Refer to the technical manual for a listing of supported devices. End session.	The device cannot be programmed using this application card. A new application card must be obtained.
DIAGNOSIS CHANGE All screening history and baseline information will be cleared. Select OK to change patient diagnosis.	Changing patient diagnosis will delete all screening history and baseline information associated with the current patient diagnosis.
EXIT APPLICATION Select OK to exit application.	Selecting OK will end this programming session. The application will return to the Neurostimulation Desktop screen.
EXIT GUIDED PROGRAMMING Select OK to exit Guided Programming.	Selecting OK will end Guided Programming.
GP UNAVAILABLE Guided Programming cannot be used with the current program settings. Select OK to clear current program settings and use Guided Programming.	Guided Programming is not available because programs in the group have different pulse widths, a program in the group has a bipolar configuration, or a program in the group has a unipolar configuration with more than 1 active electrode.
INITIAL SETTINGS Press OK to reset all parameters to values in effect at start of session.	Initial settings are the settings observed on the Programming screen at the beginning of the current session. Returning to initial settings will delete any values that were changed in the current session.
INVALID DATA This application card is not compatible with the screening and session history stored in this device. Select OK to use this application card and clear screening and session history.	The format of the history data stored in the neurostimulator is not recognized by this application card. To retain history data, insert a newer version of the application card.
INVALID DATA Invalid data have been detected. All screening and session history will be cleared.	History data stored in the neurostimulator is corrupt.
INVALID SETTINGS Invalid settings have been detected. All settings will be cleared.	The device cannot be programmed using the detected settings. Selecting OK will clear the settings, and require reprogramming of the device.
MAGNET PRESENT A magnet has been detected by the programming head. Remove the magnet to continue.	The magnet is used to program SynchroMed and SynchroMed EL pumps only.
MEASUREMENT SETTINGS Electrode pairs will be tested. Stimulation will change to the settings listed below during this measurement.	During the measurement test, stimulation parameters will be set to the values that are listed. This will affect patient stimulation while the test is in progress.
MEASUREMENT SETTINGS Notify patient that stimulation may change during this measurement. Press OK to start measurement.	During the group (therapy) impedance measurement, stimulation may change to the parameter values for each program as the impedance is measured for the group. This will affect patient stimulation while the test is in progress.
OUT-OF-REGULATION The delivered amplitude may be lower than the selected amplitude for one or more programs.	The neurostimulator cannot deliver amplitude at the programmed value. Follow the instructions on the screen to increase the delivered amplitude.

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Table 10. Error and informational messages (continued)

Message	Explanation
PARAMETER CHANGES The limits associated with the current parameter settings will be deleted. Select OK to continue.	Changing the parameter settings will cause the current limits to exceed charge density threshold. The limits associated with the changed parameter settings will be deleted.
POSSIBLE OPEN CIRCUIT At least one measurement indicates a possible open circuit at: Select OK to repeat the electrode impedance at:	The electrode impedance measurement indicated one or more potential open circuits. To further evaluate the existence of an open circuit, repeat the measurement at the higher setting, which has a larger measurement range.
POWER ON RESET Power On Reset has occurred. Session will restart.	The neurostimulator has reset. The current session will end and any unsaved data will be lost. Contact Medtronic technical services. Service Code: _____
PROGRAM SELECTION This program is incompatible with the active program(s) due to interlocks or electrode selections.	The program cannot be imported from screening history because it is incompatible with other programs in the group.
RATE DECREASE Before decreasing rate by more than X Hz, decrease amplitude to 0.0 on all programs to prevent possible uncomfortable or unexpected stimulation.	In some cases, reducing the rate can cause a slight increase in the amplitude of the remaining program(s). Reduce the amplitude to 0.0 before reducing the rate to prevent any effects caused by this possible increase.
RATE INCREASE The selected system rate increase may decrease the therapy output which may require adjustment to the amplitude. Select OK to continue.	In some cases, increasing the rate can cause a slight decrease in the amplitude of the remaining program(s). Adjust the amplitude to maintain therapy at the desired level.
SESSION DATA MANAGER Session Data Manager is full. Select OK to open the Session Data Manager and delete old records. Select Cancel to proceed without deleting any records (data will not be saved).	The session data manager is full. Records must be deleted before more records can be added.
SESSION HISTORY At least one group must be deleted before the Session History can be imported.	A maximum of four groups is allowed. If there are already 4 defined groups, one group must be deleted before a group from Session History can be imported.
SESSION INFORMATION There is a problem with the application card. Session information will not be saved to the application card. Contact Medtronic technical services.	Application error. Session information cannot be saved. Obtain a new application card.
SESSION INTERRUPTED Another programmer has communicated with the neurostimulator. Exit application.	A different programmer has communicated with the neurostimulator and could have changed settings.
STIMULATION OFF Neurostimulator is off. Select OK to turn the neurostimulator on and continue with changes.	The neurostimulator must be on when programming certain operations.
TELEMETRY FAILURE There was interference while communicating with the neurostimulator. Reposition the programming head or move away from potential sources of interference and select Retry. Select Cancel to exit application.	Telemetry did not complete because of electrical or magnetic interference from the environment or other devices nearby. To complete telemetry, the programming head must be placed closer to the neurostimulator or you must move away from sources of the interference.

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Table 10. Error and informational messages (continued)

Message	Explanation
TELEMETRY FAILURE There was no response from the neurostimulator. Reposition the programming head and select Retry. Select Cancel to exit application.	Telemetry did not occur because of the location or movement of the programming head during the telemetry attempt.
WELCOME If neurostimulator will be implanted, select OK to proceed. This will begin device service life. If neurostimulator will not be implanted at this time, select Cancel to end session.	Neurostimulator service life or battery level status can be checked without beginning device life. Device life begins the first time lead configuration is programmed.

Table 11. Iconic error messages

Error message	Explanation
	Application card missing
	Application card error
	Therapy-stop key pressed with no application active
	Programming (P) key pressed with no application active
	Hardware/software failure message Contact the appropriate Medtronic representative listed on the inside back cover of this manual.

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Observation window messages – The Observation box appears on the **Start Session** screen when the **Start Session** menu () is accessed. The Observation box provides brief messages about significant system events that need to be investigated. These messages and their explanations are displayed in Table 12.

Table 12. Observation box messages and explanations

Event message^a	Explanation
Check TestStim clock	The time difference between the ENS clock and the clinician programmer clock is greater than one hour. Check the ENS clock setting to ensure it is set properly.
Check INS clock	The time difference between the INS clock and the clinician programmer clock is greater than one hour. Check the INS clock setting to ensure it is set properly.
INS is at EOS	The INS has reached end of service (EOS) and therapy is not available. Replace the device.
INS is at ERI	The INS is within 2 months of its scheduled end of service, please schedule a date to replace the INS.
Stimulation OFF	Stimulation was off when the ENS/INS was interrogated by the programmer at the start of the session.

^a Messages remain in the Observation box from session to session until the needed action is taken.

Patient programmer messages – The patient programmer also displays text and iconic error and informational messages. Some messages provide an error code and tell the patients to contact their physician. These error codes and their troubleshooting procedures are displayed in Table 13. Contact the appropriate Medtronic representative listed on the inside back cover of this manual if additional assistance is needed.

Table 13. Patient programmer Contact Physician error codes

Error code	Explanation
574	No programs or groups were saved by the clinician programmer. The neurostimulator must be reprogrammed.
OOR	Out-of-Regulation situation has occurred. The neurostimulator cannot deliver amplitude at the programmed value. The patient must come into the clinic, and the clinician programmer must be used determine how to increase the delivered amplitude. If OOR occurs while using current mode, switch to voltage mode.
POR	The neurostimulator has undergone a power on reset. No therapy is available until the device is re-activated. The patient programmer can be used to re-activate the neurostimulator after some PORs. If the patient programmer cannot reactivate the neurostimulator, the clinician programmer must be used to reactivate the neurostimulator.
ERI	The INS is within 2 months of its scheduled end of service, please schedule a date to replace the INS.
EOS	The INS has reached end of service (EOS) and therapy is not available. Replace the device.
575/578	Invalid settings were detected in the INS. The device must be reset and valid settings entered.
0 to 250	Invalid settings were detected in the patient programmer. The patient should remove the programmer batteries and re-insert them after a few seconds. The error code should disappear. If it reappears, the patient programmer may need to be replaced.

Table 13. Patient programmer Contact Physician error codes (continued)

Error code	Explanation
	The ENS you are trying to communicate with is not configured for use with Activa Therapy. Use the clinician programmer to configure the ENS for the appropriate therapy.

No stimulation, intermittent stimulation, or unexpected stimulation

No stimulation, intermittent stimulation, or unexpected stimulation may be caused by any of the sources listed below. If you suspect one of these problems, refer to "Noninvasive troubleshooting for no stimulation, intermittent stimulation, or unexpected stimulation" on page 86.

Causes of no stimulation or intermittent stimulation

- The neurostimulator battery is depleted.
- The patient is confused about the use of the patient programmer.
- The patient has turned off the neurostimulator.
- The amplitude is too low to be effective.
- Stimulation is in the Cycling Mode (Cycling OFF Time).
- There is a short circuit or open circuit in the lead or extension.
- The metal of the conductor wire or connection mechanism is broken, exposed, or uninsulated.
- The programmed lead configuration does not match the physical lead configuration.
- A setscrew is loose.
- There is a connection problem (lead to extension or neurostimulator to extension).
- There is a neurostimulator component failure.

◆ **Noninvasive troubleshooting for no stimulation, intermittent stimulation, or unexpected stimulation**

1. Ask the patient to describe any feeling of stimulation that he or she is experiencing at this time.

Note: Encourage the patient to accurately and completely describe the feeling of stimulation.

- A burning sensation, somewhere along the system pathway from the neurostimulator to the lead, that comes and goes when the neurostimulator is turned on and off may indicate a problem with leads, extensions, or connectors.
- A burning sensation that is constant may indicate a physiologic cause such as infection.
- A change in the therapy results may indicate lead migration.

- In a unipolar configuration (case is positive) the patient may experience skeletal muscle stimulation around the site of the neurostimulator, particularly at high amplitude settings. Consider using bipolar configurations when possible to resolve skeletal muscle stimulation.
- 2. Check for a hardware problem or battery depletion.
- 3. If the source of the problem is revealed in Step 1 or Step 2, perform the relevant test listed below and resolve the problem. Otherwise, perform the following tests in succession until the problem is uncovered or resolved.
 - Programming review
 - Electrode impedance and stimulation current measurements
 - Component palpation
 - X-ray or fluoroscopic examination

Programming review

1. Ensure the patient is using the device(s) correctly.
2. Review all program settings, electrode selections, parameters, and modes to ensure that all settings are correctly programmed.

Electrode impedance and stimulation current measurements for the neurostimulator

Electrode impedance and stimulation current are electrical values that can be interrogated with the programmer. These values may help to further define the system problem. Look for the expected measurement values for short circuit (low impedance, high stimulation current) or open circuit (high impedance, low stimulation current):

- **Impedance values indicating potential short circuit = less than 250 ohms**
 - **Impedance values indicating a potential open circuit = unipolar: greater than 2000 ohms; bipolar: greater than 4000 ohms**
- △ **Caution:** DO NOT rely solely on the results of impedance testing for troubleshooting. Accuracy of the data generated during impedance tests can fluctuate based on the neurostimulator that is being tested and on the programmed settings.

Component palpation

Try a palpation test to further interrogate the system:

1. Firmly palpate or massage the skin over the implanted system components, beginning at the neurostimulator pocket.
2. Continue to palpate the skin along the pathway to the lead-extension connection near the neck, ensuring that all components and connections are firmly palpated.
3. Watch for these results:
 - Stimulation recurs when implanted components are palpated, indicating a possible loose connection that must be surgically repaired. Contact Medtronic Technical Services for additional information before proceeding with the invasive procedure (surgery). If applicable, refer to "Invasive troubleshooting for no stimulation, intermittent stimulation, or unexpected stimulation" on page 88.

- Patient feels a burning sensation, particularly at a connection or along the extension pathway, indicating a possible exposed wire or connection that must be surgically repaired. Contact Medtronic Technical Services for additional information before proceeding with the invasive procedure (surgery). If applicable, refer to "Invasive troubleshooting for no stimulation, intermittent stimulation, or unexpected stimulation" on page 88.

Note: If the burning sensation continues when the neurostimulator is off, a physiologic cause, such as infection, may be the cause.

X-ray or fluoroscopic examination

Obtain an x-ray or use fluoroscopy to investigate lead position, loose connections, and possible broken wires.

- Because x-ray imaging detects metal, a continuous path of metal should be seen from the neurostimulator to the stimulating electrodes.
- An opening or "blank spot" in the path may indicate a broken wire or an open connection.
Note: Lack of visualization of the extension metal conductor might not indicate a discontinuity. Contact Medtronic for more information.
- Confirm that no connections have been pulled apart.

Lead migration, loose connections, and broken lead wires all require surgical intervention. Contact Medtronic Technical Services for additional information before proceeding with the invasive procedure (surgery). If applicable, refer to "Invasive troubleshooting for no stimulation, intermittent stimulation, or unexpected stimulation" on page 88.

◆ *Invasive troubleshooting for no stimulation, intermittent stimulation, or unexpected stimulation*

If none of the noninvasive troubleshooting tests have identified the problem or if these tests have demonstrated that the problem is with an implanted component, contact Medtronic Technical Services for additional information before proceeding with the invasive procedure (surgery).

Supplies needed for invasive troubleshooting include the following:

- Alligator clip cable
- Test stimulation (screener or ENS), optional
- Backup system components (lead, extension, neurostimulator)
- Programmer
- Accessories (hex or torque wrenches as appropriate, connector boots, medical adhesive, stylets, anchors)
- Other supplies as needed

Note: All supplies must be sterile except the test stimulator or ENS and the programmer.

If you have identified specific component problems, perform the corresponding troubleshooting procedure from the following:

- Exposed wire or connection
- Connection problem
- Lead migration

Exposed wire or connection

If the patient presents with a "burning" sensation that is only present when the neurostimulator is on, perform the initial surgical incision over the site of the reported burning. Be careful not to damage any insulation.

Note: A constant burning that continues when the neurostimulator is off may indicate a physiologic cause such as infection.

If the burning is at a connection site, redo the connection using a new connector boot, then:

1. Inspect for full lead insertion into the extension connector.
2. Inspect connection for any damage.
3. Clean connections with sterile water and wipe dry with surgical sponges prior to reconnecting.
4. Inspect setscrews for proper tightness using the appropriate hex or torque wrench.
5. Place the newly redone connection back into the incision and retest the system prior to wound closure.

If the burning is at the neurostimulator site, be certain that:

1. The Medtronic logo on the neurostimulator is facing towards the skin, not towards the muscle.
2. The rubber grommets remain in all setscrew sockets on the neurostimulator connector block and that no leaf within a rubber grommet is stuck open.
3. The extension is fully seated in the connector block and that there are no nicks or cuts on the underside of the neurostimulator or anywhere that might result in bare metal exposure.

Note: If the rubber grommets appear to be damaged or open to fluid infiltration, use a small amount of medical adhesive on the surface to seal. Do not force adhesive into the setscrews.

Connection problem

If there is a connection problem between the neurostimulator and the extension, or between the extension and the lead, perform the surgical incision near the connection site (as determined by fluoroscopy or x-ray), disconnect components, clean the connectors, and reconnect the components. Test for system integrity prior to wound closure.

Note: Do not overtighten lead or extension connections. Tighten each setscrew clockwise until it touches the extension connector pin—if using the hex wrench, continue tightening for a maximum of 1/4 turn only or if using the torque wrench, continue tightening until the torque wrench clicks once. After you remove the wrench, check that the rubber grommet on the device has closed.

Lead migration

If the lead has migrated, consult with a surgical clinician experienced with deep brain stimulation lead placement.

Changes in seizure reduction

Changes in seizure reduction may be caused by any of the sources listed below. If you suspect one of these problems, perform the following procedure.

Causes of change in therapy response

- There is lead migration.
- There is a short or open circuit resulting in reduced current delivered to the stimulating electrodes.

◆ ***Noninvasive troubleshooting for change in therapy response***

1. Try different electrode combinations. Be certain to have at least one electrode negative and one electrode positive.
2. Palpate along the extension-lead connection. If the patient reports feeling a change in stimulation, there may be a break in the insulation or a loose connection. An insulation break or loose connection must be invasively repaired. Contact Medtronic Technical Services for additional information before proceeding with the invasive procedure (surgery).
3. Obtain an x-ray to determine if the lead has migrated.
4. If the patient feels a burning in the neurostimulator pocket, there may be a short or open circuit (eg, exposed wire). Short or open circuits must be invasively repaired. Contact Medtronic Technical Services for additional information before proceeding with the invasive procedure (surgery).

◆ ***Invasive troubleshooting for change in therapy response***

If none of the noninvasive troubleshooting tests are able to recapture appropriate stimulation, **contact Medtronic Technical Services for additional information before proceeding with the invasive procedure (surgery).**

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System and programmer settings

This section covers the programmer and operating system settings that can be changed by the user.

Setting localization options

The **Localization** screen allows you to change the language, date, time, and decimal format.

Note: The first time the programmer is turned on, or after the lithium backup battery is replaced, the **Localization** screen does not allow you to change the language selection. To change the language selection, reenter the **Localization** screen through the slider bar.

◆ To set language, date, decimal, and time format

1. Access the slider bar.
2. Select the **Localization** button (📄).
3. Select a language, date, decimal, or time format option (Figure 45).

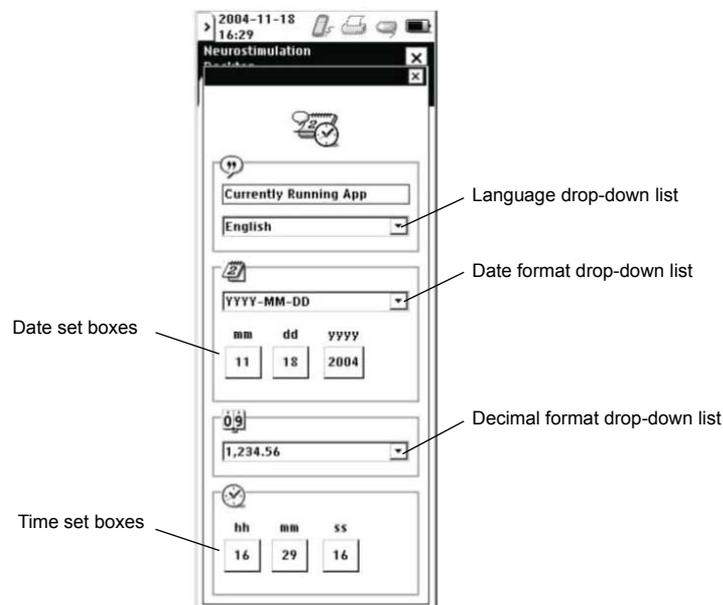


Figure 45. Localization screen.

4. Select the desired format from the drop-down list.

Changing programmer settings

The programmer settings control the contrast, volume, and key click. The speaker volume setting adjusts the volume for tones that signal programming events and conditions (eg, success, error, alert, failure). This setting does not control the volume of the key click sound. The key click is the sound made when the stylus contacts the touchscreen. The key click sound can be turned on and off.

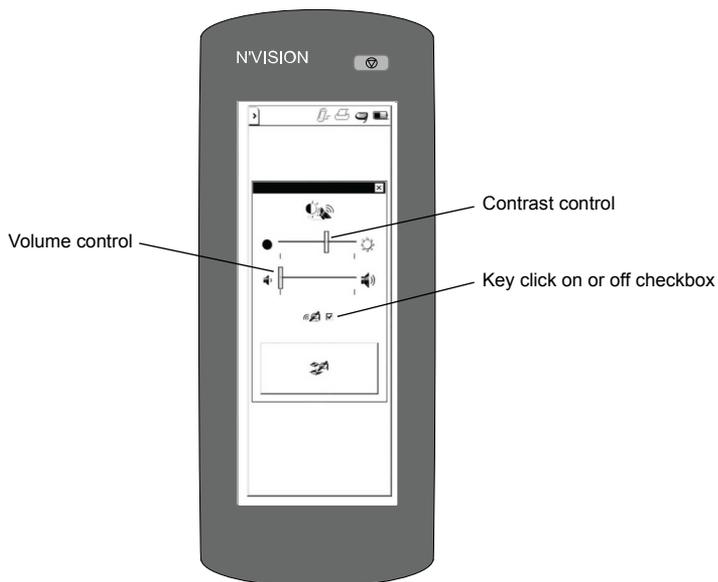


Figure 46. Programmer settings screen.

◆ To set contrast

1. Access the slider bar.
2. Select the **Settings** button (☰).
3. Slide the contrast control bar to desired setting (Figure 46).

Note: Two shades of gray should be visible for optimal viewing of icons and text in the application.

◆ To set speaker volume

1. Access the slider bar.
2. Select the **Settings** button (☰).
3. Slide the speaker volume control bar to desired setting (Figure 46).

◆ To turn key click sound on or off

1. Access the slider bar.
2. Select the **Settings** button (☰).

3. Select the Key click on or off checkbox (Figure 46).

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Programmer maintenance

This section covers changing the programmer batteries, cleaning the programmer, and calibrating the touchscreen.

- △ **Caution:** If the clinician programmer or application card was transported or stored above or below the operating temperature range [10 °C (50 °F) to 38 °C (100 °F)], allow the items to stabilize at room temperature until they return to operating temperature. Using the programmer within operating temperature range ensures device functionality.

Changing the programmer batteries

The programmer operates on four AA alkaline batteries. Batteries should be replaced after 40 hours of use or when the battery status icon indicates a low battery (🔋). Batteries must be replaced when the battery status icon indicates the batteries are depleted (blinking).

When no AA batteries are installed, the programmer clock runs on a lithium back-up battery that is supplied with the programmer. The life expectancy of the lithium battery is 3 years.

△ **Cautions:**

- Check the battery status to determine if the batteries in the programmer will last the entire programming session. Loss of power during a programming session may cause unsaved data to be lost.
- If the programmer will not be used for several weeks, remove the AA batteries from the programmer. Batteries left in the programmer may corrode, causing damage to the electronic components.

◆ **To replace the programmer batteries**

1. Ensure that the appropriate application card is in place.
2. Exit the application, if necessary.
3. Turn the programmer off.
4. Press down lightly on the battery compartment cover and push the cover in the direction of the arrow, then lift the cover upwards (Figure 47).

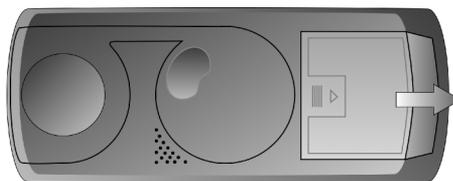


Figure 47. Removing the battery compartment cover.

5. Replace all 4 AA batteries. (Do not use rechargeable batteries.) Correct battery polarity is indicated inside the battery compartment.
6. Replace the battery compartment cover by sliding the cover until it snaps into place.

7. Turn the programmer on. If the programmer does not turn on, verify that the batteries have been installed with the correct polarity.

Note: Dispose of depleted batteries in accordance with local regulations.

◆ **To replace the lithium back-up battery**

1. Remove the AA programmer batteries.
2. Remove the lithium battery from the compartment located inside the AA battery compartment.
3. Insert a new lithium battery (BR1225 standard lithium coin cell).
4. Replace the AA batteries.

Notes:

- After replacing the lithium back-up battery, you may need to reset the Localization parameters. For instructions, refer to "Setting localization options" on page 91.
- Dispose of depleted batteries in accordance with local regulations.
- Return nonfunctioning devices to Medtronic for disposal.

Cleaning the programmer

◆ **To clean the programmer**

1. Clean the exterior surfaces of the programming head, IR lens, and magnet with a damp sponge or soft cloth moistened with water, mild detergent, or alcohol. Be careful to not allow liquid into any programmer components.
2. When programming in a sterile field, if the programming head comes in contact with a patient's skin, wipe the programming head with an antibacterial solution.
3. Clean the touchscreen only with a soft, dry, lint-free cloth. Do not use cleansers on the touchscreen.

△ **Caution:** Scratches on the touchscreen may interfere with selecting an option. If the touchscreen is not responding appropriately, return the programmer to Medtronic for repair or replacement.

Calibrating the touchscreen

The touchscreen may require periodic calibration. When calibrating the touchscreen, the programmer compares the points of contact with known locations.

If the calibration fails, the programmer restarts the calibration procedure until the procedure is successfully completed.

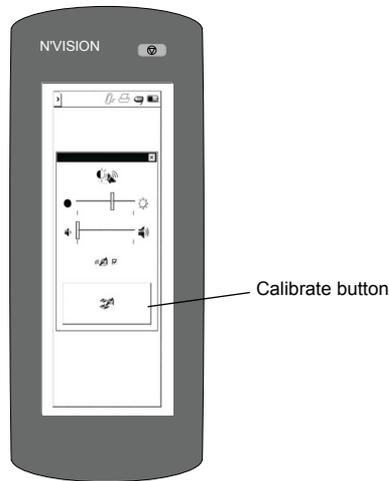


Figure 48. *Calibrating the touchscreen.*

◆ **To calibrate the touchscreen**

1. To begin calibration do one of the following:
 - Press and hold the **Programming (P)** key while the programmer is powering up.
 - From the slider bar, select the **Settings** button (⚙️), then select the **Calibrate** button (Figure 48 on page 96).
2. Select the center of each of the four calibration targets as they appear. To ensure proper calibration, make your selection as close to the center of the calibration target as possible.

Glossary

- Application card** - Provides the software to program the ENS and INS for procedures.
- Current Mode** - Device holds current flow steady by dynamically adjusting voltage in response to changes in impedance.
- Current settings** - Settings the patient experiences during a patient session.
- Cycling off time** - In cycling, the length of time between stimulation periods; the time of the “resting” period.
- Cycling on time** - In cycling, the length of time that stimulation is delivered.
- Depleted** - The battery status of a nonrechargeable battery; a state of reduced energy of a battery. Condition requires that the external device battery be replaced or the implanted device be replaced.
- Elective Replacement Indicator (ERI)** - Notification that the INS is nearing end of service.
- Electrode impedance measurements** - Measurements of the resistance of the lead(s), extension(s), and body tissue that can provide information about the condition of the implanted system (eg, short circuit, open circuit).
- Electrode polarity** - State of each electrode for all implanted leads: positive, negative, or off.
- End of Service (EOS)** - Condition of an implantable device at the time it is no longer able to operate successfully.
- Final settings** - Settings in effect at the end of the patient session.
- Groups** - A Group is a specific combination of programs that are delivered sequentially. It can include up to 4 programs (2 programs per hemisphere).
- Guided Profile** - Steps the user through the capture of a standard set of patient and system information, including lead configuration, patient data, lead data, baseline, and device data.
- Guided Programming** - Offers a systematic, step-by-step approach to programming basic therapy parameters. On-screen prompts guide you through each of the basic steps, from the initial electrode selection, to testing and recording the effects of various amplitudes, to programming the final selections.
- Initial settings** - Settings in effect at the start of the patient session.
- Input box** - An area on the programmer touchscreen that, when activated, initiates the appearance of another screen or an action by the programmer.
- Localization parameters** - Options for selecting country-specific formats for date, time, numbering schemes, and language.
- Power On Reset (POR)** - A neurostimulator safety feature that turns stimulation off.
- Programs** - A specific combination of amplitude, rate, and pulse width parameters acting on a specific electrode set that determines the stimulation pulses that are delivered.
- Session Data Manager** - Allows collection and storage of patient data information gathered during patient sessions. Report data from previous sessions can be viewed and printed.
- Stylus** - A blunt pen-shaped or pencil-shaped device used to make contact with a touchscreen on a device such as a computer or programmer.
- Target value** - Before programming, the intended value of a parameter.

Telemetry - Radio-frequency communication between a clinician programmer and an implanted neurostimulator.

Therapy impedance measurements - Impedance and stimulation current measurements taken at the programmed settings.

Voltage Mode - Device holds voltage as set, and current flow varies as impedance changes.

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