

June 2018

A PATIENT'S GUIDE TO:

EXABLATE NEURO TRANS-CRANIAL
MR GUIDED FOCUSED ULTRASOUND
SURGERY FOR Tremor Dominant Parkinson's Disease

INSIGHTEC

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1. GLOSSARY

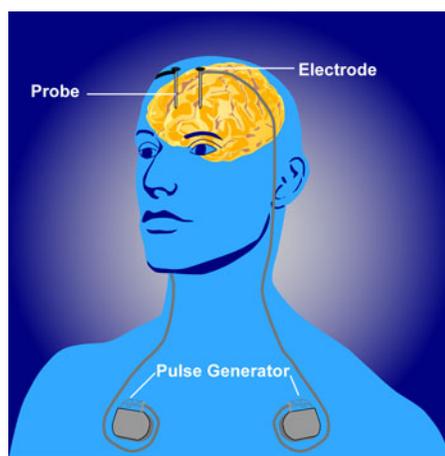
NAME	DESCRIPTION
CT or CAT Scan	Computed Tomography is an imaging technique that uses multiple cross sectional x-rays to create an internal image of a body structure
DBS	Deep Brain Stimulation is a method to control Tremor Dominant PD via stimulation through wires from a generator similar to a pacemaker.
MRI	Magnetic Resonance Imaging is an imaging technique that uses strong magnetic forces to excite the spins of molecules that behave differently when radio waves are bounced off of them to create an image.
MRgFUS	Magnetic Resonance guided Focused Ultrasound Surgery
Sham / placebo	Used in a clinical trial to demonstrate effectiveness against a known standard which would be No Treatment
Randomized	Method used to assign subjects to a treatment arm of the study so that the actual treatment allocation remains unknown to participating subjects until the end of the study
Thalamotomy	Type of brain surgery in which the thalamus, a tiny portion of the brain, is destroyed.
Sonication	A pulse of ultrasound energy delivered over a period of 10-20 seconds.
TDPD	Tremor Dominant Parkinson's Disease
Vim	ventral intermediate nucleus

2. WHAT IS A THALAMOTOMY AND HOW IS IT PERFORMED?

Your thalamus is a tiny area deep in the brain that is associated with tremor in Tremor Dominant Parkinson's Disease (TDPD) patients. TDPD is a particular subset of PD patients that can be diagnosed based on their disease symptoms being primarily tremor symptoms. An effective target for TDPD treatment is the thalamus *ventromedialis*. For other subtypes of PD, other effective targets have been identified.

Traditionally, **Thalamotomy** is an invasive procedure where a selected portion of the thalamus is surgically destroyed (ablated). Neurosurgeons use specialized equipment to precisely locate an area of the thalamus. Prior to the operation, a neurosurgeon will use stereotactic technology to identify the exact part of the brain that needs treatment by putting in place a frame on the patient's head with four pins to keep it still. The doctor will then take a detailed brain scan using computed tomography (CT scan) or magnetic resonance imaging (MRI) in order to identify the precise location for operation as well as a path through the brain to get to that specific spot. During the surgery the patient is awake, however, the area on the scalp where the surgical tools are inserted is numbed with an anesthetic. The surgeon makes a cut then inserts a hollow probe through a small hole drilled in the skull to the specific location. Different methods can be used to kill the brain cells, including circulating liquid nitrogen inside the probe destroying the targeted brain tissue, or by inserting an electrode heated up to near 200° Fahrenheit to burn the cells.

Today, the most common approach to treating Tremor Dominant Parkinson's Disease when medications no longer help is deep brain stimulation (DBS) in the thalamus. This form of treatment consists of staged surgeries to implant probes deep into the brain, tunnel the wires under the skin down the neck, and implant pulse generators below the skin near your collar bones. Additional surgeries may be required throughout the life of the generator(s) to replace batteries or malfunctioning parts. As with conventional thalamotomy brain surgery, DBS poses inherent risks. Your doctor will discuss all your options in order for you both to decide which method is best for you.



3. WHAT IS AN EXABLATE NEURO TREATMENT AND HOW DOES IT WORK?

A new non-invasive thalamotomy technique is now available to neurosurgeons where sound waves can be focused through the skull to target this location without the need for incisions or holes (i.e. “non-invasive”). Your doctor has prescribed the Exablate Neuro[®] procedure to treat your Tremor Dominant Parkinson’s Disease because you are a good candidate. This is determined by evaluating whether or not medication can provide sufficient control of your tremors and by measuring the shape and density of your skull using CT or CAT Scan. The information collected by the CT Scanner will be uploaded into the software of the Exablate Neuro device to aid it in focusing energy through the unique shape of your skull.



The Exablate Neuro[®] device uses sound energy that is generated by an ultrasound source inside a helmet. The ultrasound waves are then focused on a specific point in the brain to create a tiny ablation or burn. This focus is similar to how the sun’s rays can generate enough heat to ignite paper when focused under a magnifying glass. Just like the magnifying glass, if the magnifying glass is raised or lowered, the point of focus changes and the cumulative effect of the energy is lost.

The Exablate Neuro system is fully integrated to a Magnetic Resonance imaging scanner (see Figure 2). The whole procedure is actually conducted inside the imaging scanner. During this procedure, the Exablate Neuro will use the MR imaging for planning your treatment, guiding the ultrasound energy, and determining how hot the point of focus and surrounding tissue gets.

Ultrasound is a form of sound energy that passes through skin, muscle, fat, and bone without the need for incisions, electronic leads, or inserted probes. The ultrasound energy is non-ionizing, meaning you are not being exposed to radiation during the surgery. High intensity focused ultrasound energy, when focused on a small target volume, provides a therapeutic effect by raising the tissue temperature of the target high enough to destroy it. Only tissue at the target is heated to a level needed to kill the tissue.



4. WHY DOCTORS USE IT?

Your doctor has determined that thalamotomy is the most appropriate method to treat your Tremor Dominant Parkinson's Disease . Exablate provides a non-invasive approach to performing this procedure. Based on the clinical study that served to gain FDA approval, the procedure has a very good chance to help your condition. Additionally, it may allow you to regain certain movements the tremors had previously impacted. It may also improve your quality of life.

Your doctor will be discussing the full risks and benefits of this procedure with you in greater detail when you discuss all your options.

5. AM I SUITABLE FOR THE EXABLATE THALAMOTOMY PROCEDURE? – CONTRAINDICATIONS

Exablate Neuro is not suitable for all patients. Patients who have any of the following should inform their doctor so he can suggest appropriate treatment options for you.

- If you have any kind of metallic implants, such as pacemakers, neurostimulators, spine or bone fixation devices, total joints, metal clips, screws, etc. you may not be a candidate. Any metallic implants must be non-magnetic to prevent injury to the patient from the MR's strong magnetic field.
- If you are not generally healthy enough to withstand the treatment and lie still in the same position for approximately 3 hours you may not be a suitable candidate for this treatment. Health related issues such as a recent myocardial infarction (heart attack), congestive heart failure (fluid around the heart), unstable angina pectoris (chest pain), or spinal conditions may be issues that you should discuss with your doctor.
- If you have extensive scarring on the scalp, you may not be a good candidate.
- If you have any brain tumors, aneurysms requiring treatment, or other degenerative neurological conditions, you may not be a good candidate.
- If you have any bleeding disorders, or have had a stroke or brain bleed, you may not be a good candidate. If you are taking anticoagulants or blood thinners, you may need to discuss this with your doctor.
- If you have a history of seizures within the past year, you may not be a good candidate.
- If you have or have had a deep brain stimulator implanted, you are not a good candidate.
- If you are on dialysis you may not be a good candidate.
- If you have psychiatric disease, severe depression not controlled by medication, or other mental illness, you may not be a good candidate.

Please discuss all these conditions with your physician so your doctor can properly evaluate your suitability for the Exablate therapy.

6. THINGS YOU MUST DO TO AVOID INJURY – WARNINGS

- Tell your physician of any medication allergies that you may have including and not limited to recent or past medications.
- Your physician will need to perform a full medical evaluation and full review of your medical chart to fully assess your overall condition. This is necessary to ensure a safe and effective Exablate Neuro treatment for your condition.

- Show your physician any scar on your head. Scar tissue is different from surrounding tissue and is more susceptible to heat damage and could cause pain if located in the beam pathway. Alternate beam paths may be available to avoid the scar tissue.
- You will be given a Stop Sonication button before initiating treatment. In the event of pain or patient motion, activate the stop sonication button so that you will not be harmed. If you are experiencing pain, tell your physician so he can alter the treatment, or alter the pathway to minimize the pain, slow the sonications down to allow for longer heat dissipation times, or provide medication to make you more comfortable. Failure to communicate this with your physician could result in serious injury. The Stop Sonication button is a safety feature built into the system for the patient.

7. THINGS YOU MUST DO TO AVOID OTHER HARM – PRECAUTIONS

- Tell your physician of all medications you take and of any risks or tendencies you may have for blood clots. Due to the period of immobilization required for the Exablate treatment, the risk of a blood clot forming can increase because you must lie still for so long during this treatment. If your risk for blood clots is high, your medical team may perform additional tests and prescribe additional medications during the procedure that may avert any potential problems. Compression stockings or other measures may be taken to minimize this risk which is no different than any other procedures with similar durations.
- Tell your physician of any medical conditions you have that could affect your ability to lie on the table for long periods of time. Medical conditions could include neck or back problems (herniated discs or pinched nerves), severe arthritis, claustrophobia, etc.
- After a head shave, a stereotactic frame will be attached to your skull by the neurosurgeon to prevent movement during the treatment, but it is still recommended that you remain still during each sonication. Cool water will be circulated around your skull to prevent any burning. You may also be given medication to increase your comfort during the treatment.
- You will be given a **Stop Sonication** button before the treatment starts which you will hold during the treatment. If you experience great pain or discomfort, push the button to stop the treatment and tell your physician why you stopped it. Your feedback will allow your physician to make adjustments and address your issue.

8. RISKS OF HAVING THIS DONE

Infrequent complications have been reported following Exablate Neuro MRgFUS treatments which are described below:

8.1. SHORT TERM RISKS – DAY OF TREATMENT UP TO 3-MONTHS POST-TREATMENT

The most common potential risks associated with the Exablate Neuro device and thalamotomy procedure are transient numbness and tingling. These sensations are typically mild to moderate in intensity and can last as briefly as the length of the sonication or up to several days. Headaches or head pain during sonication and imbalance or unsteady were other potential risks, but most often ended shortly after treatment.

Nausea/Vomiting were also reported in some instances. It is unclear if this is related to medications used during the treatment or the procedure itself.

You may experience bruising in the area of the iv catheter following the procedure similar to that experienced after blood draws. Any bruising should resolve on its own within a week.

You may experience some pain, bleeding or swelling around the pin site location from the stereotactic frame. These should resolve with a little bit of time (approx 1 week).

8.2. LONG TERM RISKS – LONGER THAN 3-MONTHS POST-TREATMENT

Overall, Exablate MRgFUS is a reasonably safe procedure for treating Tremor Dominant Parkinson's Disease with minimal risk. Infrequent complications that have been reported following Exablate treatment include long-term numbness and tingling. Additionally, if (unintended) brain tissue is damaged, there may be muscle weakness, numbness, or sensory loss that may resolve after several months, or it may be non-reversible.

If you experience a blood clot or DVT after the procedure that is not treated emergently, you may have long term complications related to it if it does not resolve quickly. You could have muscle, heart, brain, or lung damage.

9. BENEFITS OF HAVING THIS DONE

During the study, using a validated tremor rating scale, investigators reported significant reductions in tremor which resulted in patient improvement of their daily functional disabilities involving eating, drinking, hygiene, dressing, working, and social activities. Most patients reported improvements in these activities to normal or near normal conditions.

In addition to possible improvements in functional daily activities, the procedure is non-invasive (i.e., no surgical incisions or holes drilled through the skull), conducted with the patient fully awake, and may be performed on an out-patient basis.

It is possible that you do not gain any tremor relief or improvement in quality of life. This procedure does not treat the underlying disease nor prevent the exacerbation or progression of the disease.

10. HOW TO DECIDE ABOUT THIS TREATMENT

You must explain all your medical conditions to your physician. Your physician will evaluate whether you are a good candidate for the Exablate Neuro treatment. Together, in consultation with your physician and caregivers, you will need to decide if you can tolerate the treatment and are a suitable candidate. Your physician will also discuss any other treatment options that are available to you.

11. WHAT HAPPENS BEFORE THE TREATMENT

Once you have been evaluated to see if you are a suitable candidate as described above, and the surgeons have explained to you all the risks associated with the device and the procedure, you may be scheduled for a CT scan to determine if the shape and thickness of your skull are suitable for the Exablate Neuro device. Once confirmed, your entire scalp will be shaved and cleaned. You will have a urinary catheter placed to drain your bladder during the procedure and you will likely wear some form of compression stockings during the procedure. Your physician may start you on medication to minimize risks of DVT.

An intravenous catheter will be placed into your arm to administer fluids and medications. You will be administered medications to make you comfortable. You will have the stereotactic frame attached to your head to prevent any movement of your skull during the sonications. A silicon diaphragm will be placed around your head to allow cool water to circulate minimizing potential heating near your scalp. Your heart rate, blood pressure and blood oxygen levels will be monitored throughout the procedure.

12. WHAT HAPPENS DURING THE TREATMENT

You will be given a **Stop Sonication Button** to hold during the procedure. You will be moved inside the MR device (see **Figure 2**). If you get claustrophobic, tell someone so that you can receive medication to keep you calm. The procedure will be performed from a computer in the room adjoining the MR suite. A circulating nurse will be close to check on you and to administer medication.

A series of MR images is taken for the purpose of planning the treatment. The physician will mark the area to be treated and sub-lethal sonications can be used to illicit physiological responses from you to ensure they have located the proper spot in the brain.



Figure 1: Exablate Software Graphical User Interface: 1) Graphical user interface uses buttons and icons to identify functions during treatment, 2) the software overlays graphical displays on MR image(s), 3) treatment parameters and treatment progress easily accessible during treatment.

After each sonication, a neurologist or neurosurgeon will evaluate you to receive feedback regarding your sensations as well as determine the effect of the sonication on the tremor itself. You must remain still throughout the treatment session. Your procedure may last anywhere from 1 to 3 hours depending on the amount of energy that can be focused during each sonication. The time is dependent on many factors associated with the shape and thickness of your skull.

13. WHAT HAPPENS AFTER THE TREATMENT

You will be removed from the machine, and you will have the stereotactic frame removed. Once you have been determined to be stable, all the monitoring equipment and catheters will be removed. You will be moved to a recovery room for observation for several hours. Your physician will decide when to release you. He will also explain to you the post treatment care that you may need. Your physician will let you know when you can go home and when you will need to return for any follow-up visit.

14. WHEN TO CALL YOUR DOCTOR

If you experience severe pain, lightheadedness, discomfort, or fever of 100°F or higher within 48 hours of treatment, call your physician. You may receive a follow-up phone call the next day, or you may be scheduled for a post-treatment follow-up visit as routine standard of care whether you have any side effects or not.

15. WHERE YOU CAN FIND OUT MORE

If you desire more information about this procedure, please visit the sponsor's website to learn more about the device “ www.INSIGHTEC.com ”, or you may call our customer service toll-free line at **1 866-392-2528**.

16. HOW CLINICAL STUDIES WERE DONE

The study that forms the basis of this indication in TDPD patients was a prospective, multi-center, randomized, sham-control, double-blinded clinical trial. Subjects with idiopathic TDPD with medication-refractory tremor who were at least 30 years old were recruited into the study. Both the subject and the movement disorder specialist measuring the PD assessment were blinded to the treatment assignment until after Month 3. Randomization was based on a 2:1 ratio. Qualified subjects were randomized at a 2:1 ratio to either active Exablate treatment arm or Sham control (with sonication energy disabled). At the Month 3 visit, Sham subjects were permitted to Crossover to an active Exablate treatment. All subjects were followed to Month 12 following an Exablate treatment. The study design used here was the same as was used in the pivotal trial for Exablate thalamotomy to treat Essential Tremor (FDA approval in July-2016 under PMA P150038).

Two sites participated in this TDPD patient cohort study. One site enrolled 25 subjects and a second site joined the study late and enrolled 2 subjects.

Exablate *Vim* thalamotomy for TDPD subjects resulted in significant improvement in treated side upper extremity tremor that was maintained through the 12-month study visit. Primary effectiveness was evaluated using validated scores: on medication, Upper Limb tremor-motor subscore from Parts A & B of the CRST. In the TDPD cohort study, the percent change from baseline for the Exablate-treated group was 51.6% compared to 12.7% for the Sham Control, a difference which resulted in a Wilcoxon rank-sum value of $p = 0.030$.

Out of the 100 adverse events reported in the Exablate-treated TDPD cohort (50%) were transient, resolving within 72 hours; 21 (21%) were unrelated to the device or procedure, 2 were related to progression of Parkinson's disease, 2 were procedure related and 22 (22%) were thalamotomy related.

Thalamotomy related events were those associated with ablation of the Vim regardless of the method based on the literature. In this study Thalamotomy related events accounted for 22/100 (22%) of the adverse events. Exablate Thalamotomy related adverse events in the TDPD study cohort occurred at frequencies as follows:

Numbness/Tingling (7, 7%), Imbalance (4, 4%), Headache (0%), Gait disturbance (2, 2%) and Unsteady (1, 1%).

Conclusion

Exablate *Vim* thalamotomy has been demonstrated to be a safe and effective treatment for upper extremity tremor in TDPD. The present investigation in Parkinson's disease subjects indicates similar effectiveness and safety of Exablate treatment for upper extremity tremor.