DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Mr. David H. Mueller
Regulatory Affairs Manager
Medtronic, Inc.
Neurological Division
Neurostimulation Business
800 53rd Avenue NE
P.O. Box 1250
Minneapolis, MN 55440-9087

JUL 31 1997

Re: P960009
Medtronic® Activa™ Tremor Control System
Filed: May 1, 1996
Amended: May 3, June 26, October 17 and November 18 and 27, 1996; January 21, February 26, March 24, May 16, June 2 and 30, and July 7, 15 and 31, 1997

Dear Mr. Mueller:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Medtronic® Activa™ Tremor Control System which includes the Model 3387 DBS™ Lead, Model 7495 Extension, Model 7424 Implantable Pulse Generator (IPG), Model 7458 Memory Module, Model 7432 Console Programmer, Bur Hole Ring and Cap, Model 7452 Magnet, Model 3625 Test Stimulator (Screener) and Model 3353/3354 Lead Frame Kits and Accessories, and is subject to the conditions described below and in the "Conditions of Approval" (enclosed). This device is indicated for unilateral thalamic stimulation for the suppression of tremor in the upper extremity in patients who are diagnosed with essential tremor or Parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act. Implanting physicians should be experienced in stereotactic and functional neurosurgery.

In addition to the general conditions of approval enclosed, you must comply with the "Description of the Postapproval Studies - P960009" (amendment dated July 31, 1997). If appropriate, the results of the postapproval studies must be reflected in the labeling (via a supplement) when the study is completed.

Expiration dating for the generator and the lead has been established and approved at eighteen months and four years, respectively. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(8).

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

Under section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities, the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. FDA has designated your device for tracking because it is a permanent implant.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list examples of permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)). Pursuant to 21 CFR § 821.20(d), FDA will be adding the Medtronic® Activa™ Tremor Control System to these lists by publishing a notice in the FEDERAL REGISTER announcing that FDA believes that this device is subject to tracking under section 519(e)(1). This notice will also solicit public comments on FDA's determination.

If you have any questions concerning this approval order, please contact Ann H. Costello, Ph.D., D.M.D. at (301) 443-8517.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Issued: 3-4-98

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

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Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1)Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a)unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b)reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1)A mix-up of the device or its labeling with another article.

(2)Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a)has not been addressed by the device's labeling or

(b)has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

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(3)Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

(1)May have caused or contributed to a death or serious injury; or

(2)Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc. Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336)and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW

Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at 800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers Assistance (DSMA) at 301-443-8818.

Summary of Safety and Effectiveness Data
Medtronic® Activa™ Tremor Control System

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Summary of Safety and Effectiveness Data
Medtronic® Activa™ Tremor Control System

1. General Information

Generic Name:	Implantable multiprogrammable quadripolar thalamic stimulation system for the treatment of tremor
Trade Name:	Medtronic ® Activa™ Tremor Control System Model 3387 DBS™ Lead Model 7495 Extension Model 7424 Implantable Pulse Generator (IPG) Model 7458 Memory Module Model 7432 Console Programmer Burr Hole Ring and Cap Model 7452 Magnet Model 3625 Test Stimulator (Screened) Model 3353/3354 Lead Frame Kits and Accessories
Applicant's Address:	Medtronic Inc., Neurological Division NeuroStimulation Business 800 53rd Avenue, N.E. Minneapolis, MN. 55421
PMA Number:	P960009

Date of Panel Recommendation: March 14, 1997

Date of Notice of Approval to Applicant: July 31, 1997

2. Indications for Use

Unilateral thalamic stimulation using the Medtronic ® Activa™ Tremor Control System (herein after called the Activa™ System) is indicated for the suppression of tremor in the upper extremity. The system is intended for use in patients who are diagnosed with essential tremor or Parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability.

3. Contraindications

Implantation of a Tremor Control System is contraindicated for :

- Patients for whom test stimulation is unsuccessful or
- Patients who are unable to properly operate the stimulator.

4. Warnings and Precautions

The warnings and precautions can be found in the Activa™ System labeling.

5. Device Description

The Activa™ System delivers electrical stimulation to the ventral intermediate nucleus (VIM) of the thalamus to suppress the tremor of the upper extremity associated with essential tremor and Parkinson's disease.

During the surgical procedure for implant, a lead is introduced into the VIM of the thalamus, and electrical stimulation is used to establish the optimal electrode position within the VIM. Stimulation is initiated, and the patient's targeted extremity is observed for response. The optimum response of the targeted extremity determines the final position of the DBS lead within the VIM. Patients who demonstrate a reduction in tremor intraoperatively will then have a lead, extension and implantable pulse generator (IPG) implanted.

The Activa™ System components (IPG, extension, and programmer) are currently commercially available for Spinal Cord Stimulation (SCS) for the treatment of chronic, intractable pain of the trunk or limbs

(P840001/S015). The extension and screener are currently commercially available for Spinal Cord Stimulation (SCS) and peripheral nerve stimulation (PNS) for the treatment of chronic, intractable pain of the trunk or limbs (K903690, K881491, K924522, K884898, etc.).

5.1 Model 3387 DBS™ Lead

This lead has four electrodes which are stereotactically introduced into the target and fixed at the skull with a burr hole cap and ring. The lead consists of a polyurethane protective sheath and four platinum/iridium electrodes at the tip of the lead. The function of the lead is to provide a conductive pathway for electrical current to the targeted nucleus. Accessories are provided which aid in the surgical procedure, lead securement, and temporary stimulation for therapy screening, e.g., Burr Hole Cap and Ring, Lead Frame Kits, and tunneling rods.

5.2 Model 7495 Extension

The extension is an insulated set of wires connecting the DBS Lead and the implantable pulse generator (IPG). The extension is subcutaneously passed from the scalp area, where it connects to the proximal end of the DBS Lead, to the area below the clavicle, where it connects to the implantable pulse generator.

5.3 Model 7424 Implantable Pulse Generator (IPG)

The IPG is the electrical "power source" for stimulation therapy. It is implanted subcutaneously, in the subclavicular or subcostal regions. The IPG delivers electrical stimulation pulses with a variety of parameters, modes, and polarities. These stimulation parameters can be non-invasively adjusted to optimize the treatment of tremor and minimize side effects. The adjustments are made by radio-frequency (RF) telemetry by the Model 7432 Console Programmer/ Model 7458 Memory Module Software. The IPG is battery powered and must be replaced surgically; the frequency of replacement is dependent on the amount of time that the IPG is used each day and the parameters at which the IPG is set.

5.4 Burr Hole Cap and Ring

The cap and ring are made of Gorillamid (nylon). The ring has ridges that hold it in place in the skull. A trough is machined into the ring, and the burr hole cap holds the lead in the trough.

5.5 Model 7458 Memory Module

The Model 7458 Memory Module Software Cartridge ("MemMod"), is similar to the MemMod used for SCS (Model 7455). However, the software code on the Model 7458 allows pulse rates of 185 Hz rather than being limited to 130 Hz as with the SCS application. Table 1 lists the maximum stimulus parameters as well as baseline parameters for tremor suppression based on a preliminary analysis of the clinical study:

Table 1. Stimulation Parameters

Stimulus Parameter	Range (Max)	Tremor - Baseline
Voltage (Volts)	0 to 10.5	2 to 3
Frequency (Hertz)	2 to 185	> 100
Pulse Width (microseconds)	60 to 450	60 to 90

Although some combinations of stimulus parameters were not established as safe and effective, the device software will prevent the user from accidentally using these particular combinations.

6. Alternative Practices or Procedures

Several medical and surgical alternatives are available for the treatment of tremor. When managing tremor, medication is usually tried first. When medication is no longer effective or produces unacceptable side effects at doses which are required to control the tremor, surgery is an alternative. The surgical ablative procedures, such as thalamotomy, used to manage tremor are considered true alternatives to electrical stimulation. Electrical stimulation differs from ablative procedures in that the goal of the surgical ablation is to produce a permanent lesion in the brain that may treat tremor. In some cases, the implantation of the lead or the mechanical presence of the lead may produce a temporary thalamotomy-

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like effect without stimulation, but the goal is not to produce a lesion.

7. Marketing History

The Model 3387 DBS Lead has been sold outside the United States since 1991. From 1991, through October 31, 1996, approximately 1,566 Model 3387 Leads have been sold. The Activa™ System (also known as the Itrel II Stimulation System) has been commercially available in the United States and areas outside the United States since 1988 for Spinal Cord Stimulation (SCS) for the treatment of chronic pain. The Activa™ System has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

8. Adverse Effects of the Device on Health

8.1 Observed Adverse Events

The most common adverse events reported in the US Tremor Trial (≥ 5% of patients) were postoperative pain, lead repositioning, stimulation not effective, paresthesia., dysarthria, disequilibrium, and paresis. Table 2 lists the adverse events attributed to the device or the procedure reported in more than one patient.

Table 2. Adverse Events and Surgical Interventions Related to the Device or Procedure.
Reported in ≥ 1 patient, all patients enrolled, N = 424

	US Tremor	EC Tremor	Others *	Total	
Number of Patients	84	113	227	424	
Adverse Event (AE)	**Number of Patients with the AE**				**%**
ANY (one or more) adverse event	32	20	68	120	28.3%
Postoperative pain, stress or discomfort	11	9	8	28	6.6%
Lead repositioning	5	4	17	26	6.1%
Stimulation not effective/ Insufficient tremor control	5	3	17	25	5.9%
Lead migration/ dislodgment	1	1	12	14	3.3%
Intracranial hemorrhage	5	3	5	13	3.1%
DBS explantation	4	1	7	12	2.8%
Infection	1	2	8	11	2.6%
Erosion	5	0	3	8	1.9%
Paresthesia	5	1	0	6	1.4%
Component malfunction (IPG, lead, extension)	2	1	2	5	1.2%
Seizures	1	0	4	5	1.2%
Subcutaneous hematoma	1	2	2	5	1.2%
Electrical shocking or jolting	1	0	3	4	0.9%
Headaches	2	1	1	4	0.9%
Lead fractures	1	0	3	4	0.9%
Paresis	3	0	1	4	0.9%
Disequilibrium	2	1	0	3	0.7%
Allergic reaction	0	0	2	2	0.5%
Burr hole ring and cap failure	0	1	1	2	0.5%
Electrode short circuit or open circuit	1	1	0	2	0.5%

* Basic Safety and DBS for Pain Studies

Adverse events reported in one patient each included attention or cognitive deficit, cramping, diplopia, dysarthria, dysphasia, exacerbation of Parkinson's disease, facial weakness, IPG changed from cycling mode to continuous mode, insufficient oxygenation, no connection at "0" electrode, problem with lead/extension connection, broken tunneling rod, and twelfth cranial nerve palsy. Device failure was confirmed in one case, and resulted from premature IPG battery depletion due to a defective integrated circuit.

Table 3 lists the adverse events attributed to the therapy (deep brain stimulation) which occurred in more than one patient. The number and percentage of patients with adverse events (any one or more) in the US and European Tremor Trials for patients with essential tremor was 43 of 78 (55%) compared to 33 or 111 (30%) for patients with Parkinson's disease. The number and percentage of adverse events (any one or more) in the European Tremor Trial for all patients implanted bilaterally was 4 of 27 (15%) compared to 10 of 85 (12%) of patients implanted unilaterally. Table 3 combines the frequencies across diagnoses and unilateral/bilateral implants.

Table 3. Adverse Events During Stimulation (US and European Trials)
Reported in≥ 1 patient, all tremor patients, N = 189)

Adverse Event	# of Events	# of Patients	% of Patients
ANY (one or more) adverse event	242	76	40%
Paresthesia	123	63	33%
Dysarthria	22	17	9%
Disequilibrium	11	9	5%
Paresis	13	9	5%
Dystonia	17	6	3%
Gait disorder	5	5	3%
Initial jolt	8	5	3%
Headaches	5	4	2%
Pain, discomfort or local stress	7	4	2%
Attention deficit	3	3	2%
Dysphasia	3	3	2%
Initial tingling	3	3	2%
Insufficient therapeutic effect	3	3	2%
Ataxia	3	2	1%
Dyskinesia	2	2	1%
Sensory deficits	2	2	1%

Adverse events reported in one patient each included facial weakness, fatigue, intention coordination, loss of energy, numbness, other speech deficits, rebound, and transient heaviness in arm.

Most (70%) of the therapy-related adverse events were tolerated by the patients and involved no clinical intervention. Stimulation parameters were adjusted in 22% of the cases. Other interventions included: patient education; adjustment of concomitant medications; and instructions to discontinue stimulation. Nine patients required lead repositioning to regain therapeutic effect.

Five essential tremor patients had their Activa™ Systems explanted. Four patients were explanted due to loss of effectiveness. One patient was explanted due to infection.

Of the 114 Parkinson's disease patients (US and Europe), disease progression was reported in ten patients ,exacerbation of tremor in three patients (both occurred in one patient). These events were listed as adverse events, but attributed by the investigator to disease progression.

Three suicides were reported during the clinical studies. One patient implanted in the periventricular gray in a DBS for Pain clinical trial reported suicidal ideation present at high stimulation amplitudes. The suicide ideation was resolved when the stimulation parameters were decreased. Depression was reported in two patients in the tremor clinical studies. The depression was judged by the investigators to be related to disease progression and not to the therapy and procedure.

Ten patients died during the clinical studies. One patient suffered significant neurological decline resulting from a postoperative intracranial hemorrhage, and died two weeks after surgery. Two patients died from perioperative myocardial infarctions. The other seven patient deaths were judged unrelated to the therapy and procedure.

An autopsy report in one patient using a different lead showed histopathological changes within 2 mm of the implanted lead. There was no report of an associated change in the patient's neurologic status or the therapeutic effect of the stimulation.

A total of 11 leads were explanted during the United States and European Clinical Studies. Of these leads, six were replaced once. No patients had leads removed and replaced more than once, and no leads were left in place while a second lead was implanted on the same side. The long term safety associated with leads left in place without use, multiple placement of leads in the thalamus, and lead explant is unknown.

8.2 Potential Adverse Events

Adverse events which may potentially occur, but were not reported in the clinical studies, include:

- Seroma at the IPG site
- Nausea and vomiting
- Aphasia
- Leakage of cerebrospinal fluid
- Motor problems such as incoordination or muscle spasms
- Undesirable stimulation
- Undesirable sensations (temporary or permanent)

9. Summary of Preclinical Studies

Laboratory and animal testing was performed to assure conformance with design specifications. Results included testing of commercially available components of the Activa™ System, which are physically identical and which have a history of function in humans.

9.1 Laboratory Studies

9.1.1 Component Testing

9.1.1.1 Model 7424 Implantable Pulse Generator (IPG)

A summary of qualification testing performed on the Model 7424 (P840001/S015) is provided in Table 4.

Table 4. Model 7424 IPG Circuit Qualification Testing

Test	Description	Pass/Fail Criteria	units tested
Electrical output	check amplitude, rate, and PW with a 510W load	meets specifications.	1
Rate	stability under battery, temp and load extremes	130 Hz ± 5%	1
Pulse width	stability under battery, temp and load extremes	61 and 458 ms ± 5%	1
Output pulse	waveform under battery and load extremes	10.5 V maximum, 1 ms rise time, 5 V minimum	3
Rate limit	stability under battery, temp, parameter and load extremes	227 Hz	3
Reed switch	sensitivity	Activation at 1.5 inches from 90 gauss magnet	3
Crystal oscillator	stability under battery and temp extremes	± 5%	3
Battery monitor	accuracy over range of 2.0 to 3.7 V	± 5%	3
Digital IC	timing	within specification	76
Voltage reference	stability under battery, and temp extremes	± 3%	3
Telemetry	timing and data content; distance from transmitter	functional at specified distance	3 hybrids; 1 IPG
ADC	accuracy a function of output amplitude	± 3%	3
Failure modes	test shorts to ground, shorts to supply voltage	will not cause hazardous situation	1
EMC	environmental electromagnetic radiation susceptibility (including electrocautery) per proprietary protocol	per protocol	4
Power on reset	assure parameters are reset on power up	correct parameters, no latchup	3

9.1.1.2 Model 7495 Extension

Qualification testing of the Model 7495 Extension for SCS (P840001) included dimensional adherence, electrical characteristics, mechanical shock, vibration and coil testing. Pre-clinical testing included implanting ten leads in free roaming pigs for 12 months. These leads were then flex tested at a flex angle of 45° over a 3/16 inch bend radius.

9.1.1.3 Burr Hole Ring and Cap

To determine the ability of the burr hole ring and cap to stabilize the Model 3387 DBS Lead, three sets of five electrode samples were inserted by unqualified personnel into an agar medium. When the burr hole cap was locked into position, the deviation of the lead position was observed. Average lead movement was slightly less than 1 mm. A second test on five leads was used to observe the creep of the leads under tension. No deformation of the lead coil was observed on any of the five samples when a 0.5 lb. tensile force was applied.

9.1.1.4 Model 7458 Memory Module Cartridge and Software, and Model 7432 Console Programmer

The methods/procedures for the acceptance of software, and its specifications, for the Model 7458 are the same as those for the previously approved Model 7455. The Model 7458 Memory Module software testing was conducted to verify the software's response to commands and conditions programmed by the Model 7432 keyboard. Software validation and verification was also successfully completed, and the Model 7458 Software Safety Analysis was implemented and addressed. The Model 7458 Software conformed to specification and passed all the tests conducted.

9.1.2 Model 3387 DBS Lead

The Model 3387 DBS Lead is one of a "family" of helical coil designed leads. It shares common design criteria with other leads of similar structure, materials and manufacturing methods. The Models 3487/3487A PISCES Quad SCS Lead, used for the treatment of chronic intractable pain, is the core technology for this "family" of helical coil type leads.

Similarities in design between the SCS and DBS leads are that they are comprised of PTFE coated quadrafilar conductors terminating in multi-electrodes (4) or inline connectors (4), are contained within a polyurethane sheath, and are of a straight cylindrical (coiled) configuration. Manufacturing processes and methods are similar but each device maintains its own distinct set of manufacturing processes and quality control inspections unique to the individual model number and the material used. The DBS and SCS leads differ in materials of construction, as presented in the Table 5.

Table 5. Model 3387 Material Changes

	Model 3487A SCS Lead	Model 3387 DBS Lead
Conductor Wire:	MP35N (metal alloy)	Platinum / Iridium (80/20)
Sheath:	55D Durometer polyurethane	80A Durometer polyurethane
Stylet:	0.010" O.D.Stainless Steel PTFE coated stylet	0.014" O.D. Tungsten Parylene C coated stylet

These material changes were implemented such that the Model 3387 DBS Lead could achieve the following design criteria:

9.1.2.1 Model 3387 Lead

The body of the lead must be pliable, in so much that it will stay in the position placed when the stylet is removed. The "memory" of either the conductor wire(s) or the outer polymer jacket (sheath) shall not cause the lead to migrate from the intended anatomical position, either immediately upon removal of the stylet or over time.

9.1.2.2 Model 3387 Lead Stylet

The stylet shall be of sufficient stiffness to direct the lead to the specific anatomical site without deviating from the insertion path, yet not inflicting damage to either the components (wire coil, coating specifically) or puncturing through the lead tip.

Because of the similarity in design between the Model 3387 DBS Lead and the SCS Lead, the Model 3487 and 3487A SCS Lead testing was used as a baseline for this type of helical coil design. The sponsor relied on the results of the following testing for the SCS Lead based on its similarities to the Model 3387 DBS Lead: corrosion resistance, environmental durability, chemical resistance, tensile properties and moisture resistance. Table 6 shows the testing that has been performed specifically on the Model 3387 DBS Lead.

Table 6. Model 3387 Design Qualification Testing

Test	Description	Pass/Fail Criteria	Units tested
Polyurethane environmental stress cracking	52 week animal implant	limited to "shallow cracks" under 70X magnification	36
Dimensional measurement	correct length and spacing	within design specification	20
Electrical	coil resistance, etc.	20 to 60 Ω (ohms)	20
Flex	coil flex life of 100,000 (Weibull B50), 60 degree bend over 3mm radius at 2Hz	100,000 cycles	10
Lead body static crush	insures that lead stays in place when stylet removed	50 lbs. per nch	20
Weld	pull test & visual	<70% neckdown, <0.005 height,	20
Lead bend stiffness	resistance to bending	25 grams/mm	10
Lead insertion	accurate guidance into an agar medium	"deviating from intended insertion track" from 1.5 to 3.0 cm	15
Stylet insertion	assess damage to insulation coating of coil	DC current > 0.01nA in saline	20
Lead stabilization in	assess burr caps ability to stabilize lead	"deviating from intended insertion track"	15
burr hole ring/cap	lead doesn't get crushed from strain relief	0.5 lb. tensile	15
Multiple sterilization	affect on length, tensile force, flexion	no detectable difference between sterilized and unsterilized	22
Coating dimensions	Assure thickness of PTFE coating	within design specification	lot by lot
Coil winding	Determine coil winding dimensions	Inspection per drawing specifications	20
Shock and vibration	Assure that packaging will endure shipping	electrical and mechanical design specifications	20
Tubing	Qualify polyurethane tubing	Biostability	12
Weld and butt joint	Determine weld quality	Dimensional, Electrical and Strength	22
Flex	Assure ability to withstand flexion	100,000 cycles flexed to 60° bending	22
Surface Finish	Check for visual anomalies	according to specification	36

9.1.2.3 Process Qualification Tests for the Model 3387 DBS Lead

These tests were conducted to assure that, on a limited quantity basis, the initial tooling, preliminary manufacturing processes, inspection processes, operator training outlines, and inspector training meet the dimensional, weld quality, and general workmanship required for the intended use of the Model 3387 DBS Lead. The following tests were completed to support the Process Qualification phase:

- Coil winding dimensional conformance,
- Lead dimensional conformance,
- Workmanship requirements and conformance,
- Weld requirements, and
- Stylet conformance.

9.1.3 Reliability

The estimated maximum failure rate, based on an analysis of component reliability is 0.27% per device-month. Only one electrical component failure was known to have occurred during the clinical trials, which is within bounds of the analytic prediction.

9.1.4 Biocompatibility

The materials used in the Model 3387 DBS Lead, lead stylet, and burr hole ring, which come into contact with body tissues are MP35N (metal alloy), Polyetherurethane , Polyetherurethane adhesive, Polytetrafluoroethylene (PTFE), Platinum / Iridium, Tungsten, Nylon, and Parylene® C. The materials which are intended to have permanent contact with brain tissue and CSF include Polyetherurethane lead jacket, Polyetherurethane adhesive, PTFE, and the Platinum / Iridium electrodes. All other materials identified as patient contacting materials are intended to have minimal duration of contact, i.e., intraoperative, e.g., Parylene® C stylet coating and Tungsten stylet, or the contact is subcutaneous, e.g., MP35N and Nylon. MP35N metal alloy has had a long history of use as long-term neurological implant, e.g., aneurysm clips. Platinum/Iridium electrodes have had a history of use in neurological tissue, e.g., cortical and depth electrodes. There is a long history of use of Polyetherurethane from other medical devices. However, it is not known what the long-term biocompatibility of Polyetherurethane is when implanted directly in brain tissue. This type of new application often requires additional data to assure the device will not have long-term adverse effects associated with the biological response to the material.

A theoretical analysis of potential breakdown products for the Polyetherurethane lead jacket included several compounds that could cause neurotoxic or carcinogenic effects. Some of these compounds have been shown in the literature to cause neurotoxicity when administered intracranially; some have not been studied with intracranial administration, but are known from the literature to cause neurotoxic or carcinogenic responses with systemic administration; while others have not been studied for neurotoxicity or carcinogenicity. Because the amounts of these compounds released from the final device over time are unknown, the device labeling includes a warning that three known neurotoxins and one known carcinogen may be breakdown products of the Polyetherurethane lead jacket, and although long term human exposure to Polyetherurethane has shown no evidence of neurotoxicity or carcinogenicity in pacemaker leads, these materials have not been previously implanted in the brain.

The following biological safety tests were conducted at least in part on most of these materials in support of their biocompatibility: Tissue Culture/MEM Elution for cytotoxicity, hemolysis, USP Pyrogen Test, Modified USP Class V Plastics Test, Ames Mutagenicity Test, Modified In Vitro Chromosomal Aberration Assay, Modified In Vivo Mouse Micronucleus Test, Guinea Pig Maximization for Sensitization, and 12-Week Intramuscular Implant Test. All tests were conducted in accordance with Good Laboratory Practice. Tests not conducted on these materials and typically recommended for this type permanent duration of contact include: subchronic toxicity, chronic toxicity, and carcinogenicity testing.

Additional tests performed by the sponsor intended to support the long-term contact of Polyetherurethane tubing in brain tissue include a 12 month intracerebral sheep study and 14 to 180 day intracranial rabbit study. These studies provided some information on local tissue effects of the material on brain tissue but were not designed to study the potential physiological effects of this material.

In most cases, the biological safety tests identified above were not conducted on the final device, but on materials used to fabricate the final product. Not all of the tests were conducted on all of the fabrication materials, and some of the testing conditions were not optimal (e.g., extraction media, temperature and time). From the results of these tests, the FDA identified two remaining issues with Polyetherurethane when used as a permanent implant material in the brain: device potential for neurotoxicity, and carcinogenicity, which are reported to the user in the labeling. The sponsor provided to FDA a complete list of the proprietary materials used to fabricate the Polyetherurethane, in order to allow FDA to perform a risk assessment of use of this material for implantation in the brain.

9.1.5 Biostability

Biostability testing was performed on the Polyetherurethane lead jacket. No environmental stress cracking (ESC) beyond "Cosmetic ESC" (i.e., "very shallow cracks at 70X magnification) is expected to occur. All samples tested showed acceptable electrical results when compared with similar samples that had not been subjected to a biological environment. Additionally, no degradation of the PTFE insulation was found on any of the wires. The electrical current leakage testing performed on the individual wires supported evidence of the insulation integrity.

9.1.6 Other Testing

Shelf-life and packaging validation tests, sterilization validation tests, and manufacturing validations tests were also successfully completed per recognized protocols. Expiration dating for the generator and the lead has been established and approved for 18 months and 4 years, respectively.

9.2 Animal Studies

9.2.1 Effectiveness

Practically all significant evidence of the therapeutic effect of stimulating the VIM, is derived from humans. Animal models of Parkinson's Disease Tremor exist through the use of MPTP (1-methyl-4-phenyl -1,2,3,6-tetrahydropyridine). However, these models are antedated by the human experience which began in the 1950's. One of the methods used by clinicians to verify the target during thalamotomy procedures is electrical stimulation of the target. If stimulation suppressed the tremor, the lesion was made. Recognizing the effectiveness of the stimulation procedure itself, clinicians began to explore chronic stimulation as a therapy in humans in the mid-1980s, foregoing animal testing of effectiveness.

No specific animal tests were conducted regarding the use of the Activa™ System for the treatment of tremor for the following reasons:

- The stimulation principles are the same as previous generations of deep brain stimulation systems.
- The implant techniques are similar to those used for the previous generations of Medtronic stimulation systems (e.g., those used for deep brain stimulation for treatment of chronic pain).
- The literature contains a number of reports regarding the clinical efficacy of deep brain stimulation for the treatment of tremor.

Animal testing was conducted on the Model 3387 Lead for deep brain stimulation safety. A summary of each is given below.

9.2.2 Safety

Histopathological effects of electrical brain stimulation have been described by McCreery*et al*[1]. They determined safe parameters from cat cerebral cortex with 30 Hz stimulation. These stimulus parameters were compared to the maximum output of the Model 7424 IPG. The Model 7424 IPG with the Model 3387 DBS Lead produced the following maximum stimulation:

Electrode Surface Area	0.06 cm^2
Pulse Duration	450 microseconds
Amplitude	10.5 V, or 21.0 mA into 500 ohms
Charge per Phase	9.45 microCoulombs
Charge Density	150 microCoulombs/cm^2
Frequency	185 Hz

These stimulus parameters are above the "damage" threshold reported by McCreery. The device labeling includes a warning identifying those parameters which result in charge densities greater than 30 microCoulombs/cm^2.

9.2.3 Related Human Study

The one published autopsy from a patient who underwent thalamic stimulation for tremor relief describes small histopathological changes near the electrode. Caparros-Lefebvre et al[2] performed an autopsy on a patient who had undergone chronic thalamic stimulation with the predecessor to the Model 7424 IPG. They observed histopathological changes within 2 mm of the tip of the lead. These changes were attributed to the electrical stimulation.

Calculations based on those of Caparros-Lefebvre reveal the following stimulus parameters:

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1 Mc Creery DB, Agnew WF, Yuen TGH, Bullara L. Charge density and charge per phase as cofactors in neural injury produced by electrical stimulation, IEEE Trans. Biomed. Eng. 37:996-1001, 1990.

2 Caparros-Lefebre D, Ruchoux MM, Blond S, et al. Long term thalamic stimulation in Parkinson's Disease: postmortem anatomoclinical study, Neurology 44:1856-1869, 1994.

Electrode Surface Area	0.143 cm^2
Pulse Duration	150 microseconds
Amplitude	1.5 V, or 3.0 mA into 500 ohms
Charge per Phase	0.45 microCoulombs
Charge Density	3 microCoulombs/cm^2
Frequency	130 Hz

These stimulation parameters were within the safe limit of 30 microCoulombs/cm^2 of McCreery.

The previous animal studies of McCreery demonstrated a potential risk from electrical stimulation. The postmortem study of Caparros-Lefebvre demonstrated that thalamic stimulation for tremor relief is capable of producing histopathological changes.

9.2.4 Implant Protocol Description

Good Laboratory Practices (GLP) pig studies were conducted to determine acute and chronic effects of electrical stimulation on brain tissue. On each side of the brain, one lead was placed in a deep target intended to be the thalamus and another under the cortical surface. Animals were stimulated through one randomly selected cortical lead and one randomly selected thalamic lead. The contralateral cortical and thalamic leads which were not connected to a stimulator served as controls.

A pathologist, who was blinded as to the stimulated electrode, examined the tissue around the electrodes for damage and made side to side comparisons indicating which, if either, of the electrodes in each pair showed greater pathology in the surrounding tissue.

9.2.4.1 Acute Phase

This study employed acute stimulation under general anesthesia with the goal to delineate thresholds of stimulation that caused tissue damage. Ten pigs were implanted with the Model 3387 Leads (also used in the clinical trials). Each animal was given bilateral thalamic and cortical leads, and one of each bilateral lead was stimulated. The animals received stimulation for seven continuous hours under general anesthesia at the maximum commercially available voltage (10.5 volts), with eight of the pigs stimulated at 185 pps (the maximum frequency available in the Model 7458 MemMod) and two pigs stimulated at 130 pulses per second. The pulse widths ranged from 913 microseconds, which is greater than the commercially available Model 7424 IPG maximum, to nearly 2000 microseconds. These stimulus parameters gave a stimulus charge per phase ranging from 9.5 to 42.0 microCoulombs (assuming a 500 ohm load), and these exceeded the McCreery damage threshold of 2 microCoulombs (for the Model 3387 Lead surface area electrode). Over the course of the study one of the animals was eliminated because of seizures. None of the pigs displayed gross motor deficits. Histopathology results showed tissue damage from all leads (both stimulated and unstimulated). This tissue damage involved an inflammatory reaction, gliosis and neuronal degeneration, and it was seen in all animals studied. In each case the pathologist was asked to determine which side showed the most damage. Three of nine animals showed differential damage between the two sides; of these, the pathologist correctly predicted the stimulating electrode (one cortical, one thalamic). The pathologist incorrectly predicted the third stimulating thalamic electrode.

9.2.4.2 Chronic Phase

This study used chronic stimulation at lower amplitudes to evaluate long term effects. The primary goal was to contrast the response of brain tissue around stimulated leads, with tissue around leads implanted on the contralateral side that were not stimulated.

Eight animals were included in this study with Model 3387 Leads (each with two cortical and two thalamic leads), and each followed the stimulus protocol from 2 - 9 months with continuous stimulation. The stimulation parameters were: pulse width, 450 microseconds (Model 7424 IPG maximum setting), frequency, 185 pps; and the amplitude was variable depending upon what the pig could tolerate.

Two animals experienced seizure as stimulus amplitudes were being adjusted. One animal developed hydrocephalus and was terminated from the study. The results are based on descriptions of the histology from five histological sections from each of the seven remaining animals. Inflammation, mineralization, gliosis and neuronal degeneration were noted to be within 2 mm along the implant tracts. Differential damage was used as a means of assessing the effects of stimulation. There were 14 lead pairs evaluated from the seven remaining pigs. Eleven lead pairs (both cortical and thalamic) were judged to show different

degrees of histopathology. For 21.4% (3) of these lead pairs, there was no pathological difference found between the tissue samples exposed to stimulation and the controls (not stimulated) above the background mechanical damage caused by the lead. For the remaining 78.6% (11) lead pairs, there was a pathological difference between tissue samples. For the samples with a difference, the pathologist was able to correctly predict the stimulating lead in four sample pairs and was incorrect for seven sample pairs.

It was concluded that delivering electrical stimulation through the leads at the charge densities used in this study caused no additional observable effects to brain tissue over mechanical damage caused by the lead. However, side to side comparisons of the stimulated and unstimulated leads made in this study may not be valid due to inconsistent anatomical location of the leads.

9.2.5 Additional Studies

9.2.5.1 Intracerebroventricular Polyurethane Device Study in Sheep for 3 and 12 Months

Using a sheep model, samples of another polyurethane type device manufactured by Medtronic were implanted into the lateral ventricle. A summary of this study reported the following:

> "Six animals were implanted, with one animal terminated after 10 days due to surgical complications. The five remaining implanted animals had their intracerebroventricular pressures taken at 3 months. Two animals had elevated pressures. For these two animals, it was determined at necropsy that the device was inadvertently implanted in the thalamus instead of the lateral ventricle. Thus, the pressure readings were inaccurate. The remaining three animals did not have elevated pressures. All animals were terminated, three at 3 months and 2 at 12 months. At three months, microscopic neuropil changes ranged from minimal to mild inflammation limited to the area immediately adjacent to the device. The response observed from the device site was found to compare favorably to the tissue immediately adjacent to non-absorbable sutures used during the surgical site closure. Devices implanted for twelve months showed a minimal to mild fibrous reaction around the subcutaneous implant sites of device segments and connections, which is consistent with a 365 day implant. Inflammation was extremely minimal in all the sections and consisted mostly of histiocytes and sparse numbers of lymphocytes around suture material. No significant degeneration of the neuropil was evident adjacent to the device's tract."

Since the Model 3387 DBS Lead is also comprised of Polyurethane elastomer (although without the tantalum), and is implanted in brain tissue, the results from this study are intended to further support the biocompatibility of the Model 3387 DBS Lead.

9.2.5.2 Polyurethane Tubing Intracranial Implants in Rabbits for 14, 32, 90, and 180 Days

These studies also utilized tantalum impregnated polyurethane placed intracranially in rabbits for 14, 32, 90, and 180 days. These studies were intended to provide additional support of the biocompatibility of the polyurethane material used in the Model 3387 DBS Lead in contact with brain tissue. The test results indicated that the test material was non-irritating when compared to a USP negative control.

9.2.6 Conclusions

The non-clinical laboratory, in-vivo (animal) studies were intended to demonstrate that the Activa™ System used with the Model 3387 DBS Lead and accessories for deep brain stimulation therapy for the treatment of tremor is safe for human use. However, these studies do not obviate the risk for the development of histopathological changes near the lead site which were seen in a postmortem study and expected from other animal studies. The studies do not completely eliminate the possibility that the materials used in direct contact with brain tissue and CSF do not have long-term physiological effects.

10. Summary of Clinical Studies

Tremor is an involuntary, rhythmic, oscillatory movement produced by reciprocally innervated antagonistic muscles. Tremor may be classified as rest, postural, and action. Rest tremor occurs when a limb is supported against gravity; postural tremor occurs when a limb is held against gravity; and action tremor occurs during voluntary movement of a limb. Any of these tremors may be disabling. Patients may have only one of these tremors or may have a combination, depending on disease severity.

Tremor is a common disabling symptom of two movement disorders, essential tremor and Parkinson's

disease. Tremor is the only symptom of essential tremor. Generally, postural and action tremors characterize essential tremor, although in severe cases, rest tremor may be present. The tremors associated with essential tremor may produce significant functional disability including an inability to feed oneself, drink from a cup, or write. The incidence of essential tremor increases with age, but can occur at any age. Onset is often insidious, and progression may be variable. The upper extremities are often the most affected.

Tremor is one of the cardinal signs of Parkinson's disease. The other symptoms are bradykinesia, rigidity, and postural instability. The characteristic rest tremor is the most common presenting sign of Parkinson's disease patients. It may be present in one or more limbs and is often asymmetric. Postural tremor is not uncommon in Parkinson's disease, and action tremors may be present in severe cases. The tremor of Parkinson's disease has a variable response to medical therapies and may be the most difficult symptom of Parkinson's disease to treat with anti-parkinsonian medications.

Stereotactic neurosurgical procedures such as thalamotomy have been used to treat disabling tremor due to Parkinson's disease and essential tremor. Stimulation of the VIM of the thalamus has been proposed as a nondestructive and reversible therapy for tremor. The clinical studies conducted to demonstrate the safety, effectiveness and reliability of the Activa™ System for treating tremor of the upper extremity due to essential tremor and Parkinson's disease include the following:

1) *U.S. Tremor Study*. This multicenter prospective clinical study was designed to evaluate the short term effectiveness of unilateral stimulation of the VIM of the thalamus for the suppression of tremor associated with either essential tremor or Parkinson's disease.

2) *European Tremor Study*. This multicenter prospective clinical study was designed to assess the ability of unilateral and bilateral stimulation to suppress tremor associated with essential tremor and Parkinson's disease. A cohort of patients from four sites in Sweden participated in the European Long Term Efficacy Study which was a multicenter prospective randomized study designed to evaluate the long-term effectiveness of unilateral suppression of tremor associated with either essential tremor or Parkinson's disease in patients who had been implanted for more than one year.

These clinical studies used the Unified Parkinson's Disease Rating Scale (UPDRS) and the Tremor Rating Scale (TRS) to assess the effect of stimulation on tremor of the upper extremity in patients with Parkinson's disease and essential tremor, respectively. Neurosurgeons used standard imaging and stereotactic techniques to implant the leads in the VIM of the thalamus with minor variations in technique. Intraoperative test stimulation was used to localize the VIM and confirm tremor suppression prior to lead implant in the VIM contralateral to the target extremity.

Two additional clinical studies provided data on the safety of this device:

3) *European Basic Study*. This multicenter open-label study was designed to assess deep brain stimulation in different areas of the brain to treat various diseases or conditions.

4) *DBS for Pain Study*. This study was designed to evaluate the effect of stimulation of the periaqueductal gray or the ventroposterolateral nucleus to decrease chronic pain.

10.1 Gender Bias

Inclusion and exclusion criteria were designed and carried out to avoid gender bias in patient enrollment. Of all patients enrolled, 254 of 454 (54%) were male. This proportion (254/210 = 1.21) of males is consistent with other therapeutic trials for movement disorders, such as Essential Tremor and Parkinsonian Tremor. [3]

Separate analyses of safety and effectiveness data for males and females indicated no differences between the genders; hence, the results presented in the following analyses are representative for both men and women.

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3 Olanow CW, Hauser RA, Gauger L, Malapria T, Koller W, Hubble J, Bushenbark K, Lilenfeld D, Esterlitz J. The effects of deprenyl and levodopa on the progression of Parkinson's Disease, Annals of Neurology 38(5):771-777, 1995.

10.2 U.S. Tremor Study

The objective of this study was to demonstrate the safety and effectiveness of the Activa™ System for the treatment of unilateral tremor due to Parkinson's disease (PD) and essential tremor (ET) using the patient as their own control.

10.2.1 *Investigational Plan*

Patients enrolled in the clinical study met the following inclusion criteria:

1. patients diagnosed with either Parkinson's disease or essential tremor, where tremor constituted a significant functional disability, and who had no other supraspinal CNS disease or injury;
2. tremor was disabling as determined by the patient and neurologist, for at least three months prior to enrollment, and both agreed tremor suppression would provide significant benefit;
3. tremor was at a level 3 or 4 in the extremity intended for treatment prior to implant as determined by a neurologist using the UPDRS or TRS;
4. a neurologist determined that functional disability due to tremor was not adequately controlled by medications for at least three months prior to implant;
5. medications for patients with Parkinson's disease were held constant for at least one month prior to study enrollment and patients with essential tremor were off all tremor medications for at least 1 month prior to study enrollment;
6. age 18 to 80 years;
7. patients or legal representative understood the therapy and gave signed informed consent;
8. patients must be available for appropriate follow-up times for the length of the study.

Patients were excluded according to the following criteria:

1. patients were not surgical candidates or had clinically or medically significant disease;
2. patients had a prior thalamotomy or surgical ablation procedure;
3. patients withheld informed consent;
4. patients had demand cardiac pacemakers or medical conditions which required repeat MRIs;
5. patients had a history of dementia significantly interfering with their ability to cooperate or comply with the requirements of the study or to comprehend the informed consent;
6. patients had a history of alcohol or drug abuse;
7. patients had unpredictable fluctuations or long-term levodopa syndrome;
8. patients had Botulinum Toxin injections within the 6 months prior to enrollment.

This was a prospective, controlled, multicenter clinical study with a randomized assessment at three months. Patients were implanted unilaterally and follow-up visits occurred at 1, 3, 6, 9, and 12 months. Tremor suppression with and without stimulation was compared in the absence of medications. Medication status, demographic data, and information on pre-existing conditions were collected at the preimplant assessment. Medication status, follow-up information, safety data, and stimulation parameter information were prospectively collected at follow-up visits. Patients discontinued stimulation the night before their follow-up visit. Patients with Parkinson's Disease did not take their morning dose of medications. The patient was evaluated with stimulation OFF, then with stimulation ON. The patient was evaluated again with stimulation ON after the parameters had been optimized. Therapy adverse events and system complication profiles were collected prospectively.

Tremor suppression for Parkinsonian tremor was based on Question 20 on the UPDRS. Tremor is assessed on a 0 (absent) to 4 (marked in amplitude and present most of the time) scale. The primary measurement of effectiveness for essential tremor was based on Questions 5 and 6 of the TRS, depending on whether the right or left upper extremity was identified as the target extremity. In the TRS, tremor is assessed on a 0 (none) to 4 (severe) amplitude scale.

Questions concerning activities of daily living and functional status from the UPDRS and TRS were used to provide supporting evidence (secondary outcome measures) for functional improvements. In addition, global assessments of disability were performed by the patient and the physician.

The Wilcoxon signed rank test, a nonparametric test for paired observations, was used. Paired comparisons were made between pre-implant and stimulation OFF, between pre-implant and optimized stimulation ON, and between stimulation OFF and optimized stimulation ON at each follow-up. Comparisons for activities of daily living (ADL) scores were made between pre-implant and stimulation ON.

10.2.2 Study Centers

Table 7 lists the centers who enrolled patients along with the number of patients enrolled by etiology. Between October 1993 and September 1996, 84 patients were enrolled (39 with Parkinson's disease and 45 with essential tremor.) The data from this clinical study is for unilateral stimulation only.

Table 7. Centers for U.S. Tremor Study With Patients Enrolled By Etiology

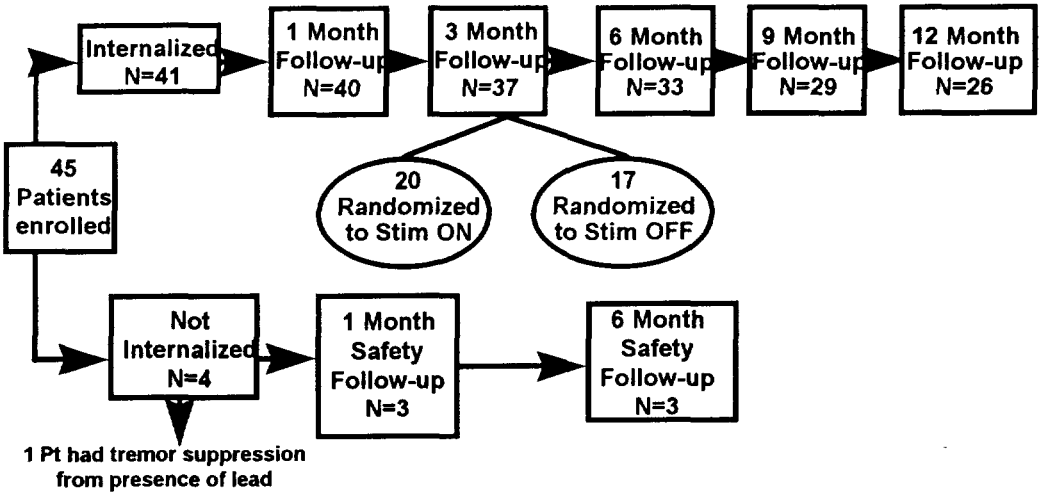
Study Center	Parkinson's Disease	Essential Tremor	Total Enrollment
University of Kansas Medical Center, Kansas City, Kansas	16	31	47
University of South Florida and Tampa General Hospital, Tampa, Florida	3	2	5
New England Deaconess Hospital, Boston, Massachusetts	3	1	4
Rush-Presbyterian-Study. Luke's Medical Center, Chicago, Illinois	0	1	1
The Toronto Hospital, Toronto Western Division, Toronto, Canada	9	6	15
The University of Minnesota and Methodist Hospital, Minneapolis, Minnesota	1	0	1
Baylor College of Medicine Houston, Texas	4	1	5
Vanderbilt University Medical Center Nashville, Tennessee	2	1	3
The Graduate Hospital Philadelphia, Pennsylvania	0	2	2
The Ohio State University Columbus, Ohio	1	0	1
TOTALS	**39**	**45**	**84**

10.2.3 Essential Tremor Patients

Table 8. Patient Demographics

Sample Size	**45**		
Gender	Males: 38 (84.4%); Females: 7 (15.6%)		
	Mean	**SD**	**Range**
Age at Implant (Years)	67.1	11.1	31.3 to 79.8
Age at Disease Onset (Years)	34.1	18.3	0.0 to 73.3
Age at Definitive Diagnosis (Years)	57.7	12.1	26.9 to 75.0
Follow-up (Months)	9.76	4.11	0.75 to 15.4
Extent of Symptoms	Bilateral: 44 (97.8%)	Left: 1 (2.2%)	Right: 0
Target Extremity	Left Upper: 3 (6.7%)	Right Upper: 42 (93.3%)	
Target Tremor	Action: 32 (71.1%)	Postural: 12 (26.7%)	Rest: 1 (2.2%)

Figure 1. Patient Flow



As seen in Table 9, tremor was suppressed at all follow-up visits when tremor scores for optimized stimulation ON were compared to stimulation OFF (p=0.0001) and when tremor scores for optimized stimulation ON were compared to preimplant tremor scores (p<0.0001).

Table 9. Mean Tremor Scores

Follow-up Assessment	Pre - Implant	One Month		Three Months		Six Months		Nine Months		Twelve Months	
Stimulation Status		OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON
N [a]	45	40	40	37	37	34	33	29	29	26	26
Mean	3.13	3.03	1.15	2.76	0.89	2.79	1.21	2.97	1.10	3.04	1.27
SD	0.41	0.83	0.74	1.01	0.80	0.93	0.98	1.05	0.77	0.89	0.92
Range	2 to 4	1 to 4	0 to 3	1 to 4	0 to 3	1 to 4	0 to 4	0 to 4	0 to 2	1 to 4	0 to 3
Difference [b]		0.13	-1.98	-0.41	-2.30	-0.36	-1.94	-0.17	-2.03	-0.08	-1.84
p-value [c] [d]		0.4565	0.0001	0.0097	0.0001	0.0236	0.0001	0.2859	0.0001	0.8254	0.0001
Difference [e]		-1.89		-1.92		-1.55		-1.86		-1.72	
p-value [c]		0.0001		0.0001		0.0001		0.0001		0.0001	

[a] Numbers between stimulation on and stimulation off may not be identical due to missing data.
[b] between stimulation status and preimplant tremor scores
[c] p-values determined using Wilcoxon Signed Rank Test.
[d] stimulation status (ON or OFF) score compared to preimplant score
[e] between stimulation ON and OFF tremor scores

As seen in Table 10, the activities of daily living were all improved at each follow-up with stimulation ON as compared to preimplant.

Table 10. Activities of Daily Living

ACTIVITY	Pre-implant	1 Month	3 Month	6 Month	9 Month	12 Month
N	45	42	38	36	29	26
Draw A	3.09	1.48	1.55	1.44	1.24	1.61
P-Value ON to Pre-implant		0.0001	0.0001	0.0001	0.0001	0.0001
Draw B	3.31	1.90	1.76	1.91	1.72	1.96
P-Value ON to Pre-implant		0.0001	0.0001	0.0001	0.0001	0.0001
Draw C	3.13	1.64	1.39	1.53	1.38	1.54
P-Value ON to Pre-implant		0.0001	0.0001	0.0001	0.0001	0.0001
Pouring	3.15	1.35	1.10	1.55	1.48	1.54
P-Value ON to Pre-implant		0.0001	0.0001	0.0001	0.0001	0.0001
Feeding food	2.80	1.28	1.00	1.14	1.21	1.31
P-Value ON to Pre-implant		0.0001	0.0001	0.0001	0.0001	0.0001
Liquids to mouth	3.46	1.28	1.00	1.28	1.28	1.58
P-Value ON to Pre-implant		0.0001	0.0001	0.0001	0.0001	0.0001
Writing	3.22	1.71	1.61	1.69	1.59	1.85
P-Value ON to Pre-implant		0.0001	0.0001	0.0001	0.0001	0.0001

Table 11 shows that both examiners and patients considered the disability due to tremor as decreased.

Table 11. Disability Assessment

	Pre-implant	1 month	3 month	6 month	9 month	12 month
N	44	42	38	36	29	26
Examiner	3.11	1.57	1.34	1.69	1.65	1.65
P-Value ON to Pre-implant		0.0001	0.0001	0.0001	0.0001	0.0001
Patient	3.20	1.57	1.37	1.58	1.69	1.73
P-Value ON to Pre-implant		0.0001	0.0001	0.0001	0.0001	0.0001

Stimulation parameters used during the clinical study are presented in Table 12.

Table 12. Mean Stimulation Parameters

		Discharge	One Month	Three Months	Six Months	Nine Months	Twelve Months
	N:	36	40	38	33	29	26
Amplitude (Volts)	mean:	2.31	2.75	3.20	2.87	2.87	2.79
	SD:	0.87	1.29	1.10	1.15	1.19	1.10
	Range:	0.70 to 4.10	0.0 to 4.90	0.80 to 6.40	0.0 to 6.20	0.0 to 5.80	0.0 to 4.90
p-value[(a)] compared to discharge:		-	0.0008	0.0001	0.0001	0.0001	0.0001
p-value[(a)] compared to three months:		-	-	-	0.2195	0.5689	0.0781
Pulse Width (mS)	mean:	82.5	93.0	115.3	107.3	95.2	86.5
	SD:	39.5	49.4	79.1	75.8	61.1	54.5
	Range:	60 to 210	60 to 270	60 to 330	60 to 330	60 to 270	60 to 270
Frequency (pulses/second)	mean:	151.8	155.8	162.2	160.8	154.9	153.3
	SD:	24.6	29.4	26.7	27.4	29.1	32.6
	Range:	100 to 185	100 to 185	100 to 185	100 to 185	100 to 185	90 to 185

[(a)] p-values determined using Wilcoxon signed rank test.

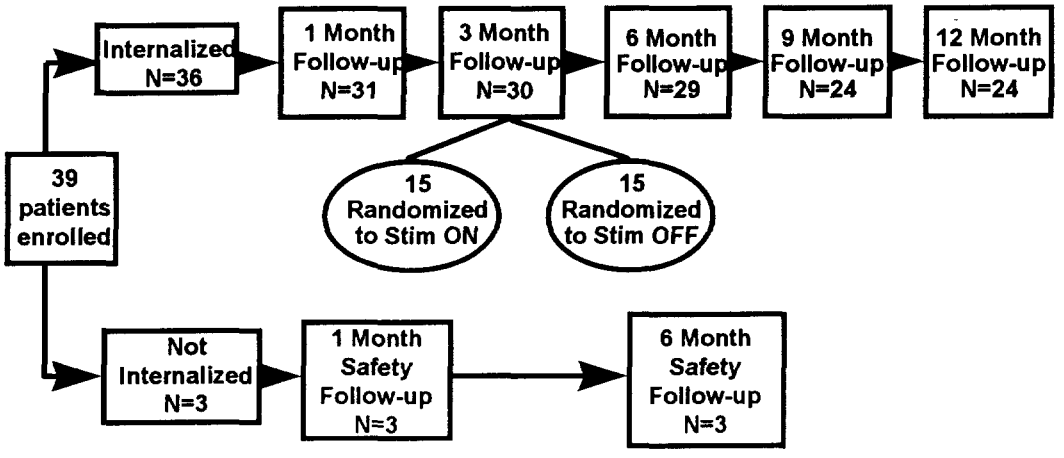
Propranolol and primidone are common medications for treating tremor due to essential tremor. During the course of the study, one patient increased his dose of primidone, one patient reinstated primidone medication, two patients decreased their dose, five patients discontinued primidone and one patient did not change his primidone dose. In the case of propranolol, three patients discontinued use, and one patient began using the medication. In addition, some patients were on other medications such as benzodiazepines that could affect tremor.

10.2.4 Parkinson's Disease Patients

Table 13. Patient Demographics

Sample Size	**39**		
Gender	Males: 31 (79.5%); Females: 8 (20.5%)		
	Mean	**SD**	**Range**
Age at Implant (Years)	65.3	10.0	38.2 to 79.7
Age at Disease Onset (Years)	55.6	9.2	30.5 to 70.0
Age at Definitive Diagnosis (Years)	57.3	9.5	33.9 to 72.0
Follow-up (Months)	10.49	3.57	0.9 to 15.9
Extent of Symptoms	Bilateral: 31 (79.5%)	Left: 3 (7.7.%)	Right: 5 (12.8%)
Target Extremity	Left Upper: 12 (30.8%)	Right Upper: 27 (69.2%)	
Target Tremor	Action: 6 (15.4%)	Postural: 10 (25.6%)	Rest: 23 (59.0%)

Figure 2. Patient Flow



Tremor suppression was assessed by determining the effect of stimulation ON and OFF in Parkinson's disease patients who had foregone their morning dose of medication. Table 14 shows that tremor was suppressed at all follow-up visits when tremor scores for optimized stimulation ON were compared to stimulation OFF (p=0.0001) and when tremor scores for optimized stimulation ON were compared to preimplant (p=0.0001).

Table 14. Mean Tremor Scores

Follow-up Assessment	**Pre-implant**	**One Month**		**Three Months**		**Six Months**		**Nine Months**		**Twelve Months**	
Stimulation Status		**OFF**	**ON**	**OFF**	**ON**	**OFF**	**ON**	**OFF**	**ON**	**OFF**	**ON**
N[a]:	39	30	31	30	30	28	29	24	24	24	23
Mean:	3.38	2.79	0.90	3.07	0.63	2.89	0.69	3.04	1.00	2.92	0.78
SD:	0.71	1.15	0.94	0.87	0.85	1.10	1.04	0.86	1.06	1.10	1.17
Range:	1 to 4	0 to 4	0 to 3	1 to 4	0 to 3	0 to 4	0 to 3	1 to 4	0 to 4	0 to 4	0 to 4
Difference[b]	-	-0.55	-2.39	-0.27	-2.70	-0.43	-2.62	-0.29	-2.07	-0.33	-2.48
p-value[c] [d]	-	0.014	0.0001	0.174	0.0001	0.044	0.0001	0.303	0.0001	0.099	0.0001
Difference[e]		-1.89		-2.43		-2.21		-2.04		-2.22	
p-value[c]		0.0001		0.0001		0.0001		0.0001		0.0001	

(a) Numbers between stimulation on and stimulation off may not be identical due to missing data
(b) p-values determined using Wilcoxon signed rank test
(c) between stimulated status and preimplant tremor scores
(d) stimulation status (ON or OFF) score compared to preimplant score
(e) between stimulation ON and OFF tremor scores

Table 15 shows the results of optimized stimulation ON compared to preimplant for the other symptoms of Parkinson's disease.

Table 15. Symptoms as Determined by the UPDRS Motor Exam

Assessment	Preimplant	1 Month	3 Months	6 Months	9 Months	12 Months
N	39	31	30	30	24	23
Rigidity	1.64	1.55	1.27	1.46	1.33	1.22
P-value ON to preimplant		.7501	.0633	.3877	.1447	.0479
Bradykinesia	1.97	1.90	2.00	1.93	2.13	2.35
P-value ON to preimplant		.2734	.8036	.9564	.6401	.1001
Postural Stability	0.87	0.77	0.83	0.83	0.63	1.00
P-value ON to preimplant		.7744	.4639	.6720	.7813	.1915

As seen in Table 16, tremor was the only activity of daily living which improved at all follow-up visits, when optimized stimulation ON was compared to preimplant.

Table 16. Activities of Daily Living

ACTIVITY	Pre-implant	1 Month	3 Month	6 Month	9 Month	12 Month
N	39	31	30	30	24	23
Writing	2.69	1.81	2.07	2.34	2.42	2.26
P-value ON to preimplant		.0007	.0195	.1971	.6863	.4608
Cut Food	1.77	1.32	1.30	1.40	1.45	1.65
P-value ON to preimplant		.0018	.0579	.4193	.7949	1.0000
Tremor	3.36	1.74	1.63	2.00	1.67	1.52
P-value ON to preimplant		.0001	.0001	.0001	.0001	.0001
Schwab & England	72.9	74.8	75.9	77.0	78.3	75.7
P-value ON to preimplant		.3258	.8968	.9468	.4084	1.000

Table 17 shows that examiners and patients rated the disability as decreased at each follow-up visit. The Hoehn and Yahr score was significantly different at the 12 month follow-up visit (p=0.0273).

Table 17. Disability Assessment

	Pre-implant	1 Month	3 Months	6 Months	9 Months	12 Months
N	39	31	30	30	24	23
Examiner	2.67	1.70	1.70	1.87	1.71	1.74
P-value ON to preimplant		.0001	0.0004	0.0056	0.0012	0.0034
Patient	2.82	1.68	1.70	1.90	1.71	1.65
P-value ON to preimplant		.0001	.0001	.0005	.0001	0.0001
Hoehn/Yahr	2.13	2.10	2.17	2.33	2.21	2.39
P-value ON to preimplant		.8242	.3667	.0869	.2578	.0273

Stimulation parameters used during the clinical study are presented in Table 18.

Table 18. Mean Stimulation Parameters

		Discharge	One Month	Three Months	Six Months	Nine Months	Twelve Months
N:		25*	29	30	29	24	24
Amplitude (Volts)	mean:	2.08	2.59	3.01	3.20	3.18	3.38
	SD:	1.17	0.99	1.18	1.19	0.94	1.11
	Range:	0 to 5.0	0.2 to 4.5	0.0 to 6.0	0.0 to 6.0	1.7 to 5.5	1.7 to 6.0
p-value[(a)] compared to discharge:		-	0.0009	0.0001	0.0001	0.0010	0.0008
p-value[(a)] compared to six months:		-	-	-	-	0.7231	0.1880
Pulse width (mS)	mean:	114.0	114.8	108.0	106.6	107.5	117.5
	SD:	59.4	53.2	45.7	38.9	44.2	50.8
	Range:	60 to 270	60 to 270	60 to 210	60 to 180	60 to 210	60 to 210
Frequency (pulses/second)	mean:	143.8	157.4	155.0	156.0	160.2	165.6
	SD:	45.8	29.9	34.1	32.3	24.5	23.8
	Range:	30 to 185	100 to 185	50 to 185	50 to 185	130 to 185	130 to 185

[(a)] p-values determined using Wilcoxon signed rank test.
*Not all patients were programmed at discharge

Medications commonly used to treat patients with Parkinson's disease include L- dopa and the anticholinergics. Over the course of the study, ten patients increased their L- dopa dose, seven patients began L- dopa, five patients decreased L- dopa and three patients discontinued L- dopa. In the case of the anticholinergics, six patients discontinued the medication, five patients were unchanged, and two began drug therapy. In addition, some patients were on other medications, such as benzodiazepines and dopamine agonists, that may affect tremor.

The data in Tables 19 and 20 are from randomization at the three month follow-up of patients enrolled in the U.S. Tremor Study between October 1993 and January 1996. Fifty-three patients were randomized; 29 essential tremor patients and 24 Parkinson's disease patients who had foregone their morning dose of medication. Patients were randomized to two groups: (1) the treatment group, which was defined as stimulation ON, and (2) the control group, which was defined as stimulation OFF. Efficacy was measured by nonparametric comparison of average tremor scores at the three-month blinded assessment between the treatment group and the control group.

Table 19. Average Tremor Score Results for Essential Tremor Patients

	N	Preimplant Baseline	Blinded 3-Month Response	Average Paired Difference	P-Values
Control:	13	3.08	2.85	-0.23	0.500 (NS) [(a)]
Treatment:	16	3.06	0.81	-2.25	< 0.001
p-Values [(b)]			< 0.001 [(c)]	< 0.001 [(d)]	

(a) Wilcoxon Signed Rank Test (paired data), "NS" = not significant at the 5% level.
(b) p-values for comparisons of the stimulated group to the non-stimulated group
(c) Wilcoxon Rank Sum Test (not paired data), comparing 2.85 with 0.81.
(d) Wilcoxon Rank Sum Test (not paired data), comparing -0.23 with -2.25.

Table 20. Average Tremor Score Results for Parkinson's Disease Patients

	N	Preimplant Baseline	Blinded 3-Month Response	Average Paired Difference	P-Values
Control:	11	3.36	2.82	-0.54	0.109 (NS) [(a)]
Treatment:	13	3.15	1.23	-1.92	= 0.003
p-Values [(b)]			0.003 [(c)]	0.018 [(d)]	

(a) Wilcoxon Signed Rank Test (paired data), "NS" = not significant at the 5% level.
(b) p-values for comparisons of the treatment group to the control group
(c) Wilcoxon Rank Sum Test (not paired data), comparing 2.82 with 1.23.
(d) Wilcoxon Rank Sum Test (not paired data), comparing -0.54 with -1.92.

10.3 European Tremor Study

This clinical study was a multicenter, international study. The objective of this clinical investigation was to demonstrate the safety and effectiveness of the use of unilateral or bilateral stimulation for the suppression of tremor in patients diagnosed with Parkinson's disease or essential tremor.

10.3.1 Investigational Plan

Patients were included according to the following guidelines:

1. diagnosed with Parkinson's disease or essential tremor;
2. tremor was drug resistant;
3. the patient experienced disabling tremor most of the day while treated with anti-tremor drugs at maximal tolerated doses;
4. tremor was disabling with tremor score of 3 or greater; and
5. patient agreed to abide by the study protocol.

Patients were excluded who:

1. were not good surgical candidates for thalamotomy;
2. had clinically significant brain damage as determined using MRI; and
3. had been diagnosed with any medical disorder which may interfere with the effectiveness of tremor suppression.

This study was designed as a prospective, clinical investigation of the treatment of tremor using the Activa™ System. The null hypothesis was that mean tremor score decreased less than two levels on the appropriate tremor scale with stimulation as compared to pre-implant.

The UPDRS was used to evaluate patients with Parkinson's Disease, and the TRS was used to evaluate essential tremor patients. Patients were assessed at 3, 6, and 12 months with stimulation ON and stimulation OFF. Medications were not discontinued prior to evaluations. The assumption was that since the tremor was not responding to the medical therapy, medications would have no effect on the evaluation since they were already at the maximum tolerable dose. Therapy adverse event and system complication profiles were collected prospectively.

10.3.2 Study Centers

One hundred and thirteen patients (38 patients with essential tremor and 75 patients with Parkinson's disease) were enrolled in this clinical investigation at 13 centers. Study enrollment ceased November 30, 1994, and one year follow-up assessments were completed by November 30, 1995. Eighty-five (28 essential tremor and 57 Parkinson's disease) patients had unilateral implants and 27 (10 essential tremor and 17 Parkinson's disease) patients had bilateral implants. The data presented is only for unilateral stimulation.

Table 21. Centers for European Tremor Study with Patients Enrolled by Etiology

Study Center	Essential Tremor	Parkinson's Disease	Total Enrollment
Algemeines Karankenhaus der Stadt Wien and Neurologisches Krankenhaus,Vienna, Austria	3	12	15
Sahlgrenska Hospital, Gothenburg, Sweden	4	7	11
Joseph Fourier University of Grenoble,Grenoble, France	10	23	33
Amsterdam Medical Center, Amsterdam, The Netherlands	1	6	7
Heilig Hart Roselare, Roselare, Belgium	0	2	2
University Hospital, Umea, Sweden	5	2	7
Karolinska Hospital, Stockholm, Sweden	5	5	10
Hopital Henri Mondor Creteil, France	3	5	8
University Hospital, Lund, Sweden	6	8	14
The National Hospital, London, United Kingdom	0	1	1
Dundee Royal Infirmary, Dundee, United Kingdom	1	0	1
Royal London Hospital, Whitechapel, United Kingdom	0	1	1
CHU Clermont Ferrand, Chamalieres, France	0	3	3
TOTALS	38	75	113

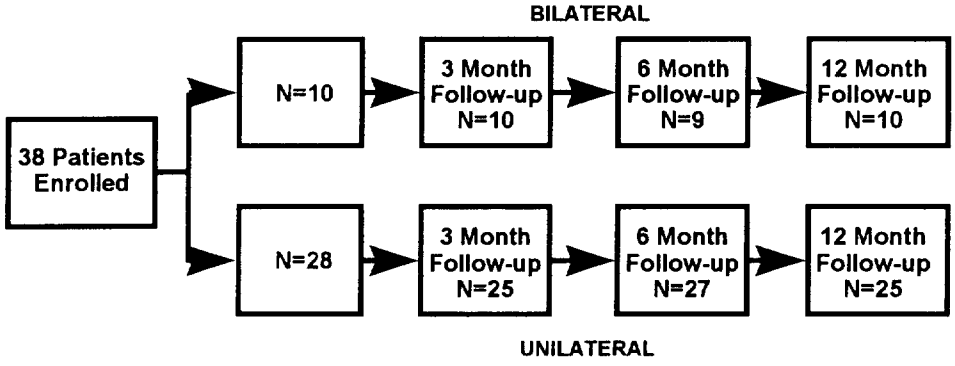
Table 22. Patient Demographics

	ESSENTIAL TREMOR	PARKINSON'S DISEASE
Sample size	38	75
Gender N (%)		
male	25 (65.8%)	48 (64.0%)
female	13 (34.2%)	27 (36.0%)
Age at implant (years)		
mean	63.7	62.1
range	31.0-83.3	29.0-77.9
Age at onset of disease process (years)		
mean	36.8	51.2
range	11.3-81.4	22.5-69.6
Extent of symptoms* N (%)		
bilateral	34 (89.5%)	57 (77.0%)
unilateral	4 (10.5%)	17 (23.0%)
Laterality of implant* N (%)		
bilateral	10 (26.3%)	17 (23.0%)
right VIM	6 (15.8%)	23 (31.1%)
left VIM	22 (57.9%)	34 (45.9%)
Follow-up (months)		
mean	12.2	11.9
range	5.8-19.8	3.2-19.5

*may not total to 113 patients due to unreported data

10.3.3 Essential Tremor Patients

Figure 3. Patient Flow

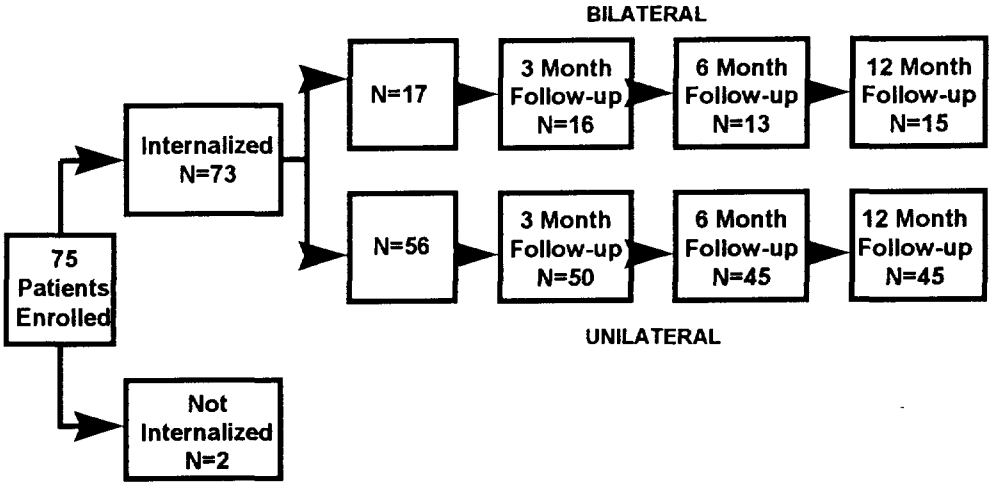


Postural tremor and action tremor were suppressed at all follow-up visits when stimulation ON was compared to stimulation OFF ($p<0.0001$) and when stimulation ON was compared to preimplant ($p<0.0001$). For essential tremor, the activities of daily living were all significantly improved with stimulation ON as compared to the preimplant baseline ($p<0.001$). Both the patient and examiner assessed the patients' disability due to essential tremor as significantly less with stimulation ($p<0.001$).

Six patients were taking propranolol at preimplant. Three patients discontinued medication and one remained unchanged over the course of the clinical study. Four patients were taking primidone at the beginning of the study. Three patients discontinued the medication and one remained unchanged. In addition, some patients were on other medications that may affect tremor.

10.3.4 Parkinson's Disease Patients

Figure 4. Patient Flow



Rest and action/postural tremor scores for Parkinson's disease patients receiving unilateral stimulation were suppressed when stimulation ON was compared to stimulation OFF ($p<0.0001$) and when stimulation ON was compared to preimplant ($p<0.0001$). The activities of daily living were significantly improved at all follow-up visits ($p<0.001$). Hoehn and Yahr staging system results indicated that disability due to tremor was not significantly changed.

Data was available on 45 patients at preimplant and the last follow-up visit. Thirty-three patients were on L-dopa at preimplant. Ten patients took less L- dopa, 12 patients took more L-dopa, one discontinued, five began, and seven patients did not change their dose of L- dopa. In addition, some patients were on other medications that may affect tremor.

10.4 European Long-Term Efficacy Study

This study was designed as an addendum to the European Tremor Study that evaluated patients enrolled in the original protocol. The primary purpose was to determine the long-term (>12 months) effectiveness of unilateral thalamic stimulation for the treatment of tremor due to essential tremor and Parkinson's disease.

10.4.1 Investigational Plan

All consecutively enrolled patients in the European Tremor Study from the four Swedish study centers were invited to participate in this trial. Thirty-six patients participated. Three patients declined to participate and two patients had died prior to initiation of this study.

This study was designed as a prospective, randomized clinical trial comparing stimulation ON to stimulation OFF in patients implanted for more than one year. Both essential tremor and Parkinson's disease patients were evaluated in the same manner as patients in the 3 month randomized assessment in the U.S. Tremor Study, i.e., stimulation ON and stimulation OFF without medications.

10.4.2 Study Centers

Table 23 lists the four centers in Sweden which participated in the study. The study was conducted in October and November of 1995.

Table 23. Centers for European (Swedish) Long-Term Efficacy Study with Patients Enrolled by Etiology

Study Center	Essential Tremor	Parkinson's Disease	Total Patients
Sahlgrenska Hospital, Gothenburg, Sweden	4	5	9
University Hospital, Lund, Sweden	6	6	12
Karolinska Hospital, Stockholm, Sweden	5	4	9
University Hospital, Umea, Sweden	4	2	6
TOTAL	19	17	36

10.4.3 Essential Tremor Patients

Table 24. Patient Demographics

Sample size:	**19**		
Gender:	Males: 12 (63.2%); Females: 7 (36.8%)		
	Mean	**SD**	**Range**
Age at Implant (Years):	66.2	10.3	40.2 to 81.0
Age at Evaluation (Years):	67.9	10.2	42.2 to 82.0
Follow-up (Months):	20.3	6.0	11.5 to 33.8
VIM Implanted:	Bilateral: 2 (10.5%)	Left: 14 (73.7%)	Right: 3 (15.8%)
Extent of Symptoms	Bilateral: 18 (94.7%)	Right: 1 (5.3%)	

Table 25. Mean Tremor Scores

	N	Baseline (Stimulation OFF)		Blinded Tremor Score		Difference from Baseline (Stimulation OFF)	P-Values
Control Group	11	Mean: SD: Range:	3.54 0.69 2 to 4	Mean: SD: Range:	3.36 0.81 2 to 4	-0.18	0.500 (NS)[a]
Treatment Group	8	Mean: SD: Range:	3.50 0.53 3 to 4	Mean: SD: Range:	1.38 0.92 0 to 3	-2.12	0.008
P-Values[d]				0.0012[b]		0.0002[c]	

(a) Wilcoxon Signed Rank Test (paired data), "NS" = not significant at the 5% level.
(b) Wilcoxon Rank Sum Test (not paired data), comparing 3.36 with 1.38.
(c) Wilcoxon Rank Sum Test (not paired data), comparing -0.18 with -2.12.
(d) for comparisons of control and treatment groups

10.4.4 Parkinson's Disease Patients

Table 26. Patient Demographics

Sample Size	17		
Gender	Males 12 (70.0%); Females: 5 (29.4%)		
	Mean	SD	Range
Age at Implant (Years):	64.6	8.5	39.8 to 73.9
Age at Evaluation (Years):	66.6	8.5	41.8 to 75.5
Follow-up (Months):	24.8	4.1	19.8 to 32.9
VIM implanted:	Left: 14 (82.4%)	Right: 3 (17.6%)	
Extent of Symptom:	Bilateral: 10 (58.8%)	Left: 3 (17.6%)	Right: 4 (23.6 %)

Table 27. Mean Tremor Scores

	Baseline (Stimulation OFF)		Blinded Tremor Score		Difference from Baseline (Stimulation OFF)	P-Values
Control Group	Mean	3.89	Mean:	3.67	-0.22	1.000
	SD	0.33	SD	0.71		
	Range	3 to 4	Range	2 to 4		
Treatment Group	Mean	3.38	Mean	0.63	-2.75	0.008
	SD	1.06	SD	0.52		
	Range	1 to 4	Range	0 to 1		
P-Values [c]			0.0003[a]		0.0005[b]	

(a) Wilcoxon Rank Sum Test (not paired data), comparing 3.67 to 0.63.
(b) Wilcoxon Rank Sum Test (not paired data), comparing -0.22 to -2.75.
(c) for comparison of control and treatment groups

10.4.5 European Basic Study

An open label clinical study was conducted to assess the safety and reliability of the Activa™ System for deep brain stimulation. Investigators at 19 clinical centers in 11 countries outside the United States participated in the study. The primary objective of the European Basic Study was to collect safety data to generate a safety profile of the Activa ™ System.

10.4.5.1 Investigational Plan

The investigators enrolled any patient whose treatment was approved by the study center's Ethical Committee. Patients enrolled had the following disease symptoms: Parkinson's disease, pain, multiple sclerosis, essential tremor, epilepsy, dystonia, dyskinesia, post-traumatic tremor, and other diseases with neurological affects. All 178 patients had leads implanted, with 33 (18.5%) patients receiving bilateral implants. Of the 178 patients enrolled, 158 had IPGs internalized (190 IPGs total). One hundred seventeen of the 178 patients enrolled had the device implanted in the VIM. Of these 117 patients, 105 patients had unilateral implants and 12 had bilateral implants.

Follow-up evaluations occurred at 3 and 6 months post-implant. Information gathered at follow-up included system status (in use or discontinued), lead performance, stimulation parameters at the end of the visit, and therapy adverse events and system complications occurring since internalization. The investigators reported individual therapy adverse events and system-related complications on separate forms at each follow-up or when the patient reported the event.

10.4.5.2 Patient Demographics

As of March 21, 1996, of the 178 patients enrolled in the study, 61 had Parkinson's disease, 32 had pain, 32 had essential tremor, 20 had multiple sclerosis, ten had epilepsy, six had dystonia, four had post-traumatic

tremor, and three had dyskinesia. Also, there were ten patients with various other etiologies. Pooling across all etiologies, 108 (60.7%) males and 70 (39.3%) females participated in the study. Mean age for the total cohort of patients at time of implant was 53.6 years of age. Adverse event data from this study are included in the "Others" column in Table 2 to support the safety of the Activa ™ System.

10.4.6 DBS For Pain Study

This multicenter clinical trial evaluated the safety and effectiveness of deep brain stimulation for the treatment of chronic intractable pain. Adverse event data from 41 patients are included in the "Others" column in Table 2 to support the safety of the Activa ™ System. The DBS for Pain Study collected safety data on deep brain stimulation in addition to effectiveness data on pain relief. The safety data from the European Basic Study and the DBS for Pain Study are combined in the "Others" column of Tables 2.

11. Conclusions Drawn from the Studies

11.1 Safety

Two multicenter trials were conducted to assess the safety and reliability of the Activa™ System. Adverse Event data were reported from 227 patients in the European Basic Study and the DBS for Pain Study indicate that the frequency of an event did not differ markedly from the frequencies reported for the overall study.

11.2 Effectiveness

Overall, the Activa™ System was implanted in 424 patients in 5 clinical studies involving 464 devices with a total device exposure of 347 device years Twenty-seven of these patients were bilaterally implanted, while the balance were unilaterally implanted. Individual patient exposure to device averaged 11 months (ranging from < 1 to 20 months). Only data from unilateral stimulation of patients in the US and European Tremor Studies were considered in reaching a determination for approval.

A total of 197 patients were enrolled in the US and European Tremor Studies. Of these, seven patients in the United States and one patient in Europe were not implanted with the Activa™ System. One patient had tremor suppression without stimulation, two patients had intracranial hemorrhages, and two patients had insufficient tremor suppression. One patient had both an intracranial hemorrhage and insufficient tremor suppression, one patient had a serious reaction to the general anesthetic, and one patient could not cooperate with the implant procedure.

A total of 220 IPGs were implanted in the remaining 189 patients. Fifty-three patients were assessed in a randomized manner at 3 months, and 36 patients were assessed long-term (mean follow-up of 20.3 months and 24.8 months for essential tremor and Parkinson's disease, respectively). For the US Tremor Study, a modified Mini Mental Status Examination completed by the patients showed no cognitive effects related to the tremor control therapy. Activities of daily living showed statistically significant improvement in seven scales for essential tremor patients. In patients with Parkinsonian tremor, ADL scores showed a trend in improvement in four scales, but only the tremor-specific ADL showed statistically significant improvement. Patient's assessment (subjective evaluation) of their disability was improved in both groups when compared to a preimplant assessment.

During the clinical study, 17 Parkinson's disease patients increased use of levodopa. Six patients decreased use of anticholinergics. Rebound is a phenomenon in which a patient's tremor appears clinically exaggerated (compared to baseline tremor) after turning off the stimulator. The exaggerated tremor generally stabilizes (returns to normal) within approximately 30 minutes. In the US clinical study a maximum of 29% of Parkinson's disease patients, and 28% of essential tremor patients experienced rebound lasting for a mean duration of 17 minutes and 22 minutes respectively.

For the European Tremor Study, activities of daily living and other functional improvements were statistically significant in both essential tremor and Parkinson's disease patients. During the clinical study, 17 Parkinson's disease patients increased use and 11 decreased use of levodopa. Two patients decreased use of anticholinergics.

11.3 Risk Benefit Analysis

Clinical studies using the Activa™ System demonstrated that in patients with essential tremor and Parkinson's disease, tremor was suppressed. Furthermore, in patients with essential tremor, the therapy had a positive impact on their activities of daily living and need for medication. The majority of adverse events consisted of paresthesia (33%) followed by dysarthria (9%). These adverse effects can be minimized by changing stimulation parameters, if necessary. An alternative therapy for tremor which is not adequately controlled by medications is thalamotomy. Since the effects produced by deep brain stimulation are reversible in most cases, surgery is still an option if stimulation becomes ineffective. Therefore, it is reasonable to conclude that the benefits of use of the Activa™ System for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

12. Panel Recommendation

At an advisory meeting held on March 14, 1997, the Neurological Devices Panel recommended that Medtronic's PMA for the Medtronic® Activa ™ Tremor Control System be approved subject to submission of the following:

1. results of additional biocompatibility testing,
2. resolution of engineering concerns, and
3. labeling changes.

13. FDA Decision

FDA concurred with the Neurological Devices Panel recommendation of March 14, 1997, and advised Medtronic, on July 30, 1997, that the PMA was approvable subject to Medtronic's response to the biocompatibility, engineering, and labeling issues, that were recommended by the Panel and required by FDA. In amendments received by FDA, the following were submitted and acceptable to FDA:

1. additional biocompatibility data on the Polyetherurethane used to manufacture the lead;
2. a warning added in the software to alert the user that tissue injury may occur if the stimulation exceeds 30 $\mu C/cm^2$/phase charge density;
3. revised labeling to limit use of the Activa™ System to unilateral stimulation (and not bilateral stimulation); and
4. a statement added to the labeling that materials used in the manufacture of the leads have been shown to be neurotoxic and carcinogenic.

FDA issued an approval order on July 31, 1997. The applicant's manufacturing facility was inspected and was found to be in compliance with the device Good Manufacturing Practice regulations.

The Activa ™ System was granted expedited review status on August 6, 1996 because FDA believed that deep brain stimulation for the treatment of tremor of Parkinson's disease and essential tremor might offer a viable alternative to surgery in some patients and because no legally marketed therapeutic device was available to treat this severely debilitating condition.

14. Approval Specifications

Directions for use: See the labeling.

Hazards to health from use of the device: See indications, contraindications, warnings, precautions and adverse events in the labeling.

Postapproval requirements and restrictions: See approval order.

The Approval Order, Summary of Safety and Effectiveness Data, and labeling can be found on the Internet at http: //www.fda.gov/cdrh/pmapage.html.

Medtronic

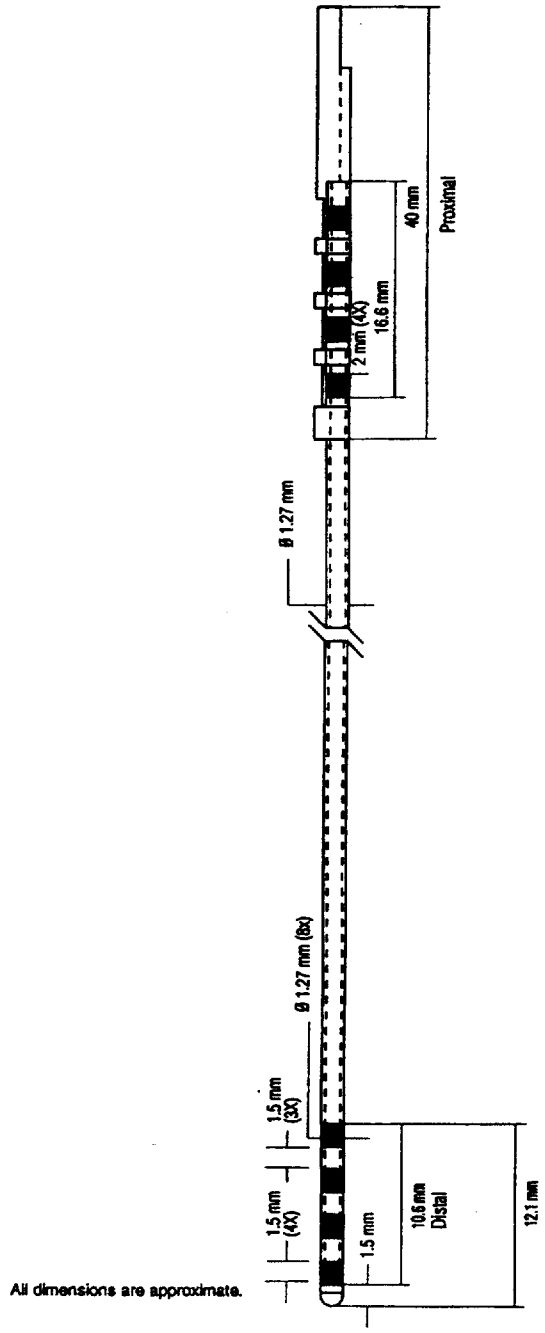
Neurological Division

DBS™

Implant Manual

Lead Kit
For Deep Brain Stimulation

Model 3387 Lead Kit



Model 3387 DBS Lead

Contents

Caution

⚠ **Federal law (USA) restricts this device to sale, distribution, and use by, or on the order of, a physician.**

Brief System Description

The Medtronic® Activa™ Tremor Control System is an implantable, multiprogrammable quadripolar system that delivers electrical stimulation to the thalamus.

Electrical signals are transmitted from the Itrel® II Model 7424 Implantable Pulse Generator (IPG) to the ventral intermediate nucleus of the thalamus via the Model 7495 Extension and the Model 3387 DBS™ Lead. The lead, extension, and IPG comprise the implantable components of the Activa Tremor Control System.

The Itrel® II Model 7424 IPG is comprised of electronic circuitry and a sealed battery, which are hermetically secured in a titanium case.

Indications

Unilateral thalamic stimulation by the Medtronic® Activa Tremor Control System is indicated for the suppression of tremor in the upper extremity. The system is intended for use in patients who are diagnosed with essential tremor or Parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability.

Contraindications

Implantation of a Tremor Control System is contraindicated for:

- Patients for whom test stimulation is unsuccessful, or
- Patients who are unable to properly operate the stimulator.

[redacted]

Warnings

⚠ **Avoid Excessive Stimulation** — There is a potential risk of tissue damage for stimulation parameter settings of high amplitudes and wide pulse widths.

The Activa™ Tremor Control System is capable of parameter settings out of the range of those used in the clinical studies. Suppression of tremor should occur at amplitudes of 1 to 3 V, pulse widths of 60 to 90 μsec, and rates of 130 to 185 Hz. Higher amplitudes and pulse widths may indicate a system problem or less than optimal lead placement. Parameter values exceeding the recommended output settings should only be programmed with due consideration of the warnings concerning charge densities and charge imbalance described in the section Directions for Use: Programming Stimulation Parameters (pages 42-46). If programming of stimulation parameters exceeds charge density limits, the following programmer warning appears: WARNING: CHARGE DENSITY MAY BE HIGH ENOUGH TO CAUSE TISSUE DAMAGE. CONSULT TECH MANUAL. PRESS CLEAR TO CONTINUE".

Rates less than 30 Hz may also be programmed. At these lower frequencies tremor may be driven, i.e., occur at the same frequency as the programmed frequency. For this reason, rates should not be programmed at lower frequencies.

⚠ **Anticoagulants**— Use extreme care with lead implantation in patients with a 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.

Precautions

Physician Training

Prescribing Physicians — Prescribing physicians should be experienced in the diagnosis and treatment of movement disorders and should be familiar with the use of the Activa™ Tremor Control System.

Implanting Physicians — Implanting physicians should be experienced in stereotactic and functional neurosurgery. Refer to the Physician Training section in this manual for further information.

Storage and Sterilization

Storage Temperature — Store the Model 3387 DBS™ Lead between -40° F (-40° C) and 167° F (75° C). Temperatures outside this range can damage components.

Resterilization Considerations — Refer to the Resterilization section on pages 23-24 for further information.

System and Therapy

Lead Materials — The polyurethane insulation of the lead may release neurotoxic or carcinogenic compounds. Data are insufficient to assess the likelihood of these effects occurring in patients who receive the device. However, long-term human exposure to this material in pacemaker leads has shown no evidence of neurotoxicity or carcinogenicity.

Component Failures — The Activa Tremor Control System may unexpectedly cease to function due to battery depletion or other causes. These events, which can include electrical short or open circuits and insulation breaches, cannot be predicted.

Components — The use of non-Medtronic components with this system may result in damage to Medtronic components, loss of stimulation, or patient injury.

Implantation / Explantation

Multiple Implants – The long-term safety associated with leads left in place without use, multiple placement of leads in the thalamus, and lead explant is unknown.

Implant Considerations — Do not implant a component of the system when:

- The storage package has been pierced or altered; or if the component shows signs of damage; or
- The "Use Before" date has expired, because this can adversely affect storage package sterility.

Handling Components — Handle the implanted components of this system with extreme care. These components may be damaged by excessive traction or sharp instruments.

- Do not bend, kink, or stretch the lead body whether or not the stylet is in place. Do not bend or kink the tungsten stylet.
- Do not tie a suture directly to the lead body. Use the burr hole cap and ring provided by Medtronic to secure the lead in place.
- When handling the lead with forceps, use only a rubber-tipped bayonet forceps.
- Be extremely careful when using sharp instruments around the lead to avoid nicking or damaging the lead body insulation.

Etched Identification—Place the Itrel® II Model 7424 IPG with the etched identification side facing outward, away from the muscle layer of the body. This helps to minimize the possibility of skeletal muscle stimulation that may be perceived as twitching or burning.

Component Disposal — If explanting an Activa System component, please remember the following guidelines:

- Do not incinerate the IPG; explosion can result if an IPG is subjected to incineration or cremation temperatures.
- Return all explanted components to Medtronic for analysis and safe disposal.

Medical Environment

Electrocautery — Electrocautery can cause temporary suppression of pulse generator output and/or reprogramming of the pulse generator. If use of electrocautery is necessary, the current path (ground plate) should be kept as far away from the pulse generator and lead as possible.

External Defibrillators — Safety for use of external defibrillatory discharges on patients with neurostimulation systems has not been established. External defibrillation may damage a pulse generator.

If external defibrillation is necessary, follow these precautions to minimize current flowing through the pulse generator and lead system:

- Position defibrillation paddles as far from the pulse generator as possible.
- Position defibrillation paddles perpendicular to the implanted pulse generator-lead system.
- Use the lowest clinically appropriate energy output (watt seconds).
- Confirm neurostimulation system function following any external defibrillation.

Magnetic Resonance Imaging — Patients with an implanted device should not be exposed to the electromagnetic fields produced by magnetic resonance imaging (MRI). Use of MRI may potentially result in dislodgment, heating, or induced voltages in the pulse generator and/or lead. An induced voltage through the pulse generator or lead may cause uncomfortable ("jolting" or "shocking") levels of stimulation. Two anecdotal reports from patients using deep brain stimulation for the treatment of chronic pain indicated pain, speech problems, temporary sensation of visual light, dizziness and nausea when exposed to MRI.

Clinicians should carefully weigh the decision to use MRI in patients with an implanted Activa Tremor Control System, and note the following:

- Magnetic and radio-frequency (RF) fields produced by MRI may change the pulse generator settings, activate the device, and injure the patient.

- Patients treated with MRI should be closely monitored and programmed parameters verified upon cessation of MRI.

Lithotripsy — Use of high output ultrasonic devices, such as an electrohydraulic lithotriptor, is not recommended for patients with an implanted neurostimulation system. While there is no danger to the patient, exposure to high output ultrasonic frequencies may result in damage to the pulse generator circuitry. If lithotripsy must be used, do not focus the beam near the pulse generator.

Diathermy — The effects of diathermy on patients with an implanted neurostimulation system are unknown. Use of diathermy directly over an implanted lead or pulse generator is not recommended since internal components may be damaged.

High Radiation Sources — High radiation sources, such as cobalt 60 or gamma radiation, should not be directed at the pulse generator. If a patient requires radiation therapy in the vicinity of the pulse generator, place lead shielding over the device to prevent radiation damage.

Effects on Other Medical Devices — The Activa Tremor Control System may affect the operation of other implanted devices, such as cardiac pacemakers and implantable defibrillators. Possible effects include sensing problems and inappropriate device responses. If the tremor patient requires concurrent implantable pacemaker and/or defibrillator therapy, careful programming of each system may be necessary to optimize the patient's benefit from each device.

Most routine diagnostic procedures, such as fluoroscopy and x-rays, are not expected to affect system operation. However, because of higher energy levels, sources such as transmitting antennas may interfere with the system.

Home or Occupational Environment

Home Appliances — Home appliances that are in good working order and properly grounded do not usually produce enough EMI to interfere with pulse generator operation.

Occupational Environments — Commercial electrical equipment (arc welders, induction furnaces, resistance welders), communication equipment (microwave transmitters, linear power amplifiers, high-power amateur transmitters), and high voltage power lines may generate enough EMI to interfere with pulse generator operation if approached too closely.

Cellular Phones — Based on tests to date, cellular phones have no effect on the Activa™ Tremor Control System. The Itrel II Model 7424 IPG does not have sensing circuitry. This circuitry contributes to the electromagnetic interference (EMI) sensing of implanted pacemakers and defibrillators.

Theft Detectors and Screening Devices — Theft detectors found in public libraries, department stores, etc., and airport/security screening devices may cause the stimulation power source of an implantable neurostimulation system to switch ON or OFF. It is also possible that sensitive patients, or those with low stimulation thresholds, may experience a momentary increase in their perceived stimulation. For other indications, higher levels of stimulation have been described as uncomfortable, "jolting" or "shocking" by some patients as they pass through these devices.

Patient Activities / Environmental Precautions — Patients should exercise reasonable caution in avoidance of devices which generate a strong electric or magnetic field. Close proximity to high levels of electromagnetic interference (EMI) may cause an IPG to switch ON or OFF. The system also may unexpectedly cease to function due to battery depletion or other causes. For these reasons, the patient should be advised about any hazardous activities that would be potentially unsafe if their tremor unexpectedly returns.

Patient Magnet — The magnet provided to the patient for device activation and deactivation may damage televisions, computer disks, credit cards, and other items affected by strong magnetic fields.

Adverse Events

The Activa™ Tremor Control System was implanted in 424 patients in 4 clinical studies involving 464 devices with a total device exposure of 347 device years. 27 of these patients were bilaterally implanted, while the balance were unilaterally implanted. Individual patient exposure to device averaged 11 months (ranging from <1 to 20 months).

Ten patients died during the clinical studies. One patient suffered significant neurological decline resulting from a postoperative intracranial hemorrhage, and died two weeks after surgery. Two patients died from perioperative myocardial infarctions. The other seven patient deaths were judged unrelated to the therapy and procedure.

Observed Adverse Events

The most common adverse events reported in the US trial (≥ 5% of patients) were postoperative pain, lead repositioning, stimulation not effective, paresthesia, dysarthria, disequilibrium, and paresis.

Table 1 lists the adverse events attributed to the device or the procedure reported in more than one patient. Adverse events reported in one patient each included attention or cognitive deficit, cramping, diplopia, dysarthria, dysphasia, exacerbation of Parkinson's disease, facial weakness, IPG changed from cycling mode to continuous mode, insufficient oxygenation, no connection at "0" electrode, problem with lead/extension connection, broken tunneling rod, and twelfth cranial nerve palsy. Device failure was confirmed in one case, and resulted from premature IPG battery depletion due to a defective integrated circuit.

Adverse Events

Table 1. Adverse Events and Surgical Interventions Related to the Device or Procedure

Reported in >1 patient, all patients enrolled, N=424

Number of patients	US Tremor 84	EC Tremor 113	Others* 227	Total 424	
Adverse Event (AE)	**Number of patients with the AE**				**%**
ANY (one or more) adverse event	32	20	68	120	28.3%
Postoperative pain, stress or discomfort	11	9	8	28	6.6%
Lead repositioning	5	4	17	26	6.1%
Stimulation not effective/ insufficient tremor control	5	3	17	25	5.9%
Lead migration/ dislodgment	1	1	12	14	3.3%
Intracranial hemorrhage	5	3	5	13	3.1%
DBS explantation	4	1	7	12	2.8%
Infection	1	2	8	11	2.6%
Erosion	5	0	3	8	1.9%
Paresthesia	5	1	0	6	1.4%
Component malfunction (IPG, lead, extension)	2	1	2	5	1.2%
Seizures	1	0	4	5	1.2%
Subcutaneous hematoma	1	2	2	5	1.2%
Electrical shocking or jolting	1	0	3	4	0.9%
Headaches	2	1	1	4	0.9%
Lead fracture	1	0	3	4	0.9%
Paresis	3	0	1	4	0.9%
Disequilibrium	2	1	0	3	0.7%
Allergic reaction	0	0	2	2	0.5%
Burr hole ring and cap failure	0	1	1	2	0.5%
Electrode short circuit or open circuit	1	1	0	2	0.5%

* Basic Safety and DBS for Pain Studies.

Adverse Events

Table 2 lists the adverse events attributed to the therapy (deep brain stimulation) which occurred in more than one patient. The number and percentage of patients with adverse events (any one or more) in the US and European Tremor Trials for patients with essential tremor was 43 of 78 (55%) compared to 33 of 111 (30%) for patients with Parkinson's disease. The number and percentage of adverse events (any one or more) in the European Tremor Trial for all patients implanted bilaterally was 4 of 27 (15%) compared to 10 of 85 (12%) of patients implanted unilaterally. Table 2 combines the frequencies across diagnoses and unilateral/bilateral implants.

Adverse Events

Table 2. Adverse Events During Stimulation (US and European Trials)

Reported in >1 patient, all tremor patients, N=189

Adverse Event	# Events	# Patients	% Patients
ANY (one or more) adverse events	242	76	40%
Paresthesia	123	63	33%
Dysarthria	22	17	9%
Disequilibrium	11	9	5%
Paresis	13	9	5%
Dystonia	17	6	3%
Gait disorder	5	5	3%
Initial jolt	8	5	3%
Headaches	5	4	2%
Pain, discomfort or local stress	7	4	2%
Attention deficit	3	3	2%
Dysphasia	3	3	2%
Initial tingling	3	3	2%
Insufficient therapeutic effect	3	3	2%
Ataxia	3	2	1%
Dyskinesia	2	2	1%
Sensory deficits	2	2	1%

Adverse events reported in one patient each included facial weakness, fatigue, intention coordination, loss of energy, numbness, other speech deficits, rebound, and transient heaviness in arm.

Adverse Events

Most (70%) of the therapy-related adverse events were tolerated by the patients and involved no clinical intervention. Stimulation parameters were adjusted in 22% of the cases. Other interventions included: patient education; adjustment of concomitant medications; and instructions to discontinue stimulation. Nine patients required lead repositioning to regain therapeutic effect.

Five essential tremor patients had their Activa Tremor Control Systems explanted. Four patients were explanted due to loss of effectiveness. One patient was explanted due to infection.

Of the 114 Parkinson's disease patients (US and Europe), disease progression was reported in ten patients, exacerbation of tremor in three patients (both occurred in one patient). These events were listed as adverse events, but attributed by the investigator to disease progression.

Three suicides were reported during the clinical studies. One patient implanted in the periventricular gray in a DBS for Pain clinical trial reported suicidal ideation present at high stimulation amplitudes. The suicide ideation was resolved when the stimulation parameters were decreased. Depression was reported in two patients in the tremor clinical studies. The depression was judged by the investigators to be related to disease progression and not to the therapy and procedure.

An autopsy report in one patient using a different lead showed histopathological changes within 2 mm of the implanted lead. There was no report of an associated change in the patient's neurologic status or the therapeutic effect of the stimulation.

A total of 11 leads were explanted during the US and European Clinical Studies. Of these leads, six were replaced once. No patients had leads removed and replaced more than once, and no leads were left in place while a second lead was implanted on the same side.

Potential Adverse Events

Adverse events which may potentially occur, but were not reported in the clinical trials, include:

- Seroma at the IPG site
- Nausea and vomiting
- Aphasia
- Seizure
- Leakage of cerebrospinal fluid
- Motor problems such as incoordination or muscle spasms
- Undesirable stimulation
- Undesirable sensations (temporary or permanent)

Clinical Studies

Tremor was studied in two multicenter trials (US and European Tremor Trials) using the Medtronic® Activa™ Tremor Control System. The DBS™ Lead was implanted in the ventral intermediate nucleus of the thalamus after a preimplant evaluation. A total of 220 IPGs were implanted in 189 patients.

Seven patients in the US and one patient in Europe were not implanted with the Activa Tremor Control System. One patient had tremor suppression without stimulation, two patients had intracranial hemorrhages, and two patients had insufficient tremor suppression. One patient had both an intracranial hemorrhage and insufficient tremor suppression, one patient had a serious reaction to the general anesthetic, and one patient could not cooperate with the implant procedure.

US Tremor Trial

The suppression of tremor due to essential tremor or Parkinson's disease was evaluated at 1, 3, 6, 9, and 12 months post-implant. Optimal stimulation parameters were selected by the investigator at each visit. At the 3 month visit, patients were randomized to real or sham activation of the IPG, and tremor assessment was done in a randomized, controlled manner (primary outcome measure). Patients stopped medications and stimulation the evening before evaluation. Effect of the tremor suppression (with stimulation ON vs. OFF) was assessed by the investigator using the Tremor Rating Scale for essential tremor (0 to 4), and the Unified Parkinson's Disease Rating Scale (0 to 4). Activities of daily living (secondary outcome measure) were evaluated with the stimulation ON.

Patients Studied: 45 essential tremor patients (38 males) and 39 Parkinson's disease patients (31 males) were enrolled. Mean age was 66 years (range 31 to 80). Mean duration of implant was 10 months (range 1 to 16 months). The 3-month randomized evaluation included 29 essential tremor and 24 Parkinson's disease patients.

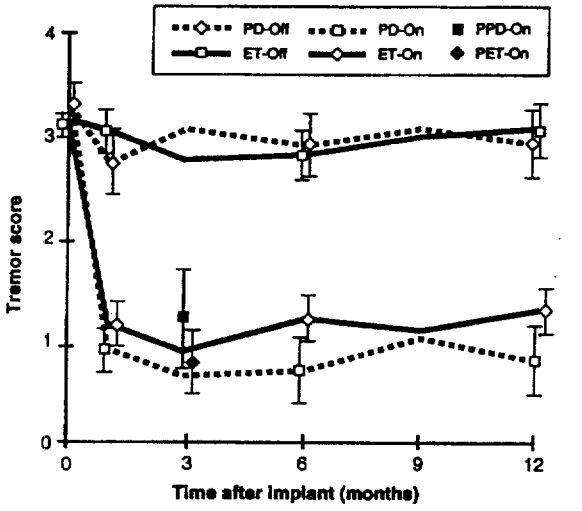
Results: A modified Mini Mental Status Examination completed by the patients in the US Tremor Study showed no cognitive effects related to the tremor control therapy. Figure 1 shows the tremor scores for thalamic stimulation over time.

Activities of daily living (ADL) showed statistically significant improvement in seven scales for essential tremor patients. In patients with Parkinsonian tremor, ADL scores showed a trend in improvement in four scales, but only the tremor-specific ADL showed statistically significant improvement. Patients' assessment (subjective evaluation) of their disability was improved in both groups when compared to a preimplant assessment.During the clinical trial, 17 Parkinson's disease patients increased use and eight decreased use of levodopa. Six patients decreased use of anticholinergics.

Rebound is a phenomenon in which a patient's tremor appears clinically exaggerated (compared to baseline tremor) after turning off the stimulator. The exaggerated tremor generally stabilizes (returns to normal) within approximately 30 minutes.

In the US clinical study a maximum of 29% of Parkinson's disease patients, and 28% of essential tremor patients experienced rebound lasting for a mean duration of 17 minutes and 22 minutes, respectively.

Figure 1. US Tremor Score (0 to 4) for Essential Tremor and Parkinson's disease with Thalamic Stimulation over Time (Mean±1.5 SEM)



Parkinson's Disease

					Primary Endpoint[1]	
Stim Off	Preimplant	1 month	6 months	12 months	Preimplant	3 months
Mean	3.38	2.79	2.89	2.92	3.36	2.82
± SD (N)	± 0.71 (39)	± 1.15 (30)	± 1.10 (28)	± 1.10 (24)	± 0.50 (11)	± 0.98 (11)
Stim On	Preimplant	1 month	6 months	12 months	Preimplant	3 months
Mean	3.38	0.90	0.69	0.78	3.15	1.23
± SD (N)	± 0.71 (39)	± 0.94 (31)	± 1.04 (29)	± 1.17 (23)	± 0.90 (13)	± 1.17 (13)

Essential tremor

					Primary Endpoint[1]	
Stim Off	Preimplant	1 month	6 months	12 months	Preimplant	3 months
Mean	3.13	3.03	2.79	3.04	3.08	2.85
± SD (N)	± 0.41 (45)	± 0.83 (40)	± 0.93 (34)	± 0.89 (26)	± 0.49 (13)	± 0.99 (13)
Stim On	Preimplant	1 month	6 months	12 months	Preimplant	3 months
Mean	3.13	1.15	1.21	1.27	3.06	0.81
± SD (N)	± 0.41 (45)	± 0.74 (40)	± 0.98 (33)	± 0.92 (26)	± 0.44 (16)	± 0.83 (16)

[1] The primary statistical comparison, using the Wilcoxon Rank Sum Test, is the 3-month Stim Off assessment vs. the 3-month Stim On assessment, in a randomized, controlled comparison.

European Tremor Trial

The suppression of tremor was also evaluated in a European trial. Essential tremor and Parkinson's disease patients were evaluated at 3, 6, and 12 months following implantation. Additionally, a cohort of patients who had completed 12 months of follow-up were randomized to real or sham activations of the IPG, and tremor assessment was done in a randomized, controlled fashion, similar to the US trial.

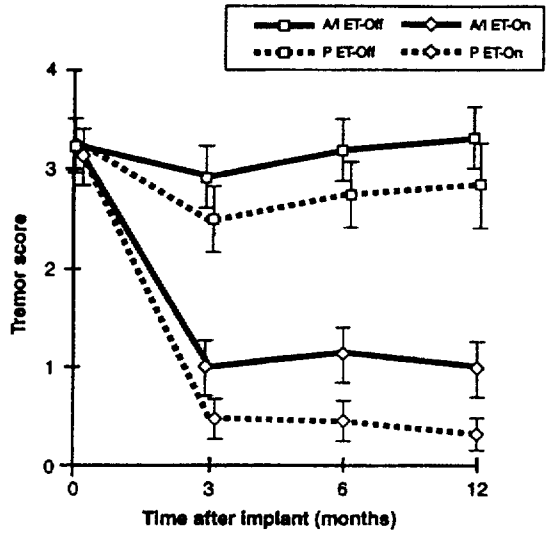
Patients Studied: 38 essential tremor patients and 75 Parkinson's disease patients were enrolled. Mean age at implant was 63 years (range 29 to 83). Mean duration of implant for all patients was 12 months.The long-term randomized, controlled evaluation included 19 essential tremor patients and 17 Parkinson's disease patients, with mean follow-up durations of 20.3 months for essential tremor patients, and 24.8 months for Parkinson's disease patients.

Results: Figure 2 shows tremor scores over time with unilateral thalamic stimulation for essential tremor patients. Both action/intention (kinetic) and postural tremor scores are provided. Figure 3 shows rest tremor scores over time with unilateral thalamic stimulation for Parkinson's disease patients. Table 3 shows tremor scores for the subset of essential tremor and Parkinson's disease patients implanted for more than 12 months who were evaluated in a randomized, controlled manner.

Activities of daily living and other functional improvements were statistically significant in both essential tremor and Parkinson's disease patients.

During the clinical trial, 17 Parkinson's disease patients increased use and 11 decreased use of levodopa. Two patients decreased use of anticholinergics.

Figure 2. European action/intention (kinetic) and postural tremor scores (0 to 4) for essential tremor patients with unilateral thalamic stimulation over time (Mean±1.5 SEM)



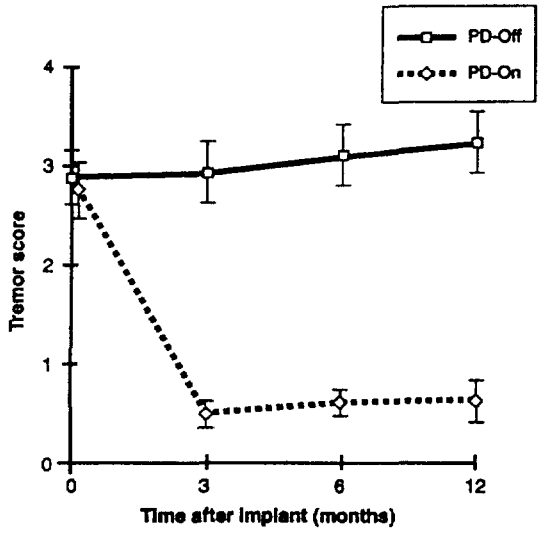
Action/Intention (Kinetic) Essential Tremor

Stim Off	Preimplant	3 months	6 months	12 months
Mean	3.29	2.92	3.15	3.32
± SD (N)	± 0.90 (28)	± 1.04 (25)	± 0.91 (27)	± 0.80 (25)
Stim On				
Mean	3.29	1.00	1.15	1.00
± SD (N)	± 0.90 (28)	± 0.82 (25)	± 0.82 (27)	± 0.76 (25)

Postural Essential Tremor

Stim Off	Preimplant	3 months	6 months	12 months
Mean	3.25	2.48	2.78	2.80
± SD (N)	± 0.75 (28)	± 1.12 (25)	± 1.09 (27)	± 1.26 (25)
Stim On				
Mean	3.25	0.48	0.44	0.36
± SD (N)	± 0.75 (28)	± 0.65 (25)	± 0.75 (27)	± 0.57 (25)

Figure 3. European rest tremor score (0 to 4) for Parkinson's disease patients with unilateral thalamic stimulation over time (Mean±1.5 SEM).



Parkinson's Disease

Stim Off	Preimplant	3 months	6 months	12 months
Mean	2.93	2.94	3.07	3.13
± SD (N)	± 1.27 (57)	± 1.28 (49)	± 1.25 (45)	± 1.24 (45)
Stim On				
Mean	2.93	0.46	0.68	0.69
± SD (N)	± 1.27 (57)	± 0.61 (50)	± 0.77 (44)	± 0.92 (45)

Table 3. Primary Endpoint: > 12 Months for Parkinson's Disease (N=17) and Essential Tremor (N=19)

Primary Endpoint[2]

Essential Tremor (N = 19)

	Stim Off		Stim On	
Mean	3.54	3.36	3.50	1.38
± SD (N)	± 0.69 (11)	± 0.81 (11)	± 0.53 (8)	± 0.92 (8)

Parkinson's Disease (N = 17)

	Stim Off		Stim On	
Mean	3.89	3.67	3.38	0.63
± SD (N)	± 0.33 (9)	± 0.71 (9)	± 1.06 (8)	± 0.52 (8)

[2] The primary statistical comparison, using the Wilcoxon Rank Sum Test, is the long-term Stim Off assessment vs. the long-term Stim On assessment, in a randomized, controlled comparison.

Indications for 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. Activa™ Tremor Control Therapy is appropriate for patients who meet the following criteria:

- Patients should have disabling tremor of the upper extremity due to essential tremor or Parkinson's disease.
- The tremor should constitute a significant functional disability.
- The tremor should be refractory to pharmacological therapies.
- Patients should be suitable candidates for stereotactic neurosurgery.

Activa Tremor Control Therapy is not intended for the treatment of Parkinson's disease symptoms such as bradykinesia/akinesia, rigidity, and/or postural instability.

Before the Activa™ Tremor Control System is implanted, the following conditions should be met:

- tremor suppression by test stimulation should be demonstrated in the operating room; and
- tremor suppression should occur at less than 3 volts, and with minimal side effects such as paresthesia and speech difficulties.

Use extreme care with lead implantation in patients with a 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 risk of initial surgery may increase with clinical conditions such as:

- Stroke or neurological disorders other than Parkinson's disease or essential tremor.
- Cardiovascular disease.
- Renal or hepatic failure.
- Diabetes mellitus.

Patients should be carefully selected to assure that their tremor is of physiologic origin. Also, patients must be appropriate candidates for surgery. 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 tremor suppression is achieved with minimal side effects. High parameter values may indicate a system problem or less than optimal lead placement. Patients should be informed of the risks of higher parameters as noted in the Warning section (see pages 2-5).

Use in Specific Populations

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

- Bilateral stimulation.
- Patients with neurological disease origins other than essential tremor or Parkinson's disease.
- Patients with a previous thalamotomy or surgical ablation procedure.
- Pregnancy or delivery.
- Pediatric use (patients under the age of 18).
- Patients over the age of 80 years.

Resterilization

The lead and accessories of the Medtronic Model 3387 DBS™ Lead Kit were sterilized with ethylene oxide before shipment. Inspect the sterile package for seal integrity and damage to the package before opening and using the contents. If you are unsure of the components' sterility for any reason, they can be resterilized at the hospital site.

> Note: If contamination is suspected because of a defective sterile package seal, leads and accessories can be returned to Medtronic for replacement or they can be resterilized at the hospital. Replacements are otherwise subject to the terms of the Medtronic Limited Warranty (U.S. Customers). Medtronic does not accept returned leads or accessories for resterilization and return them to customers.

Due to variations in hospital sterilizers, precise instructions for sterilization or aeration cannot be given here. If further information is necessary regarding the procedures to be used, contact the manufacturer of the sterilizer unit. Use biological indicators or other acceptable methods to assist in validating the effectiveness of the hospital's sterilizer unit.

Medtronic cannot accept the responsibility for the resterilization of any components. If, however, the decision is made to resterilize, usual and customary sterilization methods should be used.

Caution

⚠ Do not resterilize and use leads or accessories after exposure to body tissues or fluids.

⚠ Do not use radiation to resterilize any component. Do not autoclave the lead, percutaneous extension, or stylet.

Subject to the foregoing, the following may be considered:

Table 4 is a summary of the resterilization options and restrictions. The paragraphs following the table provide additional information.

Table 4. Resterilization Options and Restrictions.

Component	Sterilization Methods[1]		
	Ethylene Oxide 55°C (130°F) Maximum	Autoclave 121°C (250°F) 15 psig 30 minutes	"Flash" Autoclave 132°C (270°F) 27 psig 5 minutes
Lead	YES	NO	NO
Percutaneous Extension	YES	NO	NO
Stylet	YES	NO	NO
Screening Cable	YES	NO	NO
Burr Hole Ring/Cap; Connector Boot	YES	NO	NO
Other Accessories	YES	YES	YES

[1] Medtronic cannot accept responsibility for the resterilization of any components at the hospital.

Ethylene oxide is an acceptable method for resterilization when the leads and accessories are repackaged in an ethylene oxide-permeable package. The temperature during the process should not exceed 55°C (130°F). The maximum possible aeration must be allowed before implanting the lead and using the accessories.

Steam autoclaving may also be used as a sterilization method for components marked YES for autoclave or "flash" autoclave in Table 4. For autoclave, a standard cycle of 30 minutes at 121°C (250°F) and 15 psig is recommended. For "flash" autoclave, a standard cycle of 5 minutes at 132°C (270°F) and 27 psig is recommended. Do not sterilize a component using any method that is marked NO for that component.

Suggested Procedures

The implantation of the Model 3387 DBS™ Lead requires stereotactic techniques for the initial implant and close patient follow-up during the postoperative stage. Medtronic recognizes that a variety of approaches may be used to accomplish this. The following outline is presented as one possible approach for the physician's consideration.

The target site for stimulation to suppress tremor is the ventral intermediate nucleus (Vim) of the thalamus. The Vim may be localized for stereotactic implantation of the Model 3387 DBS Lead using CT Scans, MRI, or ventriculography. A test stimulation or mapping electrode may then be utilized for further localization of the target with electrical stimulation.

Use only legally marketed devices to locate target. The safety and efficacy of the Model 3387 DBS Lead for mapping is unknown.

Lead Implant Procedure

To implant the Model 3387 DBS Lead, an insertion cannula and stylet (such as the Leksell Models 60077-1 and 60079-1 or the Radionics Kit, Model MSIC) should be placed to a point approximately 15 mm proximal to the target site for stimulation. The lead should be passed through the insertion cannula and advanced to the target site. Use the applicable Medtronic Model 3353 (for Radionics) or Model 3354 (for Leksell) Lead Frame Kit to stabilize the lead in the insertion cannula.

The following steps outline the suggested lead implant procedure:

1. After placement of the stereotactic frame, use standard imaging techniques to determine coordinates for the lead's target site.
2. Prepare the patient per normal stereotactic surgical techniques.
    a. Make a skin incision, with consideration given to burr hole placement.

b. Prepare a sub-galeal pocket by blunt dissection at the top of the skull at the edge of the burr hole incision for placement of the excess lead wire and connector.

Note: Placement of the pocket may be on either the left or right side of the skull.

c. Place a 14 mm diameter burr hole in the desired location.

Note: Medtronic recommends using a 14 mm perforator, such as the Codman* or Acra-Cut**, to form the burr hole.

* Codman is a trademark of Codman & Shurtleff, Inc.
** Acra-Cut is a registered trademark of Acra-Cut, Inc.

Caution

⚠ For anchoring the lead, use only the burr hole cap and ring packaged with this lead.

3. Place the burr hole ring tightly against the bone in the burr hole, using your finger and a curved mosquito hemostat.
4. Position the guide tube or collimator in the frame so that its distal end is 1.25 to 2.5 cm from the skull.
5. Attach the lead holder assembly to the stereotactic frame (Figure 4).

Note: Refer to the Model 3353 or Model 3354 Lead Frame Kit Instructions.

6. Determine the depth of lead placement in the brain.
7. Attach the lead depth stop gauge on the lead at the point calculated in step 6.

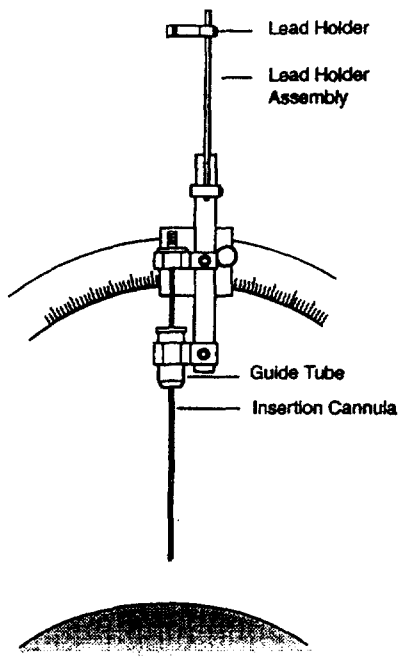


Figure 4. Attach lead holder assembly to frame

8. Advance the insertion cannula through the guide tube to a point approximately 15 mm proximal to the lead's target site.
9. Advance the lead through the insertion cannula to the target site.
10. Attach the proximal end of the lead to the lead holder to within 2.5 cm of the stylet (Figure 5).

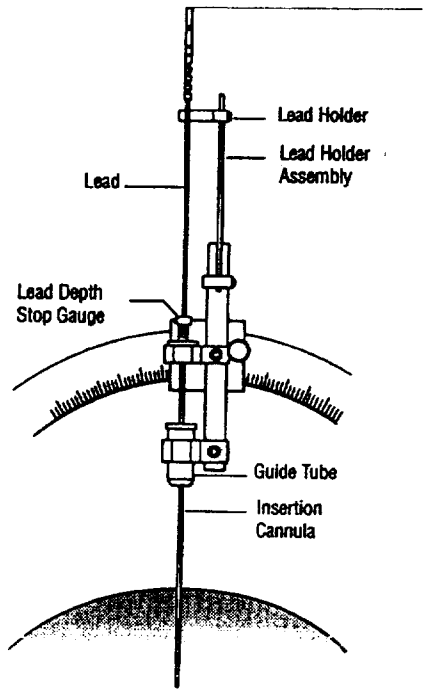


Figure 5. Attach lead to lead holder.

Intraoperative Test Stimulation

This section outlines the intraoperative stimulation test that helps confirm the desired lead position for optimum stimulation. This test requires the use of the Model 3625 Test Stimulator and the screening cable with one black and one red alligator clip. The cable's connector is configured so that the black alligator clip wire always connects to ELECTRODE SELECT switch 0 and the red alligator clip wire to switch 3 on the Medtronic Model 3625 Test Stimulator. Use the **alligator clips** to **select the lead contacts** that correspond to the electrodes you want to test. Use only the 0 and 3 **ELECTRODE SELECT switches** on the Model 3625 Test Stimulator to **select the output polarity** (+ or –) of the alligator clips.

1. Attach the screening cable alligator clips to the applicable lead contacts that correspond to the desired electrodes—Figure 6 illustrates the connection to the lead contacts for electrodes 0 and 3.

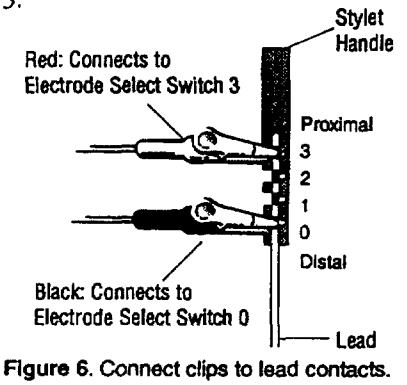


Figure 6. Connect clips to lead contacts.

2. Check that the test stimulator External **A**–Amplitude Control (Figure 7) is turned **OFF**.

Warning

⚠ Always turn External **A**–Amplitude Control OFF before connecting or disconnecting the screening cable from the test stimulator, or before changing alligator clip connections to the lead contacts to prevent possible uncomfortable patient stimulation.

Note: Refer to the *Medtronic 3625 Test Stimulator Operator Manual* for detailed instructions on using the test stimulator.

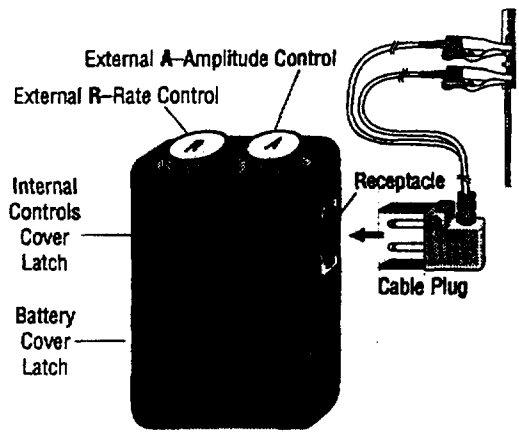


Figure 7. Model 3625 Test Stimulator External Controls and Receptacle.

3. Push the screening cable plug into the test stimulator receptacle (Figure 7). Note the correct plug orientation—it fits in one way only.

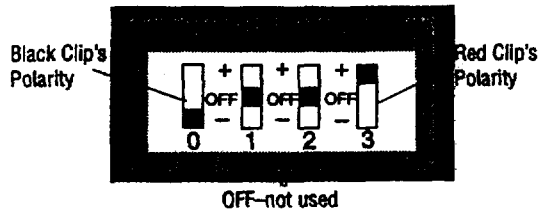
Warning

⚠ Always turn the test stimulator External **A**–Amplitude Control to **OFF** before connecting or disconnecting the screening cable from the test stimulator, or before changing alligator clip connections or Internal Controls to prevent possible uncomfortable patient stimulation.

4. Remove the Internal Control Cover (Figure 7) and set the Internal Controls (Figure 8) as follows:

   a. Set the **ELECTRODE SELECT** switch polarities as shown.

   b. Set the **RATE AND PULSE WIDTH SELECT** switch to **B**.



c. Set the **PULSE WIDTH** to 60 µsec, or as desired.

d. Set the **AMP LIMIT** control to 10 VOLTS, or as desired.

5. Set the External **RATE** to 130 Hz, or as desired.

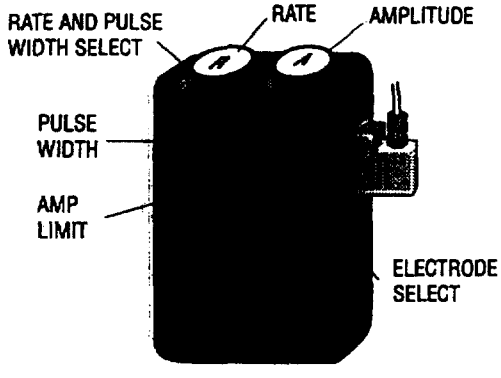


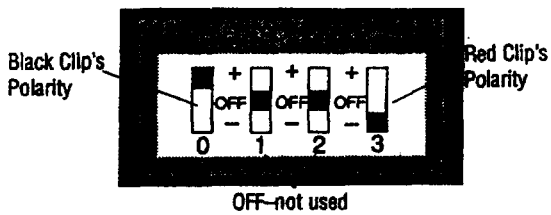
Figure 8. Set Internal/External Controls.

6. Turn the External **A**–Amplitude Control **ON** and gradually increase it until the patient indicates an effect, or until a stimulation effect such as the suppression of tremor is noted.

7. To reverse the output polarity:

   a. Set the External **A**–Amplitude Control to **OFF**.

   b. Set the **ELECTRODE SELECT** switch polarities as shown.



Note: The output polarity can also be reversed by switching the alligator clip-electrode contact connections.

c. Repeat step 6.

Note: The desired stimulation effect is an obvious suppression of tremor.

Note: Other stimulation effects that may aid in placement of lead, but may not be desirable, include paresthesia, especially in the hand and around the mouth.

Warning

⚠ Always turn the test stimulator External A–Amplitude Control to OFF before changing ELECTRODE SELECT switches or other Internal Controls to prevent possible uncomfortable patient stimulation.

8. When the intraoperative testing is completed, turn the test stimulator's External A–Amplitude Control to **OFF**.

9. Disconnect the screening cable alligator clips from the lead contacts.

Insertion Cannula Removal and Lead Stabilization

When you have determined that the lead is properly positioned, it can be secured in the burr hole ring.

Complete the following steps to remove the insertion cannula and secure the lead position.

1. If necessary, **reattach the proximal end of the lead to the lead holder** to within 2.5 cm of the stylet handle. Refer to Figure 5 on page 28.
2. Remove the adjustable lead depth stop gauge from the lead.
3. Carefully pull the insertion cannula up until the lead can be seen between the burr hole and the cannula.
4. Hold the lead **at the point it exits the skull** while loosening the stylet handle (Figure 9).

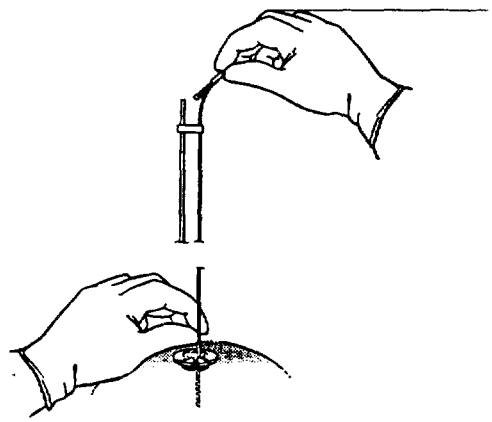


Figure 9. Loosen the stylet handle from the lead.

5. Remove the stylet from the lead.
6. While keeping the lead secure at the exit site of the skull, remove the lead from the lead holder.
7. Remove the insertion cannula.

8. Remove the guide tube or collimator and the lead holder.

9. Gently press the lead into one of the precut grooves on the inner side of the burr hole ring (Figure 10).

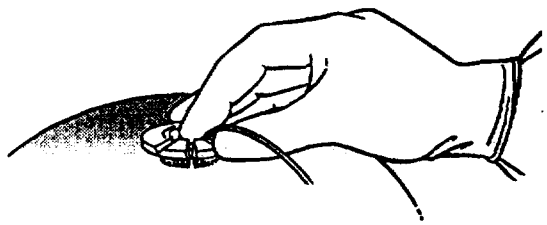


Figure 10. Gently press the lead into the burr hole ring.

10. Recheck the stimulation pattern to assure that no dislodgment has occurred.

    a. Check that the test stimulator output (Amplitude) is turned to **OFF**.

    b. Carefully attach the screening cable alligator clips to the desired connector ring contacts on the lead end.

    c. Turn on the test stimulator and recheck stimulation effects.

> Note: If lead movement has occurred, it may be necessary to remove the lead and repeat the implant procedure.

! Caution

⚠ Do not reinsert the stylet into the implanted lead if lead repositioning is required.

11. Align the tab in the burr hole cap with the slot in the burr hole ring and gently press the cap into the ring until secure (Figure 11).

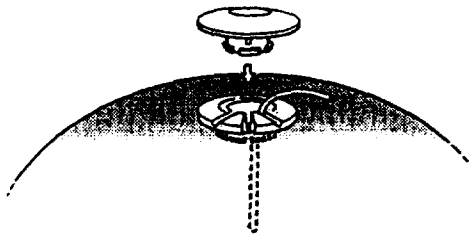


Figure 11. Gently press the burr hole cap into the burr hole ring.

12. After the lead is stabilized in burr hole ring and cap assembly, test stimulate to verify that the lead has not moved from desired target.

When suppression of tremor is noted, proceed with internalization of the remainder of the system. When internalizing the pulse generator, follow the instructions in the *Model 7424 Itrel® II Implantable Pulse Generator Physician and Hospital Manual* and the *Model 7495 Extension Implant Manual.*

Extended Test Stimulation

If a postoperative test stimulation period is desired, use the following three procedures for Extended Test Stimulation outlined in this section:

- Create Percutaneous Tunnel
- Connect Lead and Percutaneous Extension
- Interoperative Test Period

Create Percutaneous Tunnel

The following procedure provides instructions for attaching and implanting the percutaneous extension in the lead kit. The implanted wires should exit the skin above the ear during the test stimulation period.

1. Remove the percutaneous extension from its tube. Discard this tube.

2. Place one of the shorter tubes packaged with the lead over the tunneling tool. Attach the metal PERCUPASS® II Tunneling Tip.

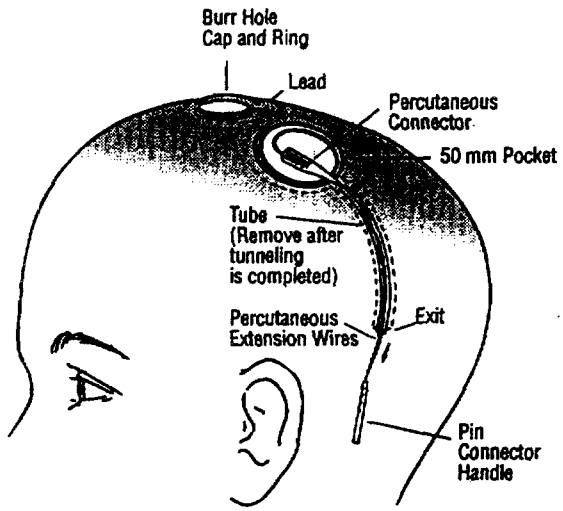


Figure 12. Tunneling and lead placement.

3. Make a small stab wound where the percutaneous extension wires will exit the skin.
4. Tunnel subcutaneously from the pocket through the exit point.
5. Remove the tunneling tool, leaving the tube in place.
6. Pass the percutaneous extension wires through the tube. Leave only the pin connector and approximately 40 mm of the fine wires protruding from the exit point (Figure 12).
7. Remove the tube.
8. Coil the lead in a circle greater than 25 mm in diameter to prevent bending or kinking. Place the coiled lead in the pocket.

Caution

⚠ Be extremely careful when using sharp instruments around the lead body to avoid nicking or damaging the lead body.

Connect Lead and Percutaneous Extension

The following procedure provides instructions on how to connect the DBS lead to the percutaneous extension.

Caution

⚠ Wipe off any body fluids from the lead contacts before connecting to the extension.

1. Push the connector boot over the exposed end of the lead (Figure 13).

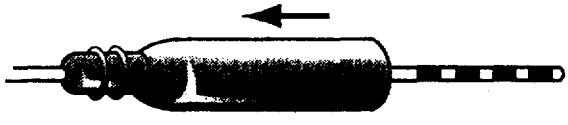


Figure 13. Push connector boot over lead.

2. Insert the exposed end of the lead completely into the percutaneous extension connector (Figure 14).

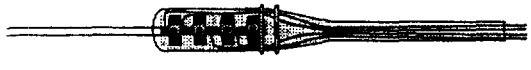


Figure 14. Insert lead fully into setscrew junction.

3. Tighten each of the four setscrews by turning them clockwise in the setscrew sockets with the hex wrench provided (Figure 15). Tighten the setscrews only until they touch the contacts. Continue tightening for a **maximum of 1/4 turn** only.

Figure 15. Tighten setscrews.

Caution

⚠ Do not overtighten the setscrews when using the hex wrench. Excessive torque on setscrews may damage lead contacts.

Note: the setscrews must engage the contacts on the lead before stimulation can be attempted.

4. Slide the connector boot into place, completely covering the lead/extension connection.

Note: If it is difficult to position the boot, sterile water may be used as a lubricant.

5. Place nonabsorbable sutures around both ends of the boot in the channeled areas of the connection (Figure 16).

Figure 16. Suture lead/extension connection.

Caution

⚠ Do not overtighten the suture because damage may occur to either the boot or the lead.

6. Place the lead/percutaneous extension connection into the small pocket made near the incision site.
7. Close the incision site and stab wound, leaving the fine percutaneous extension wires and pin connector protruding from the skin.

Interoperative Test Period

The following procedure provides instructions on how to connect the percutaneous extension to the test stimulator and begin interoperative test stimulation.

1. Check that the test stimulator output (Amplitude) is off.
2. Insert the pin connector on the percutaneous extension into the twist-lock connector on the screening cable. (Refer to Figures 17-20).

Note: The pin connector handle of the percutaneous extension fits into the cylindrical twist connector in only one way (Figure 17).

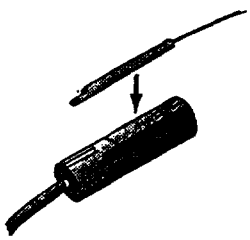


Figure 17. Position pin connector and twist-lock connector.

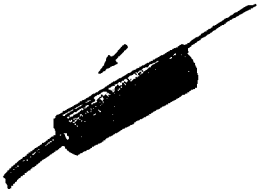


Figure 18. Secure pin connector's end in groove.

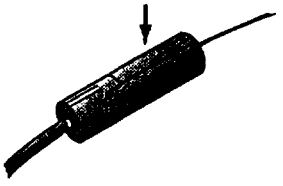


Figure 19. Insert pin connector handle into groove.

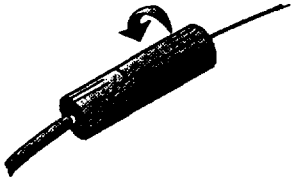


Figure 20. Lock the twist-lock connector.

3. Verify that the test stimulator output (Amplitude) is turned to **OFF**, then push the plug on the test stimulator end of the cable into the output jack of the test stimulator (Figure 21). Refer to the *Medtronic 3625 Test Stimulator Operator Manual* for detailed instructions on utilization.

Warning

⚠ Always turn the test stimulator output (Amplitude) OFF before connecting or disconnecting the screening cable.

Note: The plug end of the screening cable only fits one way into the jack closest to the Electrode Select Switches.

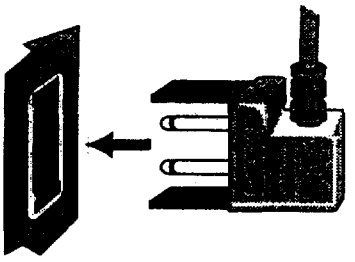


Figure 21. Connect screening cable and test stimulator.

4. Proceed with the test stimulation.

> Note: Different electrode configurations should be evaluated at various parameter settings (Rate, Amplitude, Pulse Width).

5. When finished with interoperative test stimulation, turn the test stimulator **OFF**.

6. Unlock the cylindrical twist-lock connector and remove the connector handle.

   a. Hold the test stimulator end of the twist connector stationary in the left hand and turn the lead end of the twist connector counterclockwise with the right hand until the grooves on each side are lined up (Figure 22).

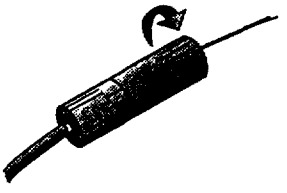


Figure 22. Unlock the twist-lock connector.

   b. Gently pull up on lead end of connector handle until it is free to remove it from the twist connector.

When the optimum stimulation mode and configuration are determined, and the suppression of tremor has been noted, proceed with internalization of the remainder of the system.

When internalizing the pulse generator, follow the instructions in the *Model 7424 Implantable Pulse Generator Physician and Hospital Manual* and the *Model 7495 Extension Implant Manual.*

Programming Stimulation Parameters

When programming stimulation parameters, give consideration to the following recommendations regarding charge density and charge imbalance.

Charge Densities — A survey of literature regarding electrical stimulation of neural tissue suggests that damage may occur above 30 microcoulombs/cm²/phase. The Activa™ Tremor Control System is capable of producing charge densities in excess of 30 microcoulombs/cm²/phase (Figure 23).

The device's maximum amplitude is 10.5 V, and maximum pulse width is 450 microseconds. The curved lines in Figure 23 represent a charge density of 30 microcoulombs/cm²/phase at various impedance measurements, calculated for the electrode surface area of the Model 3387 DBS lead. Mean resistance found in clinical studies was 1348 ohms (610-2000 ohms).

Charge density is determined by plotting a point corresponding to the pulse width setting (x-axis), and the amplitude setting (y-axis). If this point is below the appropriate resistance curve, then the charge density is below 30 microcoulombs/cm²/phase. Points above the curve indicate a charge density above 30 microcoulombs/cm²/ phase.

The shaded area of Figure 23 indicates a charge density above 30 microcoulombs/cm²/ phase at the conservative impedance estimate of 500 ohms. If stimulation parameters are selected that fall into the shaded area of the graph, the following programmer warning appears: "WARNING: CHARGE DENSITY MAY BE HIGH ENOUGH TO CAUSE TISSUE DAMAGE. CONSULT TECH MANUAL. PRESS CLEAR TO CONTINUE". Programming may continue at the desired values by pressing the CLEAR key. Refer to the *ITREL II 7458 Software Applications Manual* for further information.

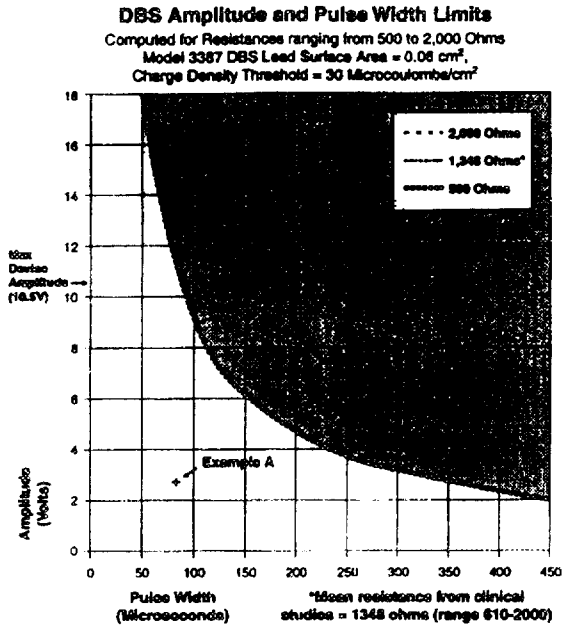


Figure 23. Charge density at various parameter settings.

Figure 23 includes two examples of charge density calculated for the Activa Tremor Control System. In Example A, the Model 7424 Itrel II IPG is set to typical parameter settings for tremor suppression: amplitude = 3.0 V and pulse width = 90 µsec. The charge density for Example A is below the shaded warning zone, thus indicating a charge density below 30 microcoulombs/cm²/ phase at the most conservative impedance of 500 ohms.

In Example B, IPG stimulation parameters are set to: amplitude = 6.1 V and pulse width = 210 µsec. The charge density at these settings is in the shaded area indicating it may be high enough to cause tissue damage at an impedance of 500 ohms. However, if the impedance in this case is 1348 ohms, the charge density would be below 30 microcoulombs/cm²/ phase.

Charge Imbalance Condition — For certain IPG stimulation parameter settings this device can produce a **CHARGE IMBALANCE CONDITION.** Charge imbalance may occur when the circuit does not recover the total negative charge that is produced by the ON activations. If the charge imbalance (net DC current) exceeds 1.5 μamps average current, tissue damage may occur. When programming the ITREL® II PULSE GENERATOR (IPG) the following operating conditions should be observed to remain below the 1.5 μamps average current:

- Cycling Mode. **DO NOT PROGRAM** the ITREL® II PULSE GENERATOR (IPG) to cycling mode for tremor therapy. This warning **INCLUDES** the "Special Ramp Stimulation Mode".
- SoftStart™/Stop. In this feature, when the device is initially turned ON, the voltage is incremental until it reaches the patient's programmed voltage. Each increment is considered an ON activation. When programming the ITREL® II PULSE GENERATOR (IPG) using the SoftStart/Stop feature, refer to Table 5 for aid in programming therapy stimulation. Check the amplitude setting and the pulse width setting. The device (IPG) should **not** exceed the number of activations listed for the selected parameters. An activation occurs when the IPG is turned ON and OFF by either the patient magnet or the programmer.

More than 50,000 activations would be required to generate a charge imbalance condition using typical settings for tremor suppression (frequency=185 pps, amplitude=3.0 V, and pulse width=90 μsec). A patient typically turns their IPG ON in the morning, and OFF at night; this counts as one device activation.

THIS WARNING **DOES NOT APPLY** TO THE OTHER OPERATING PARAMETERS OF THE ITREL® II PULSE GENERATOR.

Table 5. Maximum Allowable Device Activations* per 24 Hour Period

(for all programmable rates and electrode combinations, SoftStart ON)

Programmed Amplitude (Volts)	Device Activations Per 24 Hour Period Programmed Pulse Width 60 µSec	Device Activations Per 24 Hour Period Programmed Pulse Width 90 µSec	Device Activations Per 24 Hour Period Programmed Pulse Width 120 µSec	Device Activations Per 24 Hour Period Programmed Pulse Width 150-210 µSec	Device Activations Per 24 Hour Period Programmed Pulse Width 270-330 µSec	Device Activations Per 24 Hour Period Programmed Pulse Width 400-450 µSec
0.0 - 0.1	135,000	135,000	135,000	135,000	135,000	81,000
0.2 - 1.0	101,000	73,000	73,000	32,000	23,000	13,000
1.1 - 2.0	81,000	50,000	50,000	17,000	6,500	4,200
2.1 - 3.0	54,000	50,000	32,000	7,600	3,200	1,800
3.1 - 3.6	54,000	30,000	19,000	5,600	2,200	1,000
3.7 - 4.0	29,000	16,000	12,000	5,000	2,200	1,000
4.1 - 5.0	22,000	13,00	8,300	2,500	1,100	600
5.2 - 6.0	16,000	8,900	5,500	1,600	580	300
6.1 - 6.5	14,000	7,800	5,000	1,200	380	200
6.7 - 7.2	12,000	6,600	3,500	840	240	140
7.4 - 8.0	10,000	6,200	3,200	840	240	140
8.2 - 9.0	8,800	4,600	2,500	570	200	120
9.1 - 9.5	7,900	4,000	2,100	430	160	110
9.7 - 10.0	7,600	3,500	1,800	330	130	100
10.1 - 10.5	-6,700	3,100	1,500	260	110	90

*An activation occurs when the IPG is turned ON and OFF by either the patient magnet or the programmer.

Physician Training Information

Prescribing physicians are encouraged to contact Medtronic and request a referral to a physician experienced in the operational characteristics and function of the Activa™ Tremor Control System prior to prescribing the device for the first time. All Activa System programming should be by or under the supervision of a physician familiar with the use of the programming software.

Physicians should be thoroughly familiar with Activa System supporting material, including:

- All product labeling, and
- Education and training materials.

Patient Counseling Information

The patient and family should be advised of the known risks of the surgical procedure and the therapy, as discussed in other sections of this manual, as well as the potential benefits. The patient should also be advised to read the *Activa™ Patient Manual* for Tremor Control Therapy.

Lead Materials

A review of the materials, additives and potential breakdown products used in the DBS leads resulted in identification of four chemicals of concern, including:

- Two potential breakdown products of polyurethane have been shown to be neurotoxic in rats.
- A potential breakdown product of polyurethane is a known animal carcinogen.
- An organotin is an additive to polyurethane. Organotins are known neurotoxins.

The amount of these compounds released from the DBS lead over time is unknown. Although long-term human exposure to polyurethane has shown no evidence of neurotoxicity or carcinogenicity in pacemaker leads, these materials have not been previously implanted in the brain.

Lead Specifications

Lead Length	10-50 cm
Lead Shape	Straight
Lead Diameter	1.27 mm
Connector	In-line
Number of Electrodes	4
Distance between Electrodes (center to center)	3 mm
Material	
conductor wires	Platinum/Iridium
proximal connector	Nickel Alloy (MP35N)
stimulating electrodes	Platinum/Iridium
Insulation	
conductor wires	PTFE (Polytetrafluoroethylene)
jacket tubing	80 A Polyurethane
Conductor Resistance	< 100 Ohms
Stylet	Yes (Tungsten)
Method of Introduction	Stereotactic Frame

Note: The electrical resistance of leads is proportional to their length. Very long leads have an increased resistance, that may limit pulse amplitude at the electrodes.

Note: All dimensions are approximate.

Package Contents

- One Model 3387 DBS™ Lead with inserted stylet
- Percutaneous extension
- Pin connector
- Screening cables
  - Intraoperative clip screening cable
  - Twist-lock screening cable
- Stainless-steel PERCUPASS® II Tunneling Tool and Tunneling Tip
- PTFE (Polytetrafluoroethylene) Tubes
- Depth stop gauge
- Hex wrench
- Burr hole ring and cap

Note: The contents of the inner package are **STERILE and NON-PYROGENIC.**

Note: Each material composing the DBS Lead has been selected for biocompatibility through laboratory testing, animal testing, and clinical experience. The lead and accessories contained in the Lead Kits are intended for **Single Use Only.**

Notice

Medtronic® lead kits consist of leads and tools to connect the lead to implantable extensions. Leads are used with extensions, which are implanted in the extremely hostile environment of the human body. The warranties and disclaimers for extensions are discussed separately in the packaging information for extensions. Leads may fail to function for a variety of causes, including but not limited to, medical complications, body rejection phenomena, or failure by breakage or by breach of their insulation covering. In addition, leads and tools may easily be damaged by improper handling or use. For tools, Medtronic disclaims all warranties, both express and implied, including, but not limited to, any implied warranty of merchantability or fitness for a particular purpose. Medtronic shall not be liable to any person or entity for any medical expenses or any direct incidental or consequential damages caused by any defect, failure or malfunction of any tool, whether a claim for such damage is based upon warranty, contract, tort or otherwise. No person has any authority to bind Medtronic to any representation or warranty with respect to tools

Medtronic

Neurological Division

[redacted]

Patient Manual

[redacted]

Contents

CAUTION: Federal law (USA) restricts this device to sale, distribution, and use by, or on the order of, a physician.

Introduction

This guide was written to help you understand and use your Activa™ Tremor Control System, and the devices that control it. It provides information about the system's parts and explains how they are implanted. It shows you how to turn your system ON and OFF with a special magnet. Also, it suggests various questions you should discuss with your doctor.

The booklet is divided into the following sections:

- Introduction
- Your Activa™ Tremor Control System
- How Your Activa Tremor Control System is Implanted
- Using Your Control Magnet
- Living with Your Activa Tremor Control System
- Some Common Questions
- Replacement Surgery
- Your Identification Card

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- Glossary
- Special Notice
- Limited Warranty

General questions that you and your family may have about the system are answered in the *Some Common Questions* section. This booklet also has a *Glossary* that defines medical terms that may be new for you.

Your system uses a battery and other electronic parts and this manual explains their special requirements. In the *Living With Your Activa Tremor Control System* section, we provide guidelines for your everyday use of the system.

If you have questions not answered by this guide, or if any unusual situations or problems arise, consult your physician. He or she knows your personal medical history and can give you the detailed information you may need. In particular, you should ask about the potential complications, risks, and benefits of this therapy. As with all surgical procedures, implanting your Activa Tremor Control System involves some risks. The risks and related information are outlined in the *Physician and Hospital*

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Staff Manual that Medtronic provides to your physician.

Choosing the Treatment for Your Tremor—Your Activa Tremor Control System was prescribed in an attempt to relieve the symptoms of your medical condition. It is a deep brain stimulation system, which is indicated for decreasing (suppression) one-sided (unilateral) tremor due to essential tremor or Parkinsonian tremor not controlled by medications. It should be used only according to your doctor's instructions.

Benefits of Activa™ Tremor Control Therapy—Activa therapy delivers electrical stimulation to a walnut-sized structure in the brain called the *thalamus*. The *thalamus* is a relay station for messages from all over the body that the brain needs to control movement. In patients with tremor, these messages do not work correctly. Stimulation from the Activa system may interrupt the messages that result in tremor, and help suppress tremor.

Activa therapy helps control tremor, but it does not cure tremor. When activated by you, the Activa system will deliver stimulation that may decrease your tremor. Tremor will return when the system is turned off.

You should always discuss both the risks and potential benefits of Activa therapy with your doctor. For example, if you are currently on anticoagulant medications, your risk of bleeding inside the brain during surgery is higher.

Indications

Unilateral thalamic stimulation by the Medtronic® Activa Tremor Control System is indicated for the suppression of tremor in the upper extremity. The system is intended for use in patients who are diagnosed with essential tremor or Parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability.

Contraindications

Implantation of a Tremor Control System is contraindicated for:

- Patients for whom test stimulation is unsuccessful, or
- Patients who are unable to properly operate the stimulator.

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Risks of Surgery

Implanting the Activa™ Tremor Control System carries the same risks associated with any other brain surgery. These risks include:

- Bleeding inside the brain (intracranial hemorrhage)
- Leakage of fluid surrounding the brain
- Seizure
- Infection

Possible Side Effects of Activa Therapy

Side effects of brain stimulation usually are mild, and go away when stimulation is turned off. Your doctor can also adjust the stimulation so the side effects are eliminated or lessened, though the treatment of your tremor may not be as effective. Side effects may include:

- Tingling in the limbs or face (paresthesia)
- Facial and limb muscle weakness or partial paralysis (paresis)
- Speech problems (dysarthria)

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- Dizziness or lightheadedness
- Headache
- Double vision
- Pain at the IPG site
- Allergic reaction
- Depression
- Movement problems or reduced coordination
- Jolting or shocking sensation

There may be changes in the level of your tremor suppression over time. These changes may include:

- Tremor control that is less effective or ineffective
- Loss of stimulation
- Pauses in stimulation

In most cases your doctor can correct these by reprogramming the Activa system. However, it is possible that surgery may be required to reposition the lead, replace the system, or remove the system.

Given the progressive nature of your disease, your condition may improve, may worsen, or may remain unchanged with stimulation.

When To Call Your Doctor

Contact your doctor if you notice any of the following:

- If the implant sites become red, itch or burn.
- If your IPG stops working.
- If you think your IPG is ON but your tremor does not decrease.
- If there are any changes in your tremor related or unrelated to stimulation.

Your Activa™ Tremor Control System

Your implantable system (Figure 1) consists of:

- **The Implantable Pulse Generator (IPG):** The Activa IPG is the power source of the Activa system. It is small is size: about 6 cm long, 5.5 cm high, and 1 cm thick. It consists of a sealed oval-shaped metal container that houses a special battery, and programmable electronics that control the electrical charge the battery generates .
- **The Extension:** The extension is a thin insulated wire that connects to the IPG on one end, and the lead on the other end. The extension transports the electrical pulses from the IPG to the lead.
- **The Lead:** The lead (pronounced leed) is a thin insulated wire with a series of tiny metal parts at one end. These metal parts are called **electrodes.** The end of the lead with the electrodes is surgically positioned in the thalamus of the brain. The other end of the lead is connected to the extension. The electrical pulse that is generated by the IPG travels through the extension and lead to the electrodes, where it stimulates the thalamus to suppress tremor.

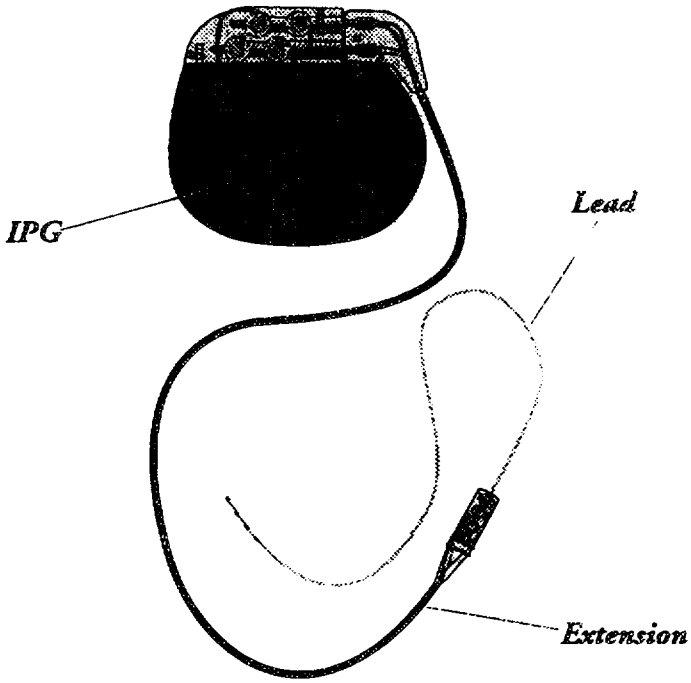


Figure 1. The Activa™ Tremor Control System

The battery contained within your IPG will eventually run down and the IPG will need to be replaced. A surgical procedure is required to remove and replace the IPG. Ask your doctor to estimate the battery life for you.

The ITREL® II IPG can be controlled by two devices (Figure 2):

- The **Console Programmer** adjusts all IPG settings for your stimulation system. It is kept in your doctor's office or at the hospital.
- The **Control Magnet** turns the IPG ON and OFF. When you switch the IPG ON using the magnet, the stimulation resumes at its previously programmed level. The magnet can also switch the stimulation from "normal" to "low", when this is programmed by your doctor. You should have received a magnet before leaving the hospital. If you do not have a magnet, contact your doctor or Medtronic's Customer Service at 1-(800)-328-0810.

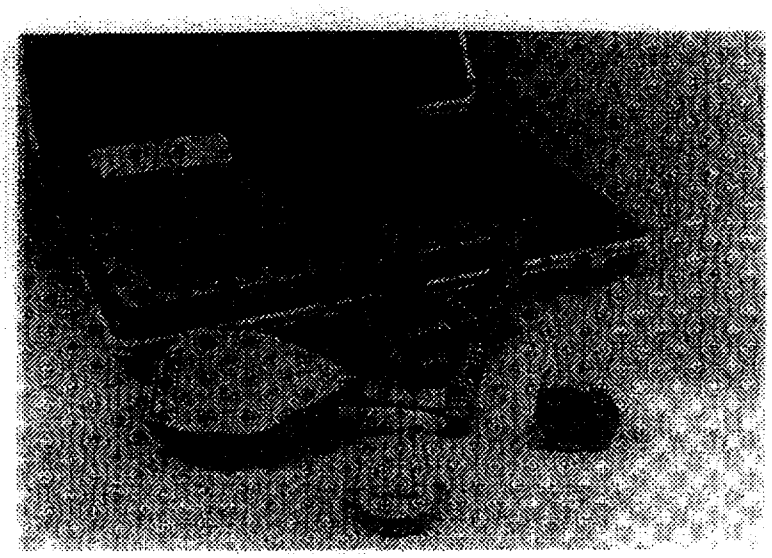


Figure 2. IPG and Controlling Devices

How Your Activa Tremor Control System is Implanted

Implantation of your Activa™ Tremor Control System has four steps and usually is done in one or two operations. The four steps are as follows:

- Test stimulation
- Lead placement
- IPG internalization
- IPG programming

During the **lead placement**, you may be under a local anesthetic. The doctor will ask you questions about your tremor and what you are feeling to help determine the best placement for the lead (Figure 3).

An external hand-held Test Stimulator is used during the operation to deliver stimulation pulses to the lead. This test stimulation assists your doctor in determining the best lead placement.

If your doctor chooses to implant the system in one operation, the IPG is implanted after lead placement. If the procedure is done in two operations, you will return to your hospital room after the lead is implanted.

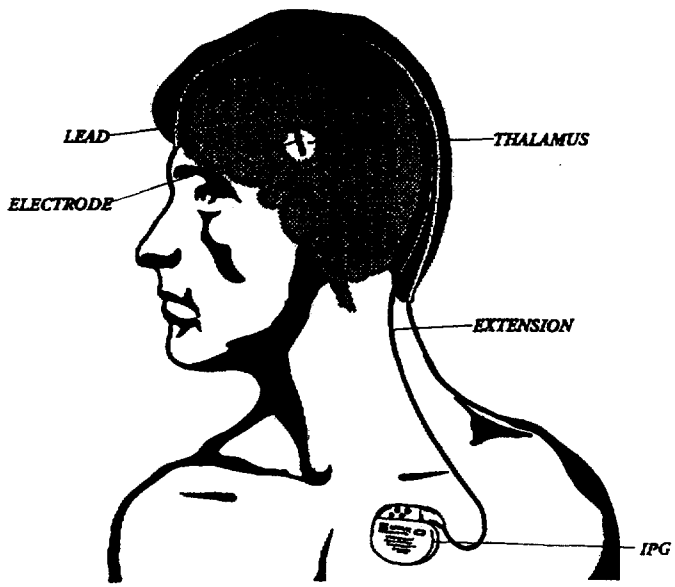


Figure 3. The lead is placed in an area of your brain called the "thalamus".
The IPG is typically placed below the collarbone.

While the IPG is **internalized**, you may be under general anesthesia or sedation. The doctor makes an incision in the skin, just below the collarbone (or sometimes in the abdomen), in order to implant the IPG (Figure 3).

The IPG is placed below the skin in a "pocket." The lead is then connected to the IPG with the extension. Your doctor will try to place the IPG in an area that is the most comfortable and cosmetically acceptable to you.

After the internalization, your doctor will use the console programmer to **program** the IPG settings. The stimulation delivered by the IPG can be controlled by programming the following settings:

- **Amplitude** is the strength of the stimulating pulse.
- **Rate** is the number of stimulating pulses per second.
- **Pulse Width** is how long each stimulating pulse lasts, measured in microseconds.

Using Your Control Magnet

When you briefly apply and then remove the Medtronic® Model 7452 Control Magnet over your implanted ITREL® II IPG, you turn it **ON** or **OFF**. If your doctor also has programmed a special setting for you, your control magnet can switch the programmed stimulation between **normal** and **low.**

Your implant site and the final placement of your IPG can vary from the examples shown in the following instructions. Have your doctor show you how to locate or position the magnet on your IPG so that it is centered as shown in Figure 4. Use the following instructions as a guide for using your control magnet.

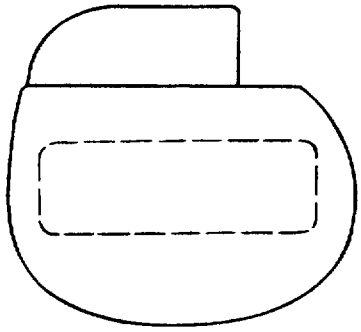
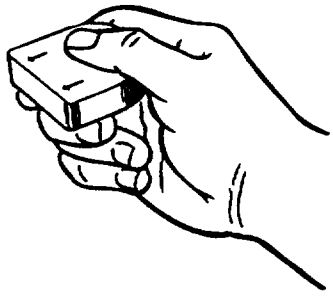


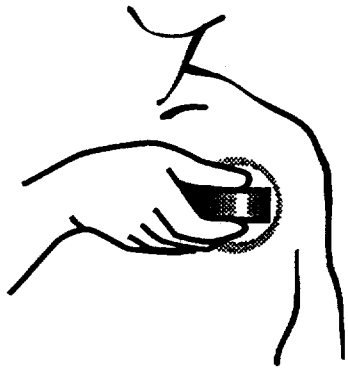
Figure 4. Magnet properly centered over IPG

Follow these simple steps to turn the IPG ON or OFF; and if programmed by your doctor, to switch the stimulation between normal and low.

1. Grasp the magnet with the flat end away from you.



2. Press the flat end of the magnet directly over and along the length of the IPG.



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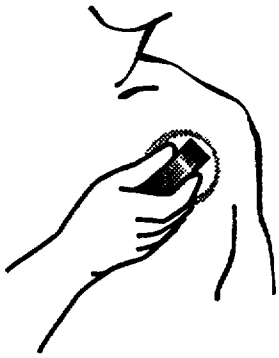
3. Hold the magnet steady, and:

- To turn the IPG ON or OFF, hold the magnet in place for 1 to 2 seconds.
- If programmed to switch between normal and low stimulation by your doctor, hold the magnet in place for 6 or more seconds.

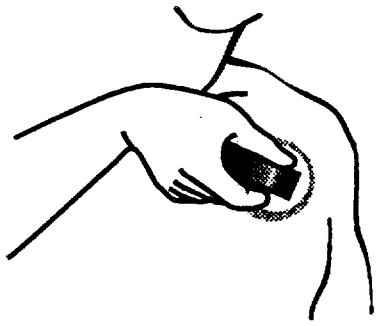
4. Remove the magnet. (This action is what actually turns the IPG ON or OFF, or switches between normal and low).

Note: If the magnet fails to turn the IPG ON or OFF or switch the amplitude, repeat the Steps 3 and 4, holding the magnet against the IPG in a different position. Try a "1 o'clock" or "4 o'clock position."

1 o'clock position



4 o'clock position



Living With Your Activa Tremor Control System

Signs To Watch For

When the IPG is switched ON, you may feel a brief tingling sensation in the area of your tremor. If you think your IPG is ON but your tremor does not decrease, contact your doctor. The IPG may simply require readjustment to a different setting. Or there could be a problem with the extension, lead, or IPG which may require surgery. Your doctor should be able to determine the cause of the problem and correct it. If there are any changes in your tremor unrelated to stimulation, contact your doctor.

Your ITREL® II IPG Identification Card

Your doctor will give you a temporary identification card, which has important information about your implant. The card is included with documents packed in the ITREL® II IPG box. Your doctor will complete an **implant registration form**, which is also in the box. The completed form becomes a record of your implanted device.

A copy of the registration form is returned to Medtronic by your doctor. Medtronic will mail you a wallet-sized, plastic-coated identification card.

You should carry your identification card at all times. In the event of an accident, this card will tell those attending you that you have an implanted medical device. This card supplies basic information about your IPG and identifies your doctor.

You can present your card if you need to move around security devices that may interfere with your IPG, like store theft detectors. Refer to pages 26-30 for more information.

Your card is especially important if you travel by air because airport security devices may interfere with your IPG and detect the metal in your IPG. Simply show your identification card to the airline clerk to obtain clearance. If you need a new identification card, list all information from your present temporary or permanent card, noting any changes, and send to:

Medtronic Neurological
Patient Registration Service
800 53rd Ave. NE
Minneapolis, MN 55421-9811

Medications

The Activa system is not a replacement for all medications prescribed for your treatment. This is especially true if you have Parkinson's disease, where medications may be used to treat other symptoms.

Doctor and Clinic Visits

It is important that you keep all of your doctor appointments. Your doctor may send you to a special clinic for routine checkups. Generally, these visits will be brief but will help to determine if your IPG is providing the desired therapy.

Be sure to inform your doctor if you change your address. If you must change doctors, your present doctor may recommend a new doctor. Also your medical history must be sent to the new doctor.Tell your other doctors and dentists that you have an implanted IPG. Then they can avoid prescribing treatments that may interfere with your tremor control system.

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Replacement Surgery

Because the IPG battery is sealed inside the IPG case, it cannot be replaced separately. Therefore, at replacement time, your doctor will remove the old IPG and implant a new unit. Your doctor will check your implanted extension and lead at the same time and, if it is working properly, he or she will connect the new IPG to these same implants.

The IPG may be explanted in the event of battery depletion or device malfunction.

Medical and Dental Procedures

With proper precautions, most medical procedures are unlikely to interfere with your IPG. Always tell any medical personnel that you have an implanted IPG. The following procedures may affect your Activa system:

- Diagnostic x-rays do not cause a problem, but some, such as mammograms, that require tight enclosure of the area where your IPG is implanted, may require adjustment of the x-ray equipment.

- Tell your dentist where your IPG is implanted, so he or she can take precautions with dental drills and ultrasonic probes used to clean your teeth. These devices should not be used directly over the implant site.
- Therapeutic ultrasound, electrolysis, radiation therapy, and electrocautery also should not be used directly over the implant site.
- Diathermy treatments that are sometimes used for muscle relaxation may affect the IPG output and/or damage its electronics.
- Magnetic Resonance Imaging (MRI) is not recommended.
- The electrical discharges from defibrillators may damage the IPG electronics.
- In the event of patient death, the IPG must be removed prior to cremation.

Activities and Exercise

You may be surprised at how fast you recover from IPG implant surgery. There will be some discomfort near the incision site at first. However, after a period of time, your awareness of the IPG will gradually diminish, and you may not even feel its presence.

On the advice of your doctor and as you begin to feel better, you should gradually be able to resume your normal lifestyle. Such activities may include:

- Traveling
- Bathing, showering, and possibly swimming
- Returning to your job
- Resuming hobbies or recreation such as walking, hiking, gardening, bowling, golfing, fishing, or hunting
- Returning to your daily activities should make you feel better, not worse. It is important, however, that you follow your doctor's advice. Ask your doctor about any particularly strenuous activities, such as lifting heavy objects.

Stimulation Changes due to Electromagnetic Interference (EMI)

Electromagnetic Interference (EMI) is either electrical or magnetic energy that is strong enough to interfere with the function of your IPG. This can cause uncomfortable stimulation (a "jolt" or a "shock"), or it can unexpectedly turn your IPG ON or OFF. Your IPG has built-in features to protect it from EMI produced by other electrical devices.

Most electrical items you encounter in an ordinary day are perfectly safe, and are unlikely to interfere with your IPG. Also, special circuits inside the IPG protect it from strong levels of EMI.

However, your Activa Tremor Control System may couple with certain strong magnetic fields to generate additional stimulation to your brain.

> **Note:** If you suspect an electrical device or magnet is interfering with your IPG, **simply move away from it or, if possible, turn the electrical device off.** If necessary, use your control magnet to switch your IPG back to the desired ON or OFF state.

WARNING: Some theft detectors (with gateways that patrons walk through) found in public libraries, department stores, etc., and airport/security screening systems may briefly cause an increase in your stimulation level as you pass through these devices.

Use care when approaching these devices. If you feel unwanted stimulation ("jolt" or "shock") as you approach the device, you may want to request assistance to bypass the device.

Note: Carry your system identification card with you at all times to verify you have an implanted device.

Your ITREL® II IPG is an electronic device which can be turned ON or OFF by the magnetic field from your Model 7452 Control Magnet. Other strong magnetic fields (electromagnetic or permanent magnet) can also switch your IPG output from ON to OFF or OFF to ON. These include Magnetic Resonance Imaging (MRI) equipment, manufacturing equipment, heavy industrial equipment, and some theft detector/security systems. Most household

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appliances, office machines, and personal radios usually **do not** produce electromagnetic fields strong enough to turn your IPG ON or OFF. However, if your IPG comes in close proximity to devices with small permanent magnets (some home or automobile stereo speakers, radios, refrigerator doors, and telephones have them) the magnetic field could turn the IPG ON or OFF. If you maintain a normal distance, most appliances will not affect your IPG.

Based on tests to date, cellular phones have no effect on the Activa™ Tremor Control System. The Activa IPG does not have sensing circuitry. This circuitry contributes to the electromagnetic interference (EMI) sensing of implanted pacemakers and defibrillators.

What You Can Do

Most electrical items you encounter in an ordinary day should pose no threat to your IPG. You can comfortably use common household appliances, including the following:

- Microwave ovens
- Televisions, AM/FM radios, stereos, cellular phones, etc.

- Tabletop appliances such as toasters, blenders, electric can openers, food processors, etc.
- Hand-held items such as hair dryers, shavers, etc.
- Appliances including washers, dryers, electric stoves, etc.
- Electric blankets and heating pads
- Vacuum cleaners, electric brooms
- Personal computers, electric typewriters, copiers, and FAX machines

What You Should Avoid

The following devices are strong sources of EMI, and have enough electromagnetic energy in them to turn your IPG ON or OFF if you are near them:

- Theft detectors
- Airport/security screening devices
- Large stereo speakers with magnets
- Electric arc welding equipment

- Electric induction heaters used in industry to bend plastic
- Electric steel furnaces
- Power lines
- Electric substations and power generators

If you suspect an electrical device or magnet is interfering with your IPG, simply move away from it or, if possible, turn the electrical device off. Then, using your control magnet switch your IPG back to the desired ON or OFF state. When switched ON with the magnet, your IPG will resume stimulation at the previously programmed level.

Close proximity to high levels of electromagnetic interference (EMI) may cause your IPG to switch ON or OFF. The system also may unexpectedly cease to function due to battery depletion or other causes. For these reasons, you should avoid any hazardous activities that would be potentially unsafe if your tremor unexpectedly returns. You may wish to consult with your doctor about this issue.

Checking Your IPG Function

For some patients, the function of the IPG may be checked through the following test (if you don't know your stimulation amplitude, you may need to first check with your doctor):

1. Turn on a small AM transistor radio to the lowest setting on the tuning dial, about 540 kHz (but not on a station). Adjust the volume to its loudest setting.
2. Hold the radio over the implanted lead at the implant site. If the output is ON, and the IPG amplitude is 1.5 volts or more, the radio should emit a strong buzzing sound.
3. If you don't hear any buzzing, your IPG may be OFF—use the magnet and try turning it ON.
4. If the buzzing still is not heard from the radio, contact your doctor.

IPG Battery Information

Your IPG is powered by a sealed battery which will eventually deplete. Typically, the IPG battery will last three to five years.

To replace the battery, your doctor must replace the IPG. This requires a surgical procedure. Typically, your doctor will only replace the IPG, and not the extension or DBS lead.

As the battery runs down, the stimulation may not be as effective in tremor suppression. These changes are normal and are no cause for alarm. When you feel this change in stimulation, make an appointment with your doctor to have your IPG battery checked.

Common Questions

1. **What is the Activa™ Tremor Control System?**

   The Medtronic® Activa™ Tremor Control System is an implantable, multiprogrammable system that delivers electrical stimulation to the thalamus of the brain. Electrical signals are transmitted from the Activa IPG to the thalamus via the Extension and the DBS™ Lead. This stimulation may relieve tremor due to Parkinson's disease or essential tremor.

2. **What is an IPG?**

   An IPG, or Implantable Pulse Generator, is the device that sends electrical pulses to the brain to control your tremor. The IPG contains a special battery and electronics to create these pulses.

3. **Will the Activa Tremor Control System get rid of all of my tremor?**

   Activa therapy helps control tremor, but it does not cure tremor. When activated, the Activa system markedly reduces tremor in the targeted area, resulting in improved use and function. Tremor will return when the system is turned off.

4. **Will the Activa Tremor Control System enable me to improve in daily activities like eating and writing, and improve personal hygiene practices, like brushing my teeth?**

   For many patients, the Activa system significantly improved activities of daily life in patients with essential tremor. Patients with Parkinson's disease may not show as significant an improvement, because other Parkinson's disease symptoms may continue to interfere with activities of daily life.

5. **What does stimulation feel like?**

   The sensation of stimulation varies from patient to patient. You may feel a brief tingling sensation when stimulation is first turned on. Higher levels of stimulation have been described as uncomfortable, "jolting,"or "shocking" by some

patients.

6. **How much is known about the material of the implanted lead when used in the brain?**

   The lead wire's insulation is made of a material that, if it breaks down, the breakdown parts are known to cause nerve damage or cancer in animals. However, the same insulation material has been used in pacemaker leads for a long time and has not been shown to have side effects on patients. This insulation material has not been previously used in the brain.

7. **Will I be able to increase or decrease the strength of stimulation?**

   If the "low" amplitude setting has been programmed by your doctor, you may select "normal" or "low" amplitude with your magnet. Otherwise, the strength of stimulation can be changed using a Console Programmer. Generally, your doctor will make these changes for you.

8. **Will I be able to turn the IPG ON and OFF?**

   Yes. The magnet provided with your system switches the IPG ON and OFF. Also, if so programmed, it switches the amplitude between "normal" and "low."

9. **What if I have trouble turning my IPG ON?**

   First, wait several seconds for tremor suppression after you turn ON your IPG. When you again try turning the IPG ON, be sure you hold your magnet directly over the implant. If you still cannot turn ON your IPG, call your doctor or Medtronic's Customer Service at 1-(800)-328-0810.

10. **How long will the IPG battery last?**

    The battery life of the IPG depends on the number of hours you use it each day and how strong the stimulation must be to control your tremor. Your doctor can give you an estimate once she or he determines your IPG settings.

11. **Can the battery be recharged?**

    No.

12. **How is the battery replaced?**

To replace the battery, your doctor must replace the IPG. A surgical procedure is required to replace the IPG. Typically, your doctor will only replace the IPG, and not the extension or DBS lead.

13. **Will the Activa Tremor Control System limit my activities?**

Generally, no. However, you should consult your doctor about any particularly strenuous activities.

14. **How large is the IPG?**

The IPG is oval and approximately 2.5 inches long at its longest point. At its widest point, the IPG is about 2 inches. It is about 0.5 inches thick.

15. **Will the IPG show through my clothes?**

Your doctor will try to place the IPG in a place that is most comfortable and cosmetically acceptable. However, depending on your body build, the IPG may be noticeable as a small bulge under the skin.

16. **What happens if the IPG stops working?**

    The stimulation will stop and your tremor may return. If you can't determine the possible cause (refer to *Living With Your Activa Tremor Control System* section), contact your doctor.

17. **What should I do if the stimulation changes or becomes uncomfortable?**

    Turn the IPG OFF with the magnet and contact your doctor.

18. **Does the IPG make any noise?**

    No.

19. **Will a microwave oven interfere with the IPG?**

    No.

20. **How often should the doctor check the IPG?**

    Your doctor will probably schedule checkups once or twice a year. However, your doctor may want to see you more or less often, depending on your situation.

Glossary

Amplitude—A measure of the electrical intensity delivered in a stimulating pulse, measured in volts.

Battery—Provides the power for Activa Tremor Control Therapy.

Control Magnet—Allows stimulation to be turned ON/OFF and can change stimulation amplitude as needed if programmed by your doctor.

Electromagnetic Interference (EMI)—Electrical or magnetic energy that is strong enough to interfere with or disrupt the function of your IPG.

Extension—A thin wire implanted under the skin that connects the lead and the IPG.

Implantable Pulse Generator (IPG)—A device that sends precise electrical pulses through the lead and to the brain. These electrical pulses control tremor.

Interference—Anything that reduces the effectiveness of the IPG or a programming transmission.

Lead—An implantable wire with a set of electrodes through which electrical stimulation is delivered to the brain.

Parameter—The conditions that can be varied to affect the
type of stimulation for you. These are amplitude, pulse width, and rate.

Programmer—Used to program the Activa Tremor Control System. It includes a computer, a programming head, and a printer.

Pulse Width—A measure, in microseconds, of the duration of each stimulating pulse.

Rate—A measure, in pulses-per-second, that provides the number of times stimulating pulses are delivered each second.