

# PATIENT SELECTION FOR ANT-DBS THERAPY

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DISCLOSURE:  
CONSULTING  
FOR MEDTRONIC



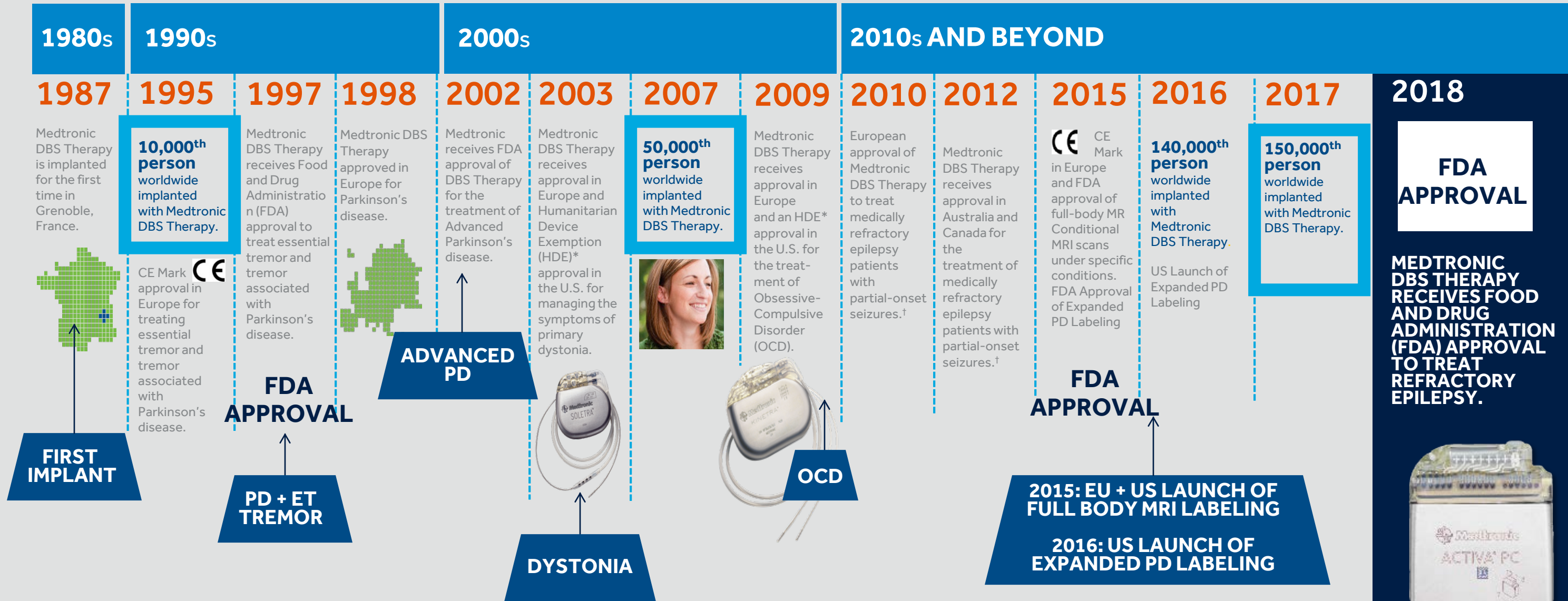
# MEDTRONIC OFF LABEL DISCLOSURE

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# MEDTRONIC DBS THERAPY – IMPROVING LIVES THEN, NOW, TOMORROW.



\*Humanitarian device exemption (HDE) in the United States; the effectiveness of this device for the treatment of dystonia and obsessive-compulsive disorder (OCD) has not been demonstrated.

## **Robert Fisher, MD, PhD**

Maslah Saul Professor of Neurology & Neurological Sciences  
Director of Stanford Comprehensive Epilepsy Program  
Palo Alto, CA



# DISCLOSURES

- Consultant for Medtronic since 4/2018, SANTE research grant
- Stock or options in:
  - Zeto (dry, wireless EEG)
  - Cerebral Therapeutics (AED perfusion in CSF)
  - Smart-Monitor (Shake detector watch)
  - Avails Medical (rapid assays of levels)
  - Eysz (seizure detection)
  - Irody (Epilepsy Care software systems)

# WHY NEUROMODULATION?

Epilepsy is one of the most common neurological conditions impacting over 65 million people worldwide<sup>1</sup>

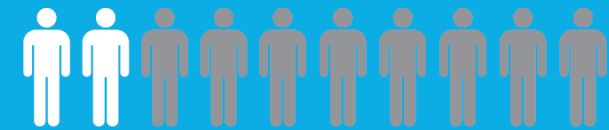
Over 60% of newly diagnosed people will enter remission upon treatment with medication.<sup>2</sup>



Approximately 30-40% of people, seizures recur in varying degrees of intensity and frequency despite anti-epileptic drug treatment and may be candidates for other therapies.<sup>2</sup>



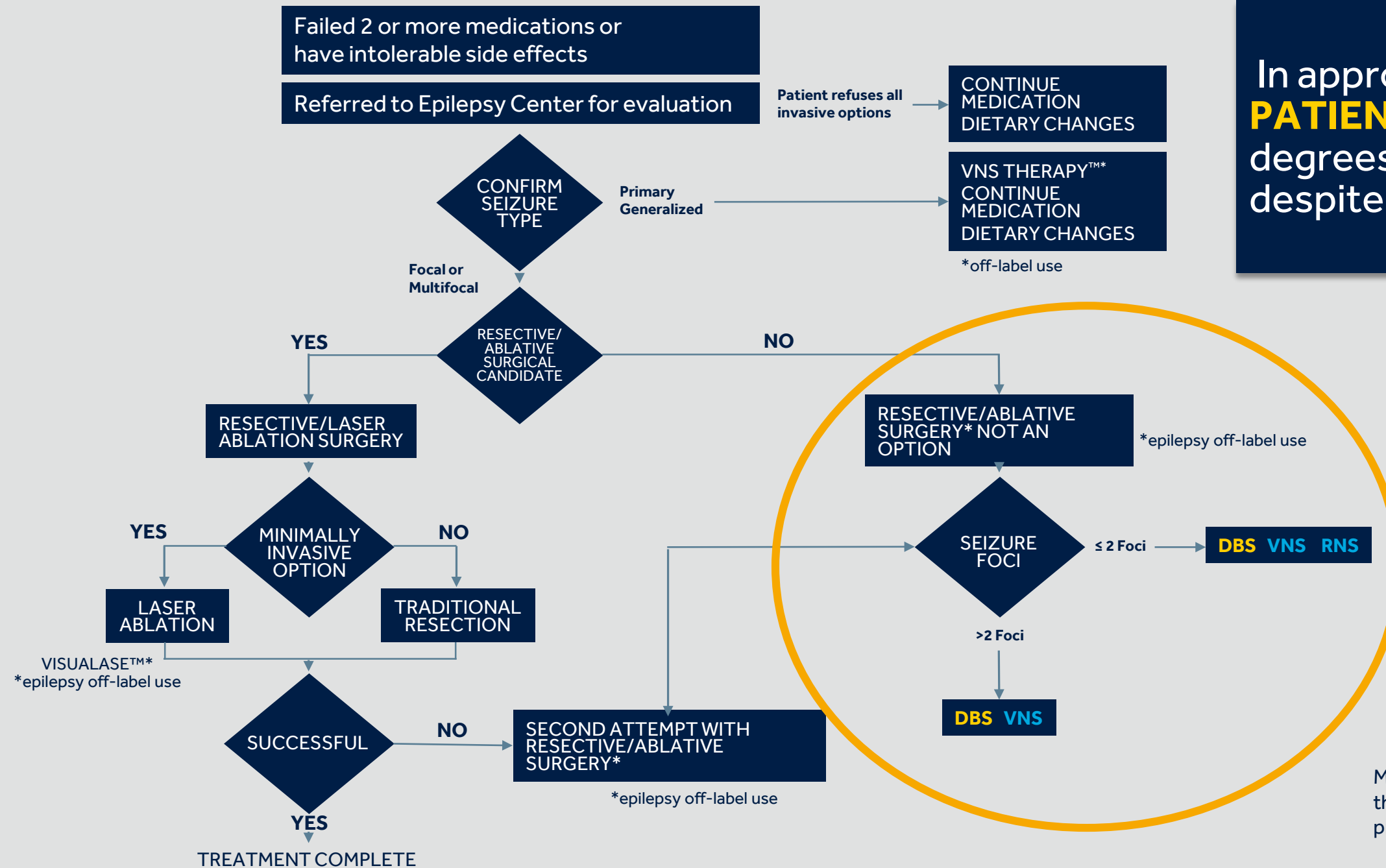
At present, only 10-20% of the people with refractory epilepsy are good candidates for resective surgery.<sup>3</sup>



**Neuromodulation may be an option for people with seizures that:**

- Are not candidates for traditional brain surgery
- Continue to have seizures after surgery

# TREATMENT PATHWAY



In approximately **30-40% OF PATIENTS**, seizures recur in varying degrees of intensity and frequency despite antiepileptic drug treatment.

Medtronic DBS indication – Refer to product labeling regarding the instructions for use, indications, contraindications, warnings, precautions, and potential complications/adverse events.

# OUTLINE

- Review of the SANTE study and the results
- How to identify patients for ANT-DBS neuromodulation
- Importance of setting and managing patient expectations



# FDA INDICATION FOR MEDTRONIC DBS THERAPY FOR EPILEPSY

- **Bilateral stimulation of the anterior nucleus of the thalamus (ANT)** using the Medtronic DBS System for Epilepsy is indicated as an **adjunctive therapy** for reducing the frequency of seizures in individuals **18 years of age or older** diagnosed with epilepsy characterized by **partial-onset seizures, with or without secondary generalization**, that are **refractory to three or more antiepileptic medications**.
- The Medtronic DBS System for Epilepsy has demonstrated safety and effectiveness for patients who average six or more seizures per month over the three most recent months prior to implant of the DBS system (with no more than 30 days between seizures). The Medtronic DBS System for Epilepsy has not been evaluated in patients with less frequent seizures.



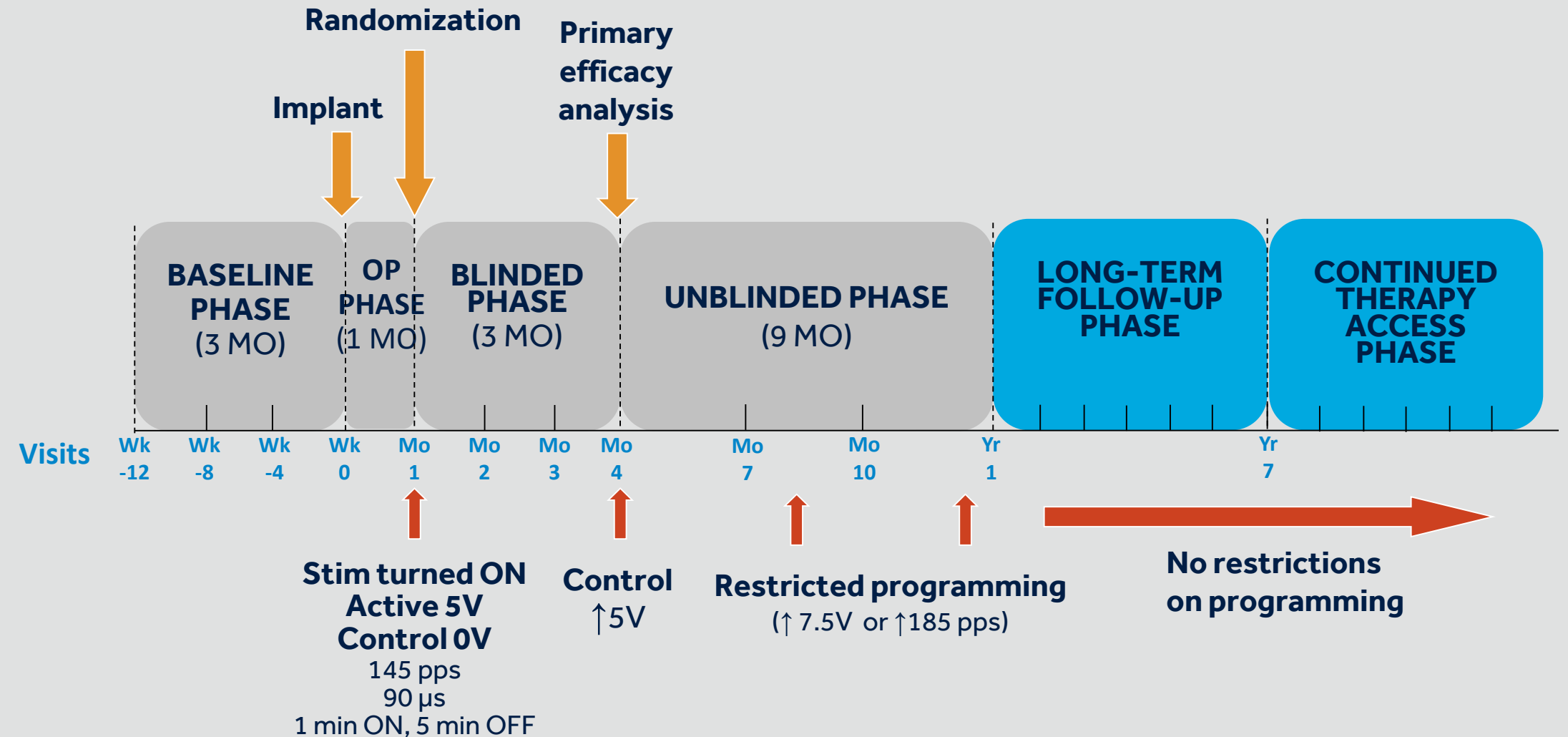
# SANTÉ CLINICAL TRIAL

## STIMULATION OF THE ANTERIOR NUCLEUS OF THE THALAMUS FOR EPILEPSY

To evaluate the safety and efficacy of bilateral stimulation of the ANT as adjunctive therapy for the treatment of refractory, partial onset seizures with or without secondary generalization

Medtronic-sponsored, multicenter, prospective, randomized, double-blind, parallel groups study

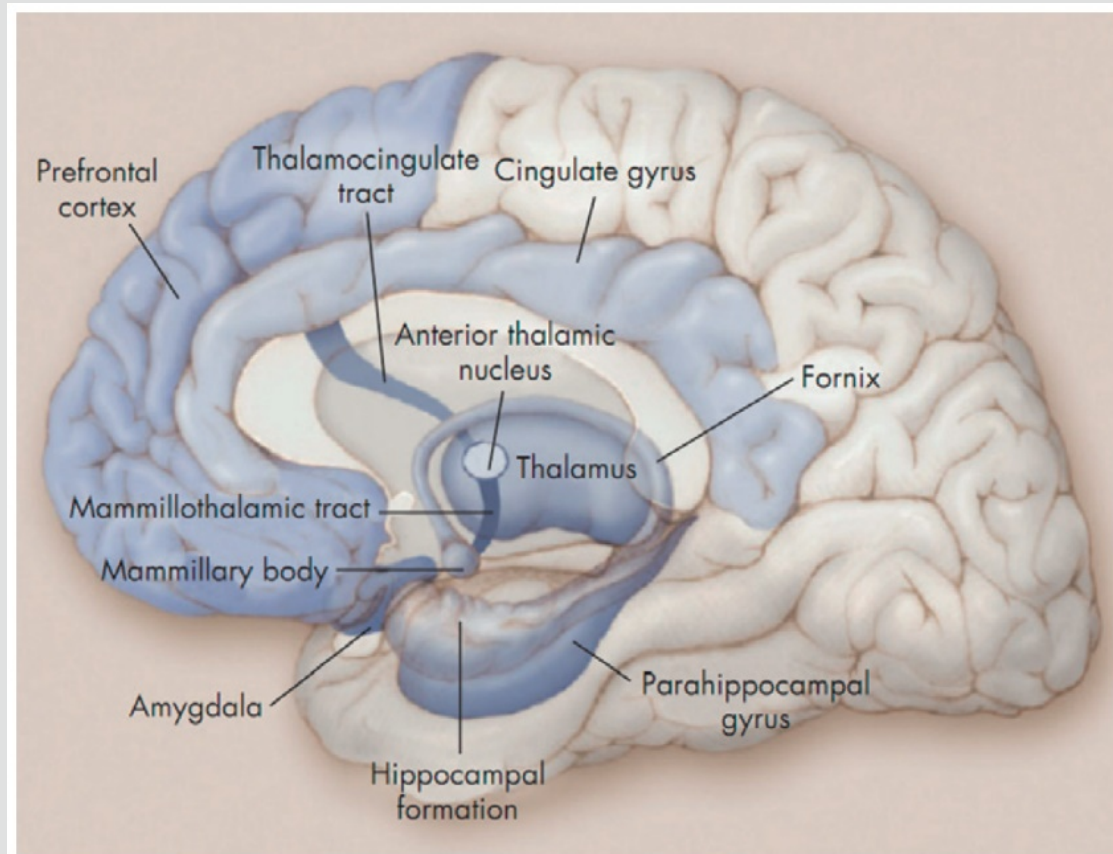
Pivotal clinical trial conducted at 17 centers in the United States with initial implant in 2004.



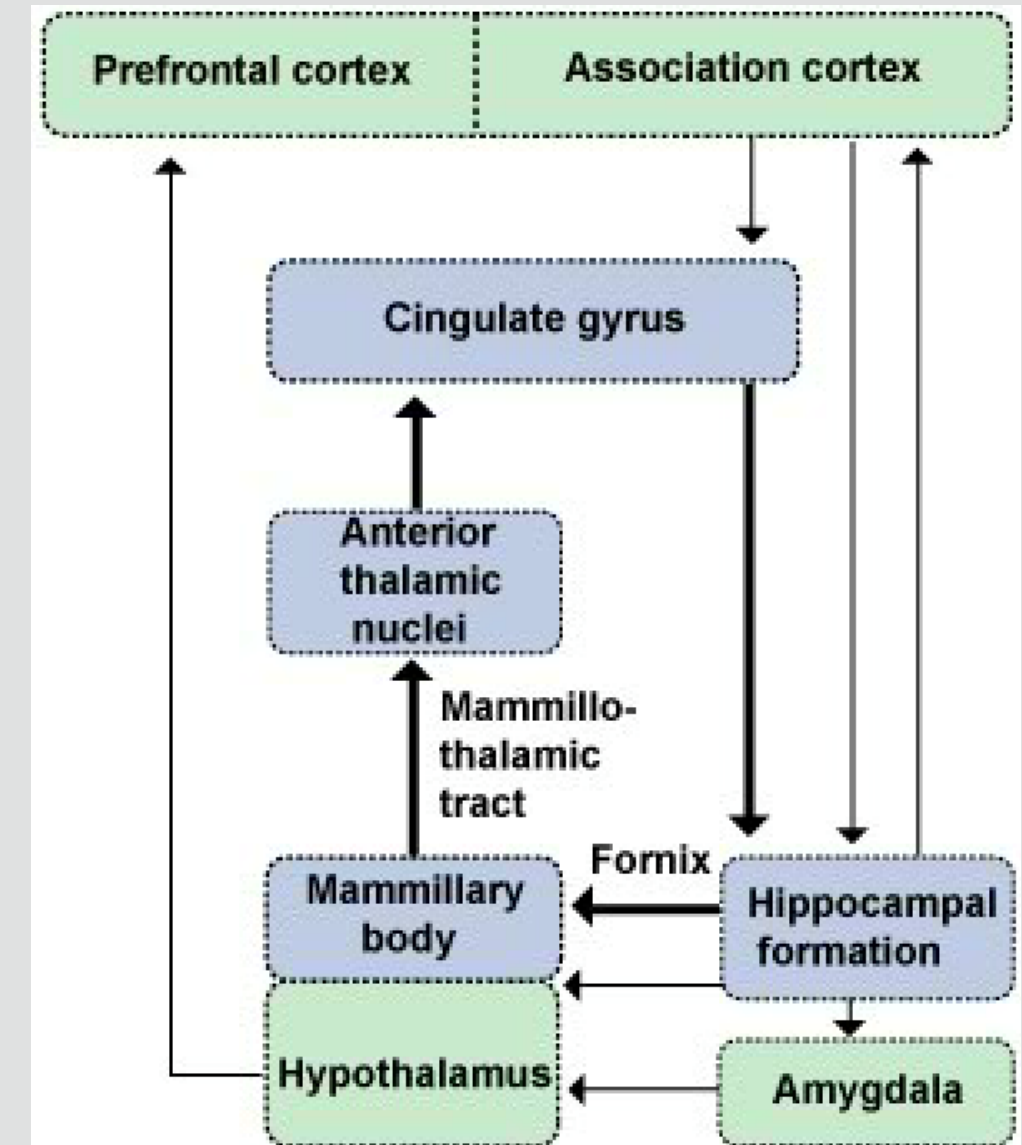
A multicenter, prospective, randomized, double-blind, parallel groups study

# CIRCUIT OF PAPEZ – ANT DBS: RATIONALE, TARGET

Irving Cooper reasoned that due to its location with the Circuit of Papez the ANT could serve as key location to disrupt limbic seizures



Wu & Sharan, Neuromodulation, 2013



# SANTÉ CLINICAL TRIAL

## STUDY POPULATION

### Eligibility Criteria (abbreviated) –

- Age 18-65, inclusive
- 6 or more partial seizures with or without secondary generalization per month
- Refractory to at least 3 antiepileptic drugs (AEDs), currently taking 1-4 AEDs

### Demographics (n=110 implanted)

AGE (MEAN)	36.1 YEARS
FEMALE (%)	50%
YEARS WITH EPILEPSY (MEAN)	22.3 YEARS
BASELINE SEIZURE COUNTS PER MONTH (MEDIAN)	19.5
NUMBER OF EPILEPSY MEDS (%):	
1	11%
2	49%
3	37%
4	3%
PREVIOUS VNS (%)	45%
PREVIOUS EPILEPSY SURGERY (%)	25%
HISTORY OF DEPRESSION (%)	46%
HISTORY OF MEMORY IMPAIRMENT (%)	34%

# LOBE OF ONSET

PIVOTAL TRIAL WAS POWERED FOR TOTAL GROUP, -NOT SUBGROUPS

TEMPORAL LOBE WAS BIG ENOUGH FOR SUBGROUP ANALYSIS, AND WAS SIGNIFICANT

OTHER LOBES IMPROVED, BUT SUBJECT # TOO SMALL FOR SIGNIFICANCE

DOES NOT MEAN THAT DBS ONLY WORKS IN TEMPORAL LOBE

<b>Location of seizure onset <sup>a</sup></b>	<b>No. of subjects</b>	<b>% (N=110)</b>
Temporal lobe	66	60.0%
Frontal lobe	30	27.3%
Diffuse or multifocal	10	9.1%
Other	10	9.1%
Parietal lobe	5	4.5%
Occipital lobe	4	3.6%

<sup>a</sup> Subjects may have seizures from more than one location

# SEIZURE FREQUENCY

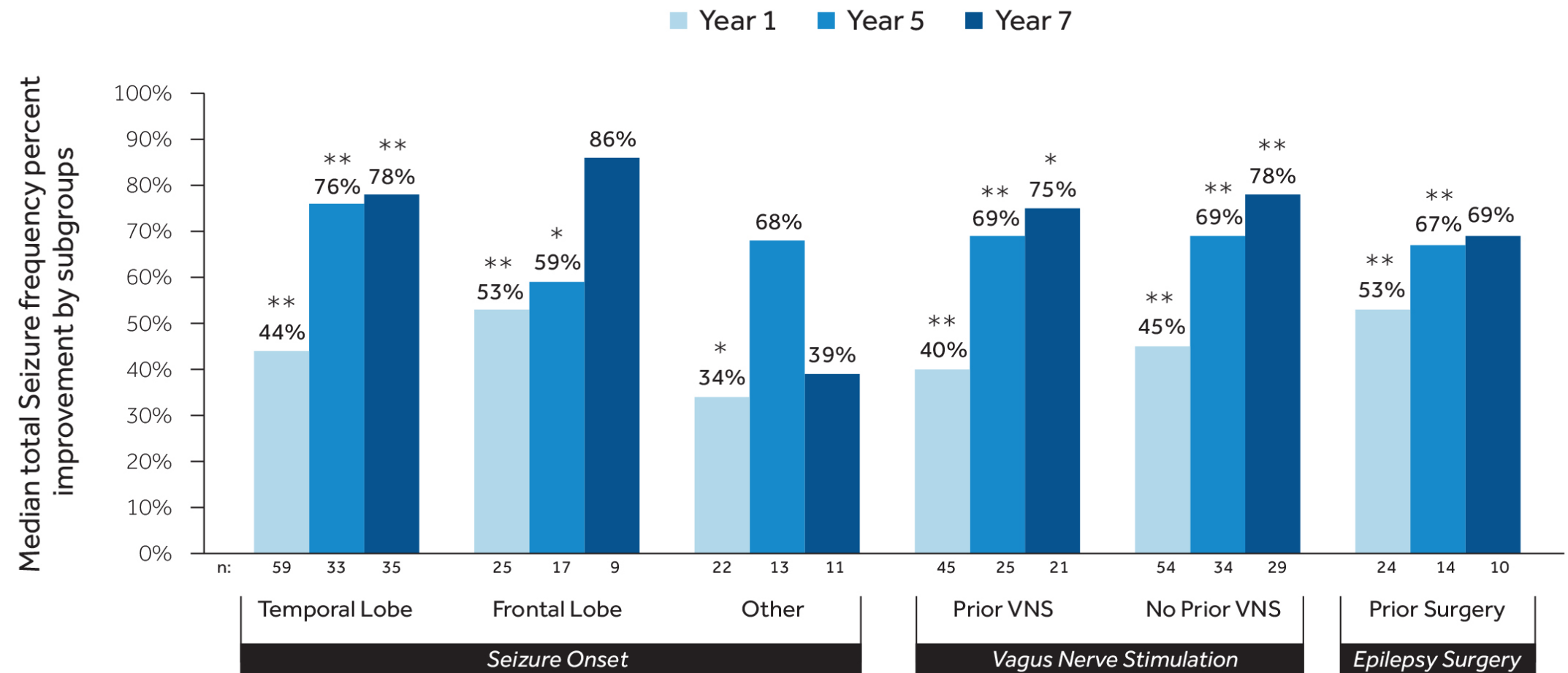
## SUBGROUPS: SEIZURE ONSET, PRIOR VNS/SURGERY

SIGNIFICANT REDUCTIONS IN SEIZURES WERE OBSERVED WHEN LOOKING AT SUBGROUP ANALYSIS:

- SEIZURE ONSET
- PRIOR VNS (NON-RESPONDERS)
- EPILEPSY SURGERY

PATIENTS SUBGROUP WITH PRIOR VNS® HAD A SIMILAR REDUCTIONS IN SEIZURES COMPARED WITH THE GROUP WITHOUT A PRIOR VNS®

PATIENTS SUBGROUP WITH PRIOR SURGERY BENEFITED FROM THE ADDITION OF ANT DBS



\*p-value ≤ 0.05    \*\*p-value ≤ 0.001

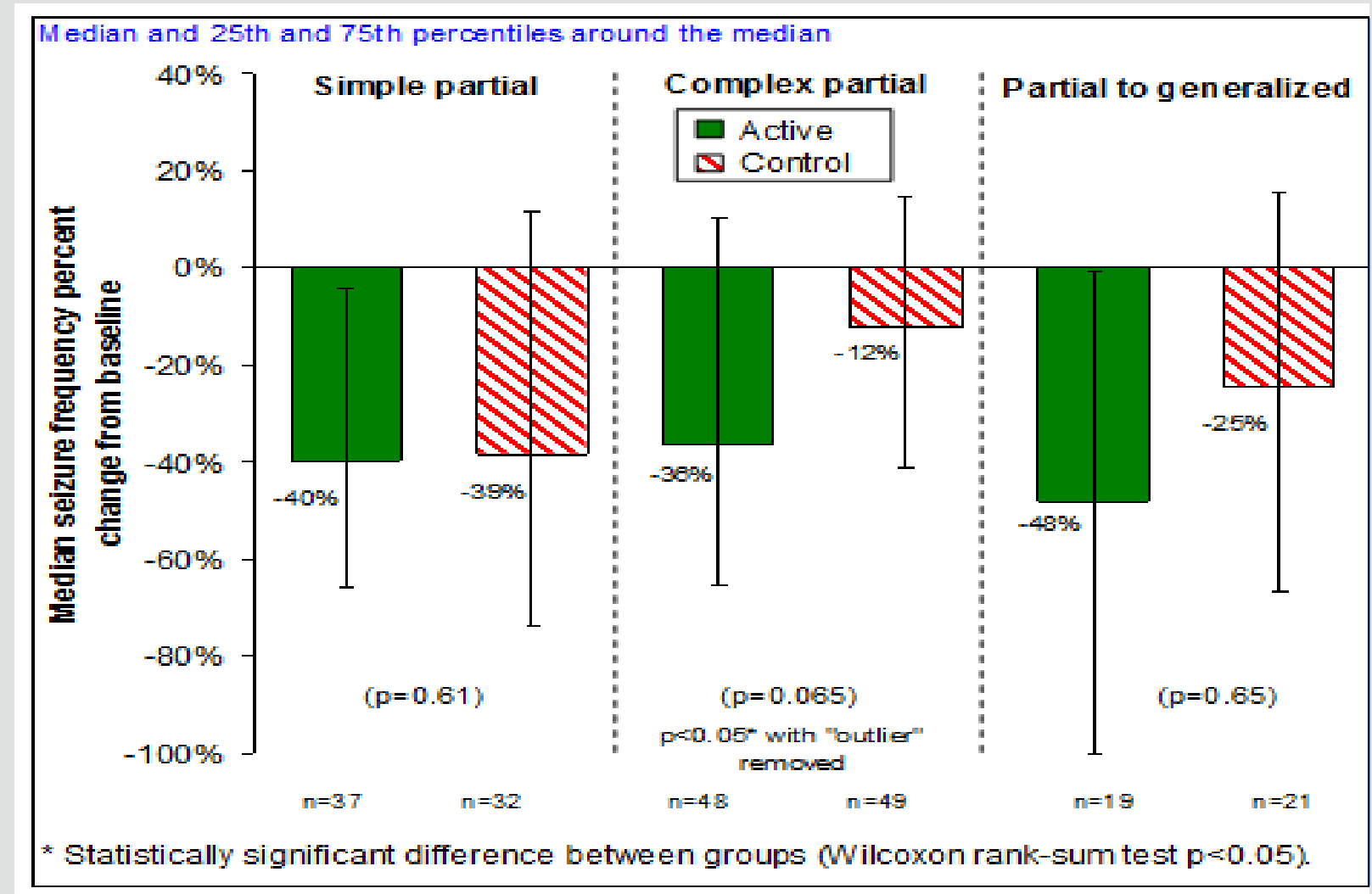
# SEIZURE TYPE

PIVOTAL TRIAL WAS DONE ON ADULTS WITH FOCAL AND SECONDARILY GENERALIZED SEIZURES

FOCAL AWARE SEIZURES DID NOT IMPROVE

FOCAL TO TONIC CLONIC DID BUT SAMPLE SIZE TOO SMALL FOR SIGNIFICANCE

## TYPE OF SEIZURE IN THE IMPLANTED SUBJECTS

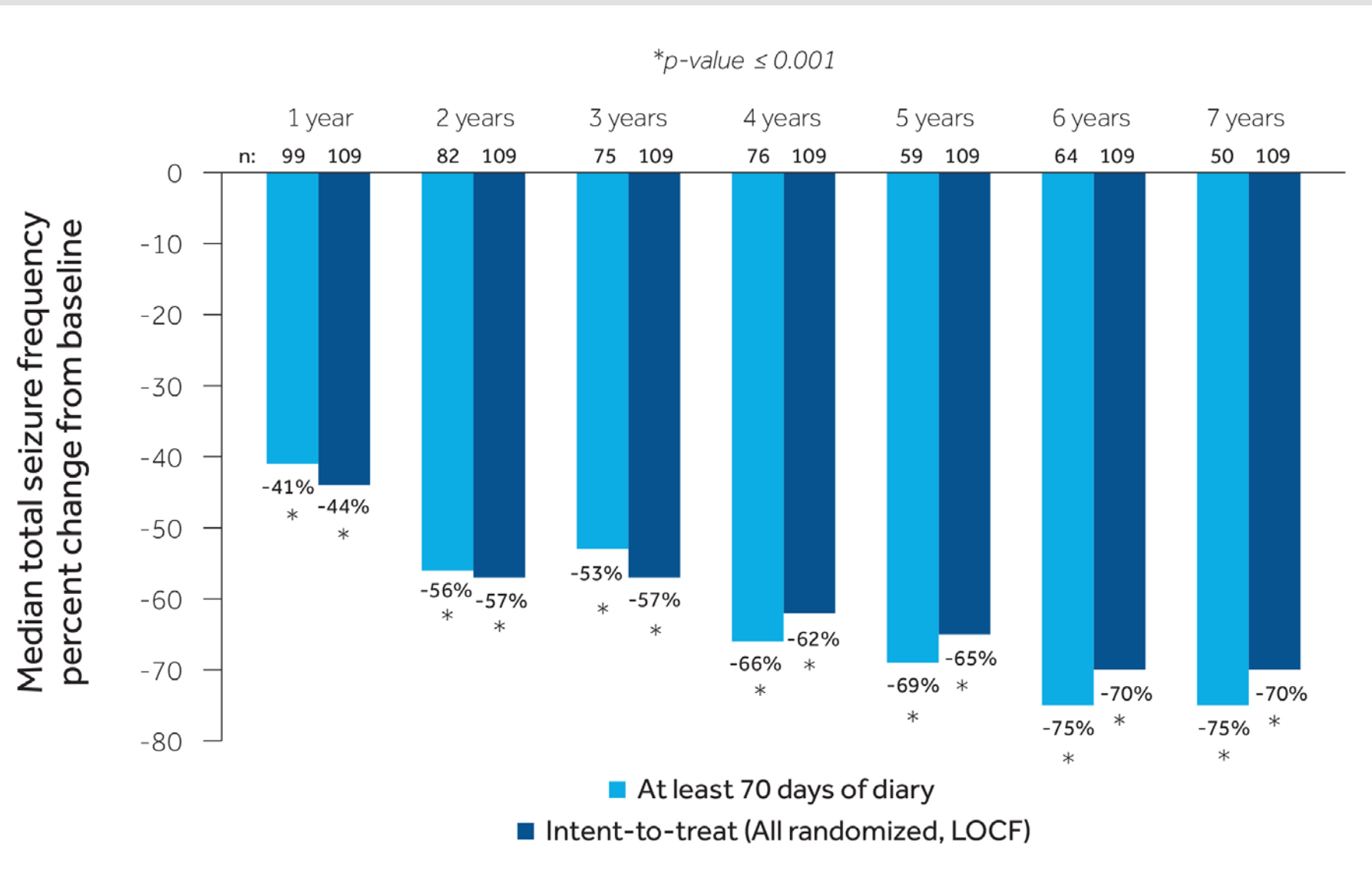


# TOTAL SEIZURE FREQUENCY

**THERE WAS A LONG TERM TREND IN AN IMPROVEMENT IN SEIZURE FREQUENCY OVER 7 YEARS OF LONG TERM FOLLOW UP**

**SEVERAL SENSITIVITY ANALYSIS WERE PERFORMED TO EVALUATION THE IMPACT OF PATIENTS LEAVING THE TRIAL**

**THE LOCF ANALYSIS (AS WELL AS OTHERS) DEMONSTRATED THAT THE LONG TERM TREND IN SEIZURE REDUCTION WAS LIKELY ALIGNED TO TREATMENT BENEFIT AND NOT DUE TO PATIENTS EXITING THE STUDY**





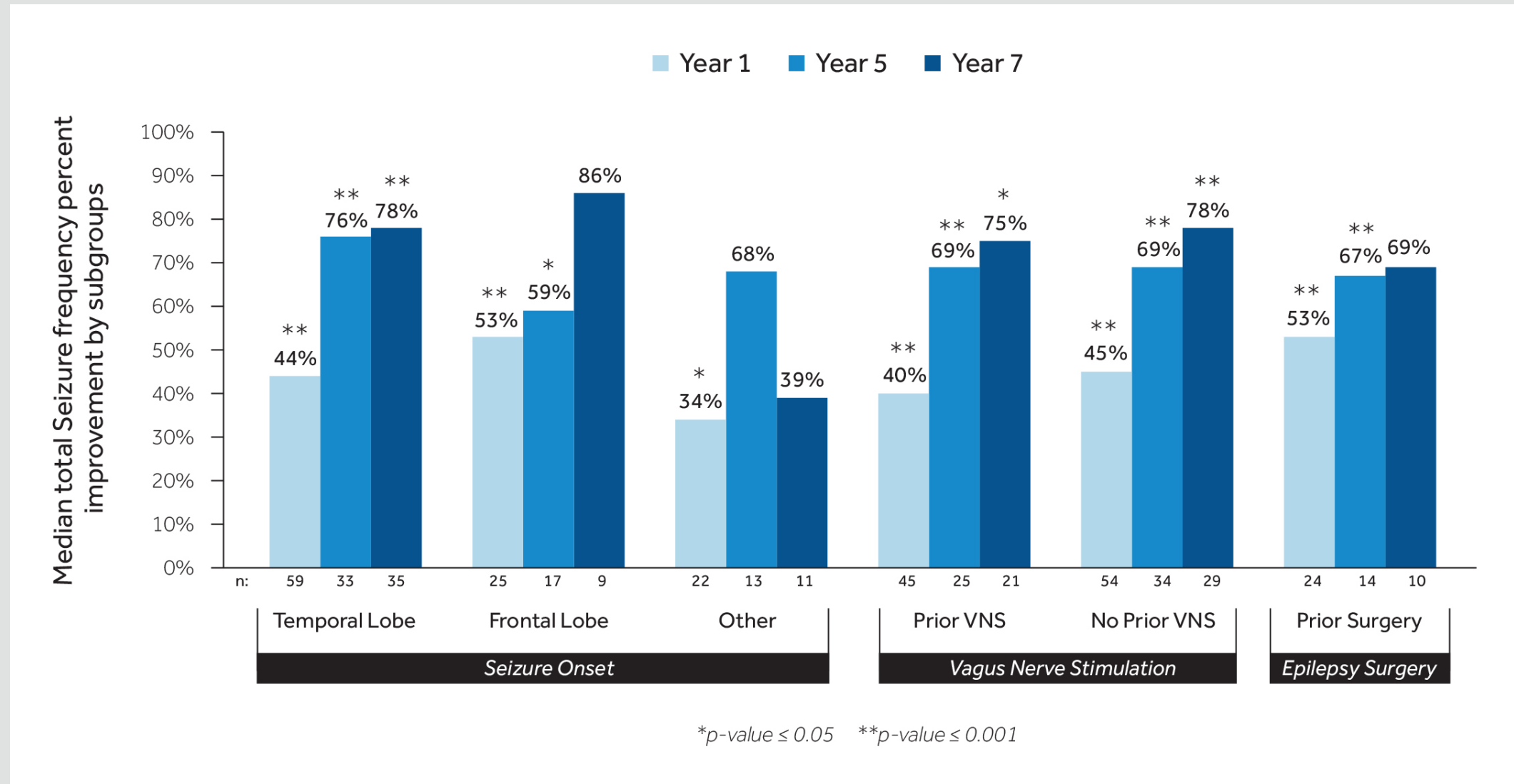
# SEIZURE FREQUENCY

## SUBGROUPS: SEIZURE ONSET, PRIOR VNS/SURGERY

**SIGNIFICANT REDUCTIONS IN SEIZURES WERE OBSERVED WHEN LOOKING AT SUBGROUP ANALYSIS: SEIZURE ONSET PRIOR VNS THERAPY® (NON-RESPONDERS) EPILEPSY SURGERY**

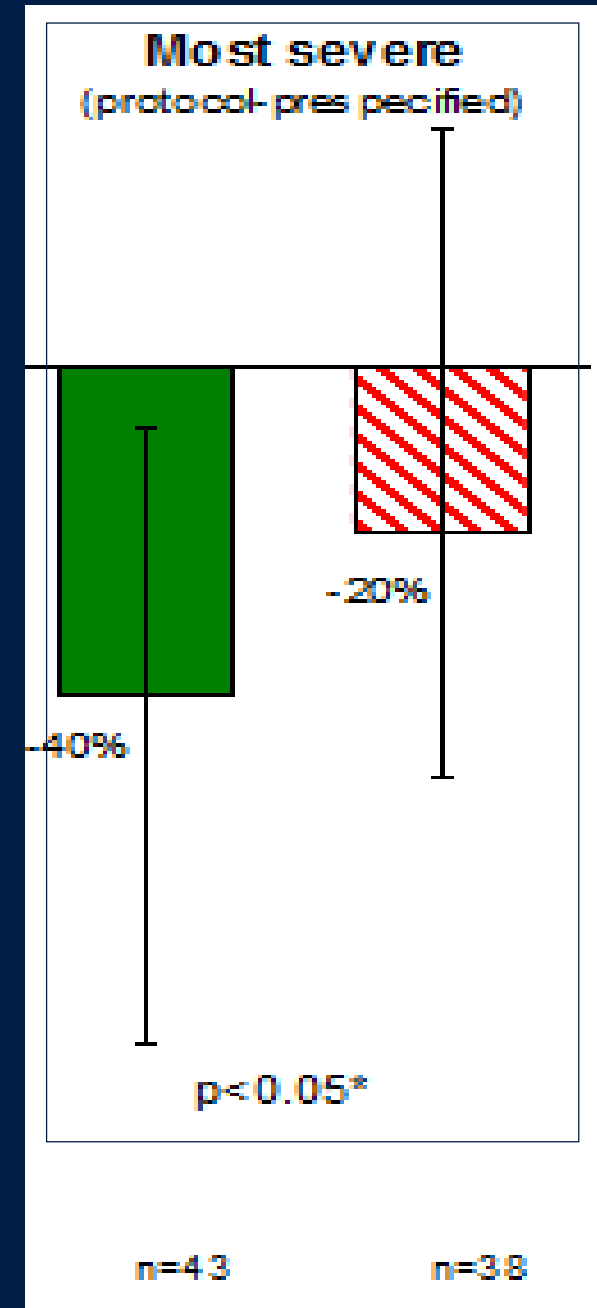
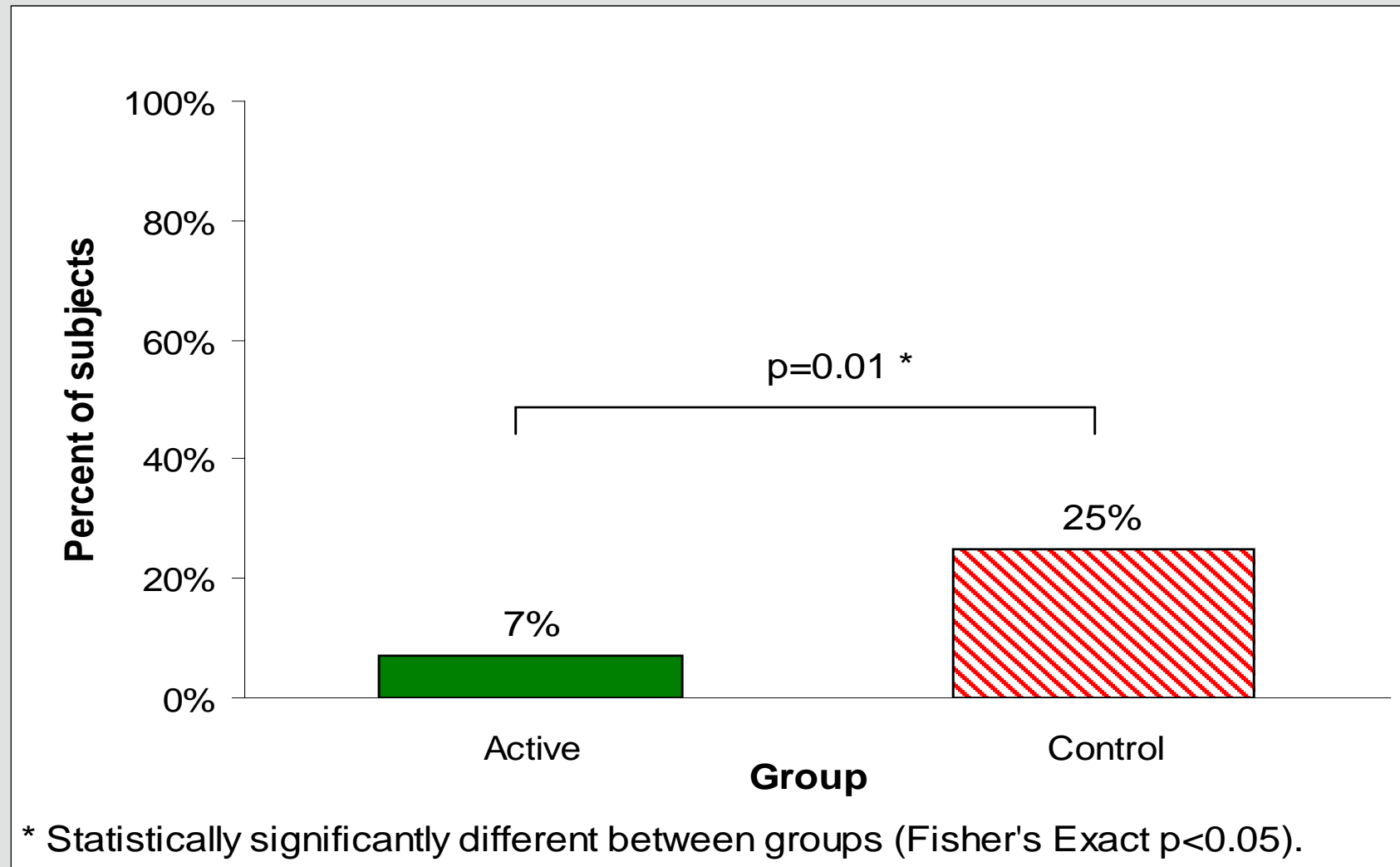
**PATIENTS SUBGROUP WITH PRIOR VNS THERAPY® HAD SIMILAR REDUCTIONS IN SEIZURES COMPARED WITH THE GROUP WITHOUT A PRIOR VNS THERAPY®**

**PATIENTS SUBGROUP WITH PRIOR SURGERY BENEFITED FROM THE ADDITION OF ANT DBS**



# PATIENTS WITH INJURIES FROM SEIZURES

## SEIZURE-RELATED INJURIES IN BLINDED PHASE



# PATIENTS WITH INJURIES FROM SEIZURES

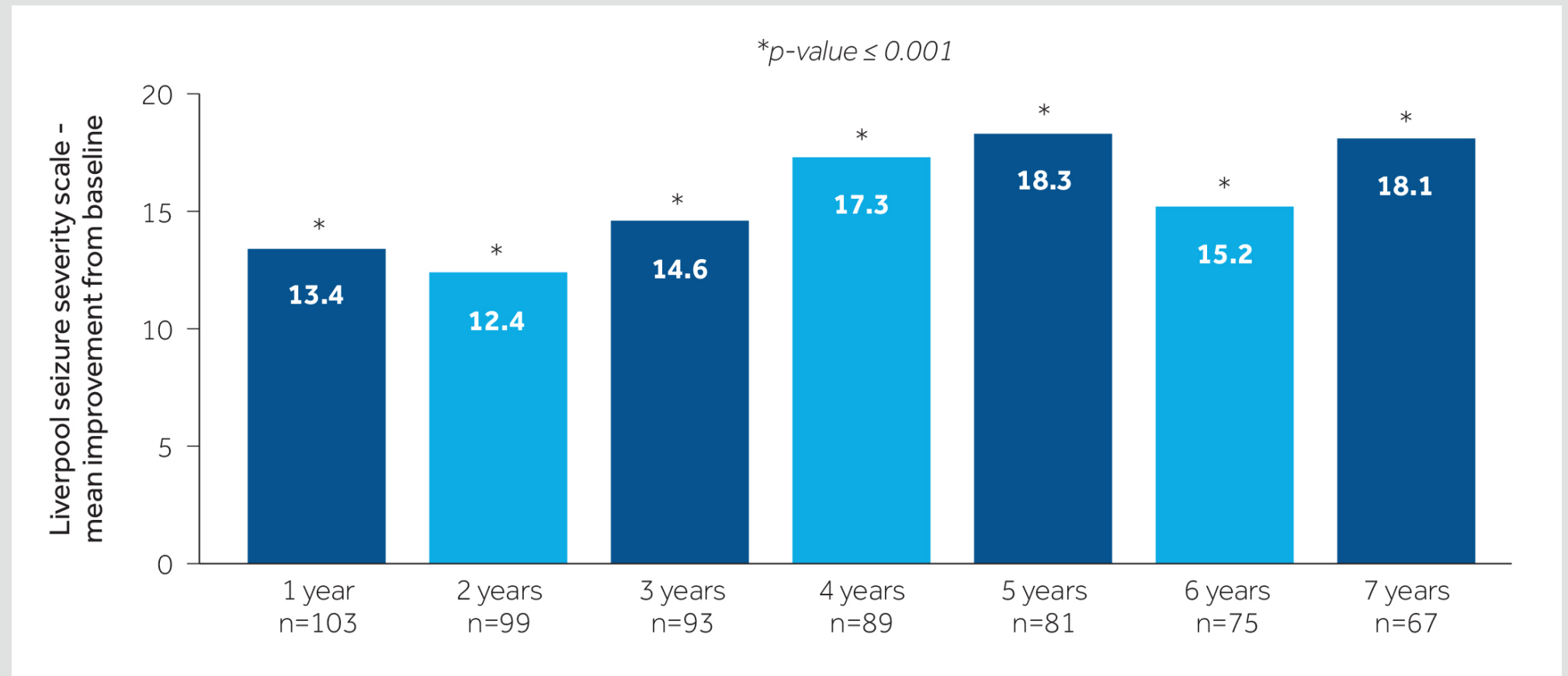
SEIZURE SEVERITY WAS MEASURED USING THE LSSS AND WITH PATIENT SELF REPORTS

DURING 3 MONTH BLINDED PHASE THERE WAS NOT A DIFFERENCE IN THE LSSS BETWEEN THE ACTIVE AND CONTROL GROUP

DURING THE BLINDED PHASE THE ACTIVE GROUP HAD A GREATER REDUCTION IN SELF-REPORTED MOST SEVERE SEIZURES THAN THE CONTROL GROUP

SIGNIFICANT IMPROVEMENTS IN THE LSSS AND SELF-REPORT MEASURES WERE OBSERVED AT THE YEAR 1 THROUGH YEAR 7 VISITS

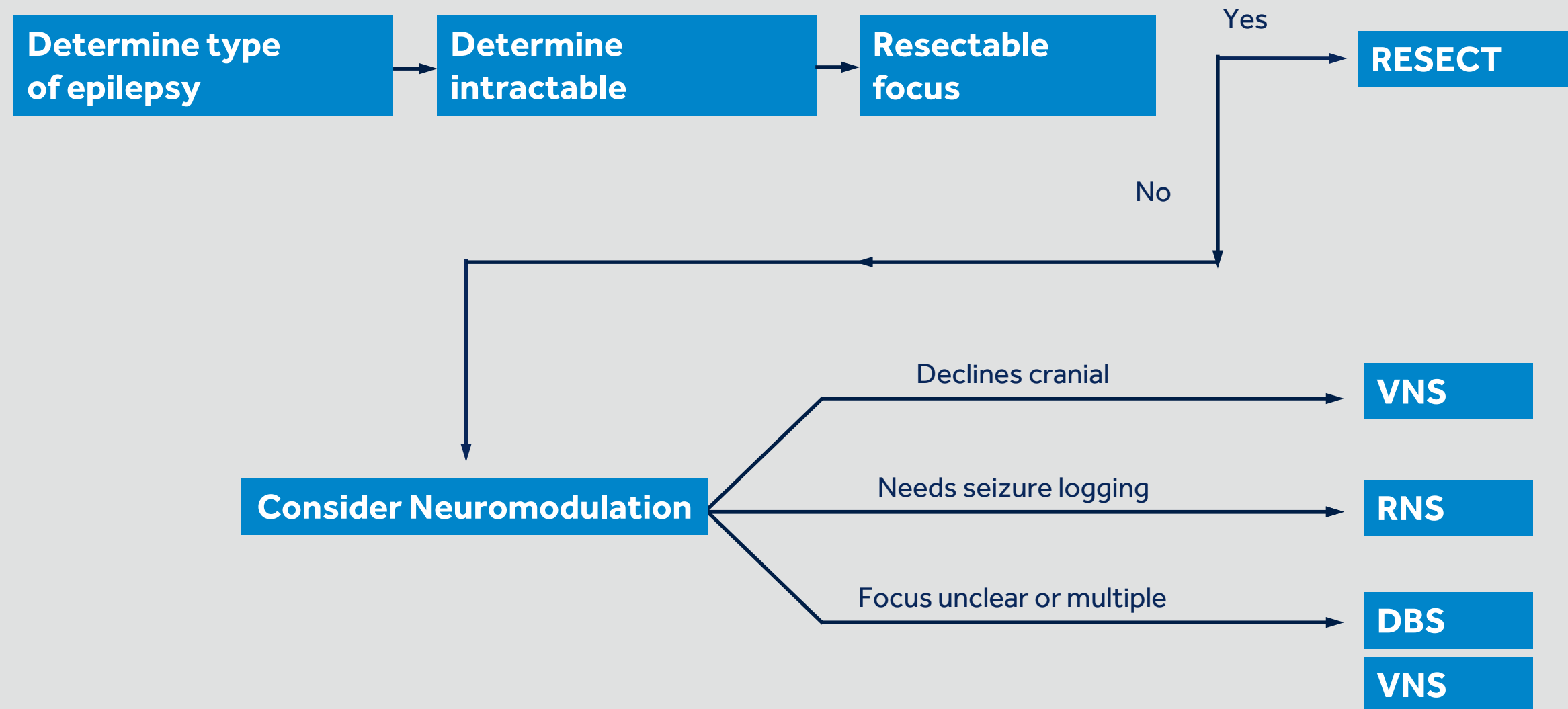
## LIVERPOOL SEIZURE SEVERITY SCALE (UP IS BETTER)



# SUMMARY - PATIENT SELECTION

- Age 18 years or older
- Not a candidate for curative resective surgery
- Inadequate benefit from  $\geq 3$  anti-seizure medicines
- Focal without or with bilateral tonic-clonic seizures
- Perhaps, temporal and frontal seizures on Circuit of Papez
- Seizures often enough to interfere with quality of life (“disabling”)
- Seizures capable of causing injuries
- Good support system and ability to follow-up

# FLOW FOR ANT-DBS TREATMENT IN REFRACTORY EPILEPSY



# SET EXPECTATIONS

## **Explain to patients and caregivers:**

- The rationale for DBS versus other options in their case
- Preoperative testing
- Surgical procedure
- Their responsibilities:  
Seizure diary, patient programmer, report side effects, medication compliance
- Usual slow course of improvement
- Not curative

# SANTE SAFETY SUMMARY AND STUDY CONCLUSIONS

## SAFETY SUMMARY

- No unanticipated adverse device effects
- Depression and memory impairment reported more frequently in Active group patients (blinded phase)
- Seizures may occur upon initiation of stimulation
- No symptomatic intracranial hemorrhages
- SUDEP rate similar or lower than reported in a similar population
- Procedural and hardware-related risks consistent with other DBS therapies
- During the study, the most frequent events related to the device, therapy, or surgery included implant site pain, tingling sensations, ineffective stimulation, and implant site infection

## STUDY CONCLUSIONS

**AT 7 YEARS,  
DBS OF THE ANT IS  
WELL-TOLERATED,  
IS ASSOCIATED WITH  
SIGNIFICANT AND SUSTAINED  
SEIZURE REDUCTION,  
AND IMPROVES QUALITY  
OF LIFE IN A REFRACTORY  
PATIENT POPULATION.**

For complete safety information about Medtronic DBS therapy, call Medtronic at 1-800-328-0810 or visit Medtronic's website at [medtronic.com](https://www.medtronic.com).

# NEUROPSYCHOLOGICAL RESULTS

## TROSTER et al. (2017)

### NEUROPSYCHOLOGICAL OUTCOMES

- **Bilateral ANT DBS was associated with subjective depression** and memory AEs during the blinded phase (3 mo)
  - Objective scales did not display difference between the control and stimulation group
- **Better** than baseline scores were observed at 7 years on measures of **executive functions and attention**.
- During year 1-7, neuropsychological tests remained at baseline level or better
- **Monitoring of memory and mood is recommended in ANT DBS**

### BASELINE SANTE STUDY POPULATION- PATIENT DEMOGRAPHIC

- **History of depression (%) 46%**
- **History of memory impairment (%) 34%**



# SANTE STIMULATION PARAMETERS

PARAMETER	TYPICAL STARTING VALUE
<b>AMPLITUDE</b>	5 V *In clinical practice clinicians may start at a lower amplitude (e.g., 2 V or 2 mA) and titrate up slower as they assess patient response and tolerability.
<b>PULSE WIDTH</b>	90 $\mu$ s
<b>RATE</b>	145 Hz
<b>ELECTRODE CONFIGURATION</b>	Unipolar (more correctly, "referential") Mode: Single electrode or two adjacent electrodes negative, case positive (all patients in the SANTE clinical trial were in unipolar mode)
<b>CYCLE OF THERAPY</b>	Cycling mode ON: 1 minute on, 5 minutes off
<b>SOFTSTART™ STOP</b>	programmed to 8 seconds

# SUMMARY

## NEUROSTIMULATION FOR EPILEPSY IS IN ITS INFANCY – QUESTIONS REMAIN

- More Effective patient selection
- Optimize consistent targeting
- How to best select stimulation parameters
- Why efficacy takes time



# AES 2019

## SYMPOSIA: DBS FOR MEDICALLY REFRACTORY EPILEPSY

### FACULTY

- Robert Fisher, MD, PhD      Stanford University
- Alexander Troster, PhD      Barrow Neurological Institute
- Robert Gross, MD, PhD      Emory University
- Dawn Eliashiv, MD      UCLA
- Fiona Lynn, NP      Rush University

**A NEW HOPE FOR EPILEPSY**  
**DBS FOR MEDICALLY REFRACTORY EPILEPSY**

Join us for an *Industry Non-CME Satellite Symposium* being held during the American Epilepsy Society (AES) 73rd Annual Meeting 2019

**Deep Brain Stimulation (DBS) Advancements in the Treatment of Medically Refractory Epilepsy**

**Friday, December 6 6-9pm**

Hilton Baltimore Inner Harbor  
Key Ballroom 10, Second Floor

**PROGRAM OVERVIEW**

In 2018, the **Medtronic Deep Brain Stimulation (DBS) System for Epilepsy** was approved by the U.S. Food and Drug Administration (FDA). Since then, there have been many important learnings that we are excited to share.

This satellite symposium will focus on several key aspects of the therapy: brain anatomy involving the anterior nucleus of the thalamus (ANT) for targeting stimulation, safety and effectiveness data, best medical practices related to device implant, programming and long-term patient care.

**PRE-REGISTRATION REQUIRED**  
<https://medtronic.cvent.com/d/myqt69/>

Dinner will be provided.  
There is no fee for attending this educational activity.

Opinions presented during the Industry-Supported Satellite Non-CME Symposium/Workshop are those of the speakers and are not a reflection of American Epilepsy Society opinions, nor are they supported, sponsored or endorsed by the American Epilepsy Society.

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**Medtronic**

The background features a blue-tinted image of a human head and neck. The brain is highlighted with a glowing, wireframe-like effect. A thin, dotted line extends from the neck down to a small, rectangular medical device labeled 'ACTIVA PC'.

# THANK YOU

## QUESTIONS?

# BRIEF STATEMENT: MEDTRONIC DBS THERAPY FOR EPILEPSY

**Medtronic DBS Therapy for Epilepsy: Product labeling must be reviewed prior to use for detailed disclosure of risks.**

**Indications:** Bilateral stimulation of the anterior nucleus of the thalamus (ANT) using the Medtronic DBS System for Epilepsy is indicated as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to three or more antiepileptic medications.

The Medtronic DBS System for Epilepsy has demonstrated safety and effectiveness for patients who average six or more seizures per month over the three most recent months prior to implant of the DBS system (with no more than 30 days between seizures). The Medtronic DBS System for Epilepsy has not been evaluated in patients with less frequent seizures.

**Contraindications:** Medtronic DBS Therapy is contraindicated for patients who are unable to properly operate the neurostimulator. The following procedures are contraindicated for patients with DBS systems: diathermy (e.g., shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy), which can cause neurostimulation system or tissue damage and can result in severe injury or death; Transcranial Magnetic Stimulation (TMS); and certain MRI procedures using a full body transmit radio-frequency (RF) coil, a receive-only head coil, or a head transmit coil that extends over the chest area if the patient has an implanted Soletra™ Model 7426 Neurostimulator, Kinetra™ Model 7428 Neurostimulator, Activa™ SC Model 37602 Neurostimulator, or Model 64001 or 64002 pocket adaptor.

**Warnings and Precautions:** There is a potential risk of brain tissue damage using stimulation parameter settings of high amplitudes and wide pulse widths. Extreme care should be used with lead implantation in patients with a heightened risk of intracranial hemorrhage. Sources of electromagnetic interference (EMI) may cause device damage or patient injury. Theft detectors and security screening devices may cause stimulation to switch ON or OFF and may cause some patients to experience a momentary increase in perceived stimulation. The DBS System may be affected by or adversely affect medical equipment such as cardiac pacemakers or therapies, cardioverter/defibrillators, external defibrillators, ultrasonic equipment, electrocautery, or radiation therapy. MRI conditions that may cause excessive heating at the lead electrodes which can result in serious injury, including coma, paralysis, or death, or that may cause device damage, include: neurostimulator implant location other than pectoral and abdominal regions; unapproved MRI parameters; partial system explants ("abandoned systems"); misidentification of neurostimulator model numbers; and broken conductor wires (in the lead, extension or pocket adaptor). The safety of electroconvulsive therapy (ECT) in patients receiving DBS Therapy has not been established. Tunneling the extension too superficially or too deeply may result in nerve or vascular injury, or tunneling through unintended anatomy. The lead-extension connector should not be placed in the soft tissues of the neck due to an increased incidence of lead fracture. Cessation, reduction, or initiation of stimulation may potentially lead to an increase in seizure frequency, severity, and new types of seizures. Symptoms may return with an intensity greater than was experienced prior to system implant, including the potential for status epilepticus. Loss of coordination in activities such as swimming may occur. Depression, suicidal ideations and suicide have been reported in patients receiving Medtronic DBS Therapy for Epilepsy, although no direct cause-and-effect relationship has been established. Preoperatively, assess patients for depression and carefully balance this risk with the potential clinical benefit. Postoperatively, monitor patients closely for new or changing symptoms of depression and manage these symptoms appropriately. Patients should be monitored for memory impairment. Memory impairment has been reported in patients receiving Medtronic DBS Therapy for Epilepsy, although no direct cause and effect relationship has been established. The consequences of failing to monitor patients are unknown. When stimulation is adjusted, monitor patients for new or increased seizures, tingling sensation, change in mood, or confusion.

# BRIEF STATEMENT: MEDTRONIC DBS THERAPY FOR EPILEPSY

## Adverse Events:

Adverse events related to the therapy, device, or procedure can include intracranial hemorrhage, cerebral infarction, CSF leak, pneumocephalus, seizures, surgical site complications (including pain, infection, dehiscence, erosion, seroma, and hematoma), meningitis, encephalitis, brain abscess, cerebral edema, aseptic cyst formation, device complications (including lead fracture and device migration) that may require revision or explant, extension fibrosis (tightening or bowstringing), new or exacerbation of neurological symptoms (including vision disorders, speech and swallowing disorders, motor coordination and balance disorders, sensory disturbances, cognitive impairment, and sleep disorders), psychiatric and behavioral disorders (including psychosis and abnormal thinking), cough, shocking or jolting sensation, ineffective therapy and weight gain or loss.

The safety and effectiveness of this therapy has not been established for patients without partial-onset seizures, patients who are pregnant or nursing, patients under the age of 18 years, patients with coagulopathies, and patients older than 65 years.

USA Rx Only Rev 06/18