Responsive Neurostimulation (RNS)

Last updated: August 25, 2019

Comparison of Neuromodulations (RNS, DBS, VNS) – see p. E11 >>

RNS = responsive neurostimulation on demand + diagnostic modality.
Advent of RNS decreased tolerance to functional consequences of epilepsy surgery.

BROCHURES

- see >>

Reading

E. Geller. Responsive neurostimulation: Review of clinical trials and insights into focal epilepsy. Epilepsy Behav, 88 (2018), pp. 11-20

O. Devinsky, D. Friedman, R.B. Duckrow, N.B. Fountain, R.P. Gwinn, J.W. Leiphart. Sudden unexpected death in epilepsy in patients treated with brain-responsive neurostimulation. Epilepsia, 59 (2018), pp. 555-561

INDICATIONS

FDA APPROVED (2013)

- *adjunctive* therapy in **reducing frequency** **of seizures** in individuals ≥ 18 years**** with **partial** **onset** seizures who have undergone diagnostic testing that localized **no more than 2*** **epileptogenic foci**, are **refractory** to ≥ 2 antiepileptic medications, and currently have ***frequent**** ***and disabling***** ***seizures***.

*Neuropace has receptacle only for two leads.

** ≥ 3 disabling seizures per month over three most recent months (with no month with fewer than two seizures); RNS® System has not been evaluated in patients with less frequent seizures.

***motor partial seizures, complex partial seizures and / or secondarily generalized seizures

****FDA indication for RNS is age > 18 years, but it likely has efficacy in adolescents and children (limitation in young children is skull thickness before it reaches adult size, so it could certainly be used in adolescents).

Summary

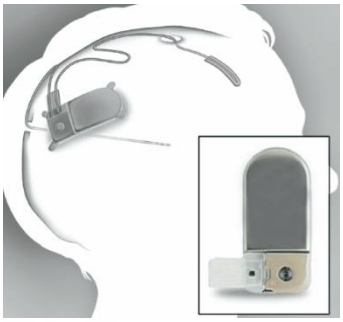
a) ≥ 2 foci
b) eloquent areas
c) mesial temporal lobe (uni- or bilateral)
d) difficult to resect (e.g. insula, large regional onsets, interhemispheric)
e) failed previous surgery or VNS (24% RNS patients have VNS)

VNS, RNS, and DBS are all palliative and comparable in efficacy, both in pivotal trials and over longer-term trials. VNS is a first choice as it is extracranial. A specific scenario where RNS may have an advantage is ***bilateral mesiotemporal epilepsy*** – RNS allows for long-term ECoG recording, which may in turn (occasionally) allow for an eventual resection (of seizure-dominant hippocampus or prove that "bilateral" disease is de facto unilateral) in a small number of patients.

PATHOPHYSIOLOGY

- Penfield and Jasper noted: inhibitory polarization caused by transmembrane currents of applied current → flattened local electrocorticography pattern.

HARDWARE



- RNS Neurostimulator Kit Model # RNS-300M-K.
- four cortical 5 mm bone screws.

DEVICE

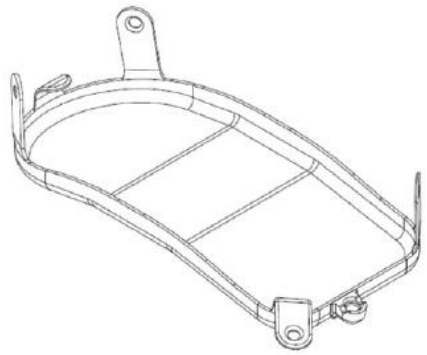
- accepts two electrode arrays; if uncertain – may implant more and leave contact end capped (may switch and reconnect later).

Feature	RNS-320-K	RNS-300M-K
Battery life	8.4 yrs (on medium settings)	3.9 yrs
Data capacity	1 MB - stores 8 ECoGs (90 sec duration each)*	0.5 MB
Price	6000 USD more expensive (31,950 USD)	25,950 USD

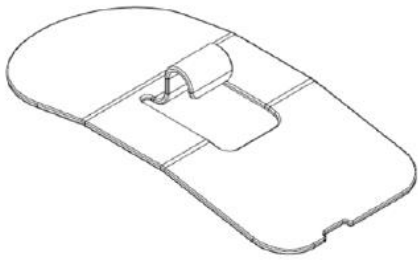
*still no warning to the patient when memory is full and data is overwritten

Q: who should be getting **model 300**? A: nobody.

Kit includes also ferrule (675 USD):



Kit does not include craniectomy template (375 USD):

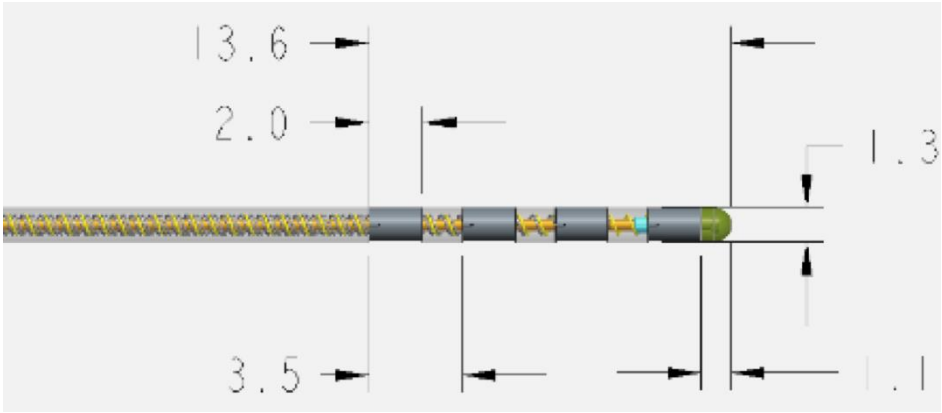


Practical tip – use nonsterile template (from rep) to plan craniotomy scalp incision; far craniectomy – use ferrule to draw lines.

STRIPS

- 4100 USD
- 4 contacts spaced 10 millimeters apart - spans 33 mm
- lead lengths (avoid unnecessarily long lead lengths):
  - 15 cm (model CL-315-10)
  - 25 cm (model CL-325-10)
  - 35 cm (model CL-335-10)

DEPTHS

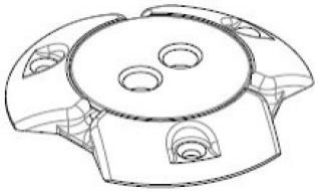


- 4100 USD
- 4-contacts
- diameter 1.27 mm (same as DBS electrode); slotted cannula 2.1 mm.

- configurations (avoid unnecessarily long lead lengths):
  3.5 mm contact spacing, 30 cm length (model DL-330-3.5)
  3.5 mm electrode spacing, 44 cm length (model DL-344-3.5)
  10 mm electrode spacing, 30 cm length (model DL-330-10) - spans 33 mm
  10 mm electrode spacing, 44 cm length (model DL-344-10) - spans 33 mm

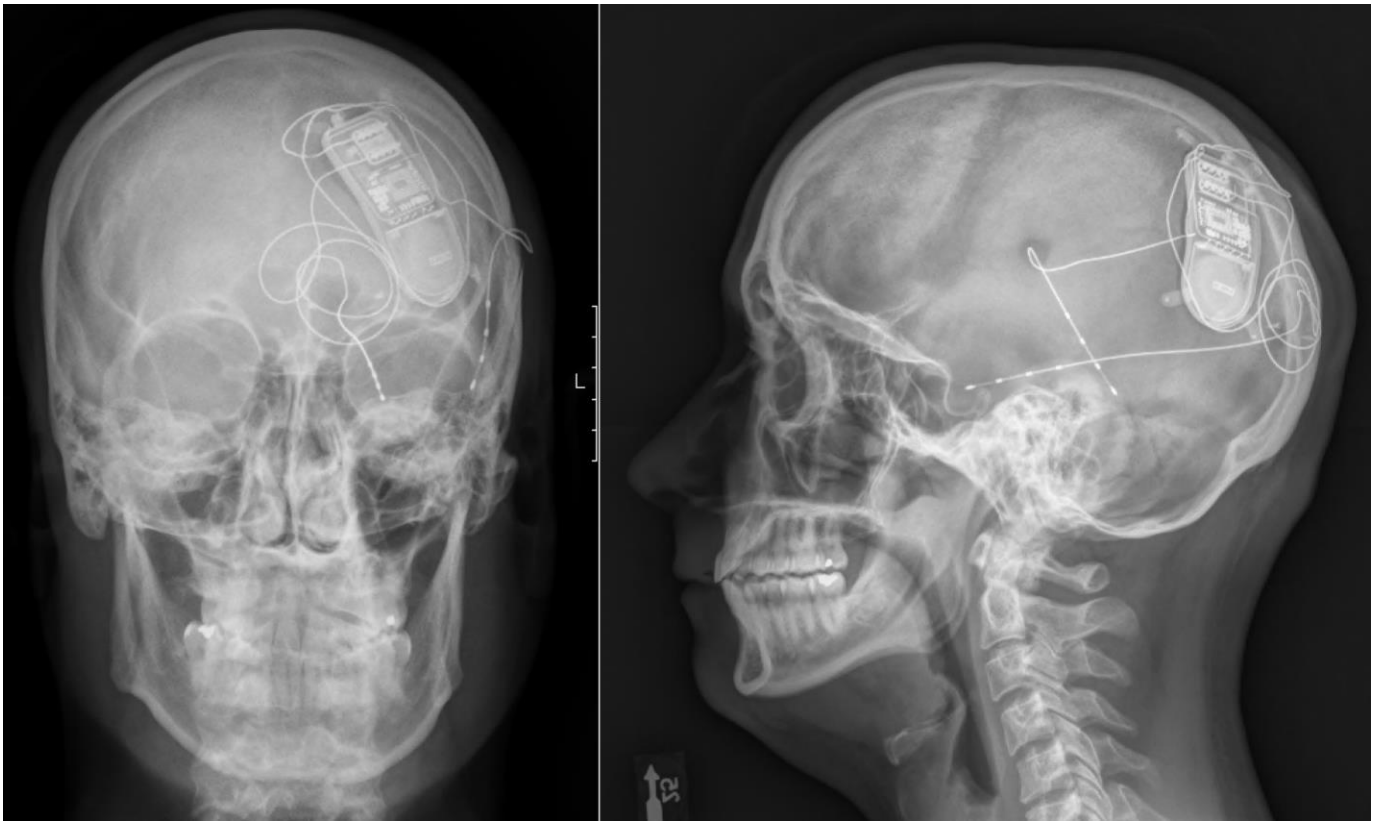
Wider spacing is for hippocampal depths!

BURR HOLE COVER



- 325 USD
- requires three 1.5 – 1.8mm screws

ON IMAGING



Source of picture: Viktoras Palys, MD >>

PREOP COUNSELLING

I explained the alternative of the VNS, pros and cons of each as well as the risks of surgery to include no change or worsening of seizures, visual fields compromise, memory compromise, or other injury to the brain. I explained that how the computer was placed to replace the skull and the electrodes that pass through the brain to the hippocampus. We talked about shaving some of the head. The patient understands the risk of an infection, which would require removal.

PROCEDURE – DEPTH ELECTRODE IMPLANTATION

HIPPOCAMPAL DEPTH

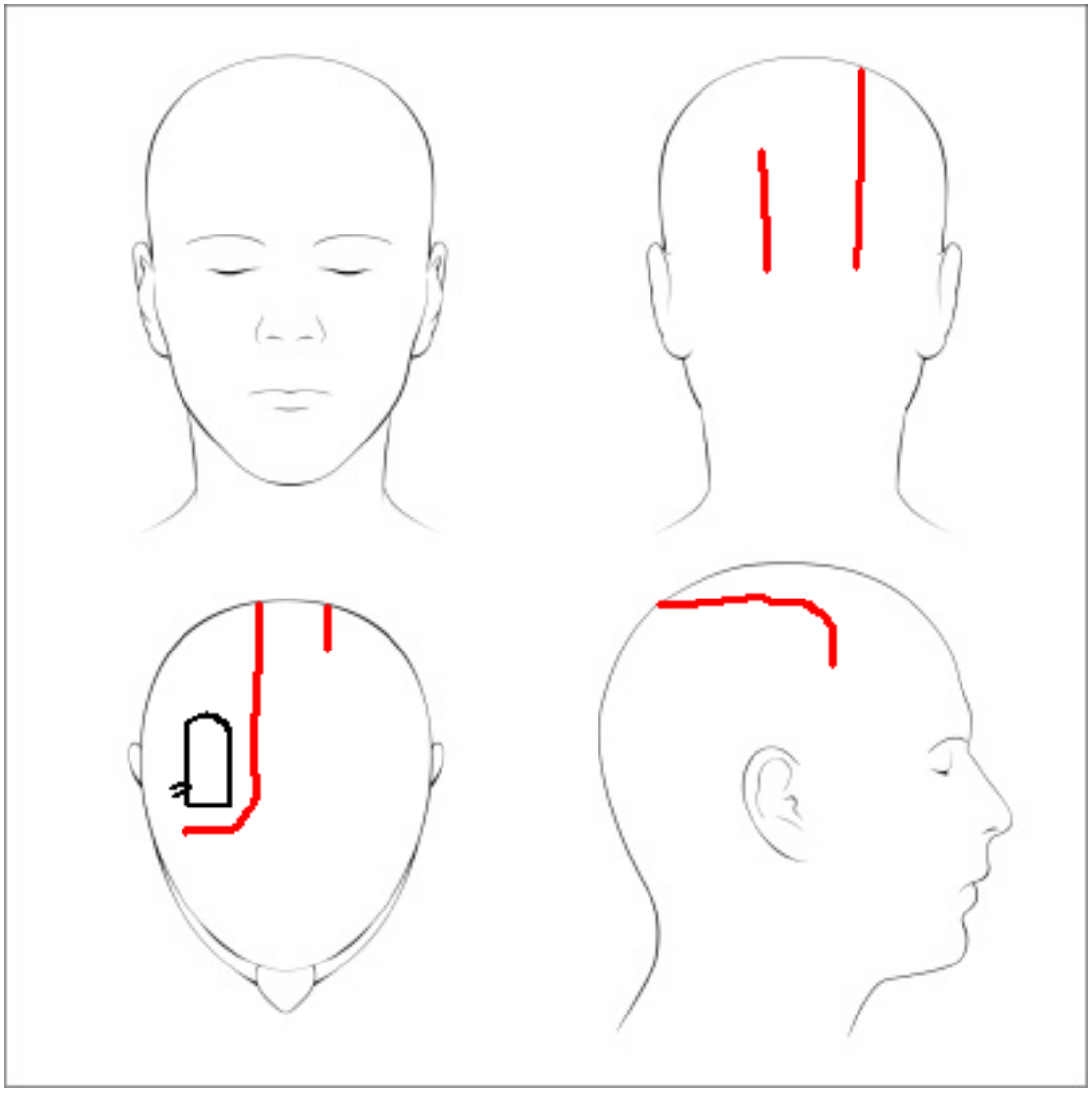
Trajectory (hippocampus cannulation) – see p. E15 >>

- prone in radiolucent Mayfield (standard metal frame has less wiggle than radiolucent frame).
- O-arm
- guidance platform: Nexframe or StarFix or ROSA
- **slotted cannula** is needed for StarFix or ROSA:

Two-piece slotted cannula (2SC-190X):

  - 1,011 USD
  - 190 mm length,
  - 2.11 diameter.
  - re-usable.
  - manufacturer: *Ad-Tech Medical Instrument Corp*.

- pins (radiolucent) – make sure pins not too posterior – will interfere with bur holes.
- incisions for bilateral leads (keeping in mind scalp blood supply and the battery replacement surgeries):

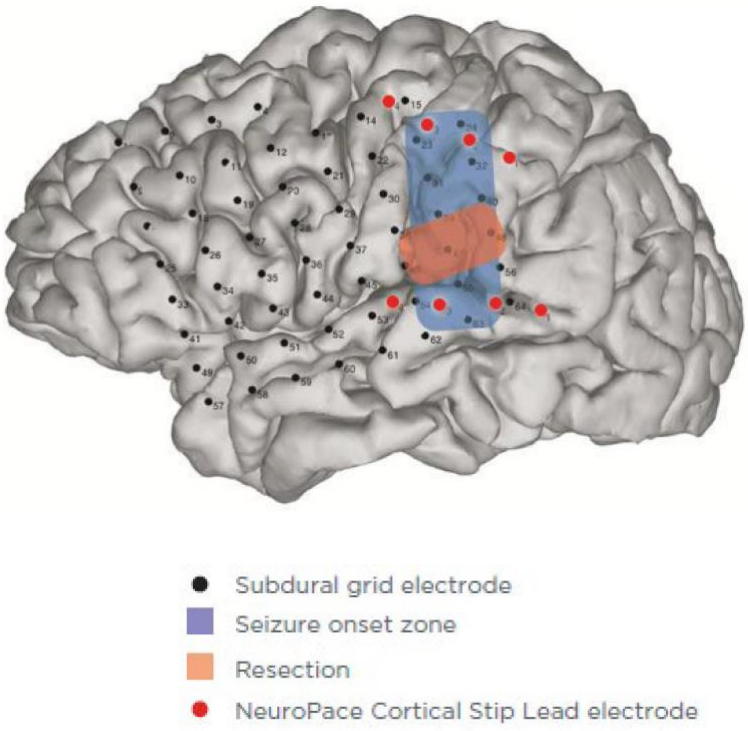


- O-arm (stays for the whole procedure but is also OK to remove after leads are placed):
  N.B. place blue drape towels first, then large DBS drape
- vertical incision (may be separate from device incision), Acra-Cut perforator (undercut laterally using M8 drill bit)
- Medtronic Nexframe (or any other platform) with double Silastic on lateral side (may even need offset bengun).
- if using Nexframe: "at target" DBS cannula with Neuropace electrode is placed into the center track to the full depth to the target along the long axis of hippocampus.
- do CT and look for contact position (10 mm lead with 4 contacts spans 33 mm) – may need to pull lead back for the best coverage.
- Stimloc or Neuropace lead **burhole anchoring device**.

Implantation of 2 leads

- if implanting 2 leads in parallel (e.g. second lead in parahippocampal gyrus), aim to keep distance > 10 mm between leads so can stimulate in bipolar mode between contacts in separate leads.
- inner diameter of Neuropace bur hole cover is 10 mm (if using one bur hole for both leads, plan entry points ≤ 10 mm apart).

PROCEDURE – STRIP ELECTRODE IMPLANTATION



PROCEDURE - DEVICE IMPLANTATION

- two antibiotics: cefazolin, 2 g IV and vancomycin 1 g IV
- plan incision so generator is not under incision.
- if incision is curved, plan generator implant so leads face away from incision; plan for battery replacements – will need to open only flat end of device curving a little bit on the side (opposite where leads exit).
- tunnel leads from other side in shortest way.

CRANIECTOMY

N.B. partial thickness craniectomy is not recommended – time consuming, bone grows and pushes device out.

- use template.
- location – anywhere where shape conforms to skull curvature, e.g. parietal area.
- one or two bur holes (some place it where ferule tab is going to be)
- discard bone flap.
- some place dural tack-ups along perimeter.

IMPEDANCES

- normal lead impedance range 250-3500 Ohm.

Case report of implanting in infraclavicular position

A Novel Approach for Responsive Neural Stimulator Implantation With Infraclavicular Placement of the Internal Pulse Generator. Lucas R Philipp, Robert E Gross, MD, PhD Operative Neurosurgery, opy025, https://doi.org/10.1093/ons/opy025 Published: 14 March 2018

- band pass detection rates increased by 50%, while line length detection rates decreased by 50%.
- number of detections decreased from 1046 to 846, with a resultant decrease in stimulations.
- although there was some compromise of function due to the elevated noise floor, more than 2 yr following the procedure the patient remains free of seizures and infection.

Case report of implanting inside prosthetic skull implant

First In-Human Experience With Complete Integration of Neuromodulation Device Within a Customized Cranial Implant. Chad R Gordon, DO Gabriel F Santiago, MD Judy Huang, MD Gregory K Bergey, MD Shuya Liu, MS Mehran Armand, PhD Henry Brem, MD William S Anderson, PhD, MD. Operative Neurosurgery, Volume 15, Issue 1, 1 July 2018, Pages 39–45

PROCEDURE - BATTERY REPLACEMENT

- enough to expose only very bottom of generator → undo 2 screws, remove strain relief plate from leads, and reflect leads.
- use Bovie set at 6 if need to dissect leads (Dr. P. Weber); do not use Bovie when new battery is in.

COMPLICATIONS

Infection (3.7-4.1%; 1.9% leading to explantations)
Hemorrhages (2.7%)

No chronic stimulation side effects!

POSTOPERATIVELY

CONTRAINDICATED PROCEDURES

1. **MRI** contraindicated (FDA is evaluating; mainly due to MRI-compatibility of lead and not device).

2. **Diathermy procedures** (any treatment that uses high-frequency electromagnetic radiation, electric currents, or ultrasonic waves to produce heat in body tissues).

3. **Electrosurgery** – conflicting info: some say not to use Bovie (use bipolar at > 2-3 cm away from device); others say it is OK to use **Bovie** (if close to device, it may reset the device – will need to reprogram). It is OK to use **Bovie** on old battery (if close to leads – use lowest settings on Bovie).

4. **Electroconvulsive Therapy** (ECT).

5. **Transcranial Magnetic Stimulation** (TMS).

6. **Radiotherapy**
   Exposure to high levels of radiation may damage the RNS® System.

The effects of high radiation sources (such as cobalt 60 or gamma radiation) on the RNS® System have not been studied - no studies to determine safe levels of irradiation for their device nor are there any recommendations for safe dose exposures. Neuropace suggests that the patient scan the device daily after each radiation fraction. This information can be transmitted to Neuropace who can determine if software repairs/re-programming can restore any lost functionality (if the device is damaged, it will try to reset itself. If unable to do that, it shuts down to a stable non-functioning state). Neuropace does not recommend prophylactically removing this device prior to radiation therapy.

ANALYSIS & PROGRAMMING

impedances - *see above >>*

RNS device stores ECoG only at certain triggers (if no triggers, device stores ECoG at certain time every day):

a) patient swipes **magnet** (e.g. if feels aura) – device stores 60 sec of preceding ECoG and 30 sec of subsequent ECoG
b) **amplifier saturation** detection (high amplitude)*
c) **long episode detection** (spikes or fast activity run > set time, e.g. 10 sec)*

*device stores ECoG if triggered stimulation does not abort activity (i.e. device stores ECoG of stimulation failures)

RNS-320 stores 8 ECoGs (90 second duration each); then it starts overwriting the oldest one without warning – so teach patient to regularly upload data to laptop.

DETECTIONS

Detection counts: counts of irregular epileptiform activity detected by the RNS (mostly composed of brief interictal epileptiform events but also include a small number of electrographic seizure onsets).

Long episode counts: counts of a specific type of detection trigger (lasting longer than a pre-specified time period) that often represent electrographic seizures.

N.B. only 10% of RNS triggers are actual seizures! (thus, it is correct to say that "RNS detects electrographic activity" and not "electrographic seizures")

- interictal discharges – potential biomarkers.

STIMULATION

Device stimulates up to 5 times if redetection happens right away.

OUTCOMES

NEUROPSYCHOLOGICAL

- some expert concerns that hippocampal (longitudinal) depth electrode placement may affect verbal memory – do neuropsychological testing 2 mos after implantation (before turning stim on).
- Loring et al. reported that there were no cognitive declines with responsive mesial temporal lobe stimulation and that there were improvements in verbal memory (small in magnitude but statistically significant) vs. progressive memory decline in nonoperated patients who continue to be treated with AEDs.

Loring DW et al. Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy. Epilepsia 2015;56:1836–1844.

QUALITY OF LIFE

- at 2 years of RNS treatment, there were clinically meaningful improvements in overall quality of life (QoL) in 41% of subjects, with only 16% reporting declines.

SEIZURES

N.B. results improve over time!

- after RNS implantation, for 2 months postop seizure frequency may increase.

Geller 2017. RNS for temporal epilepsy

- RNS uncovered that clinical seizures are only the tip of iceberg.

STUDIES

Feasibility Study

- n=65
- open-label
- assessed safety and followed adults over a 3-month preimplantation baseline and a 2-year postimplantation treatment period.

Pivotal Study

Heck CN, et al. Epilepsia. 2014 Mar;55(3):432-41

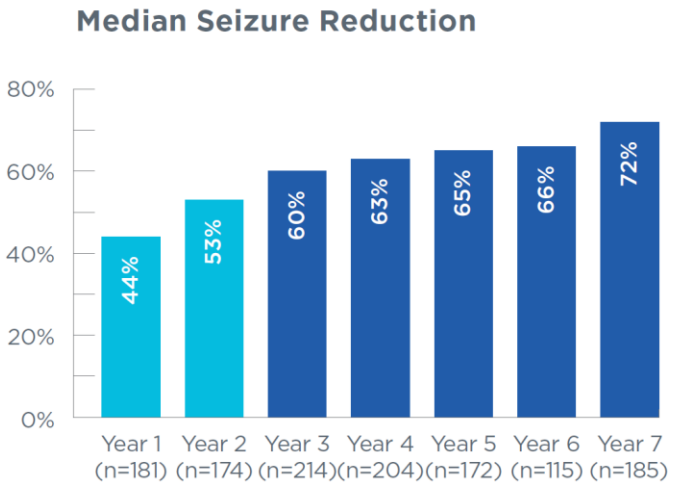
- randomized, controlled, double-blinded pivotal trial.
- enrolled adults with medically intractable partial epilepsy and an average of ≥ 3 partial seizures per month.
- n=191
- 3-month baseline was followed by a 1-month postimplantation stabilization period and then by a 4-month blinded period during which subjects were randomized 1:1 to receive active or sham stimulation.
- all subjects received active stimulation in a subsequent open-label period to collect safety and efficacy data to 2 years postimplantation.

Long-term treatment (LTT) trial

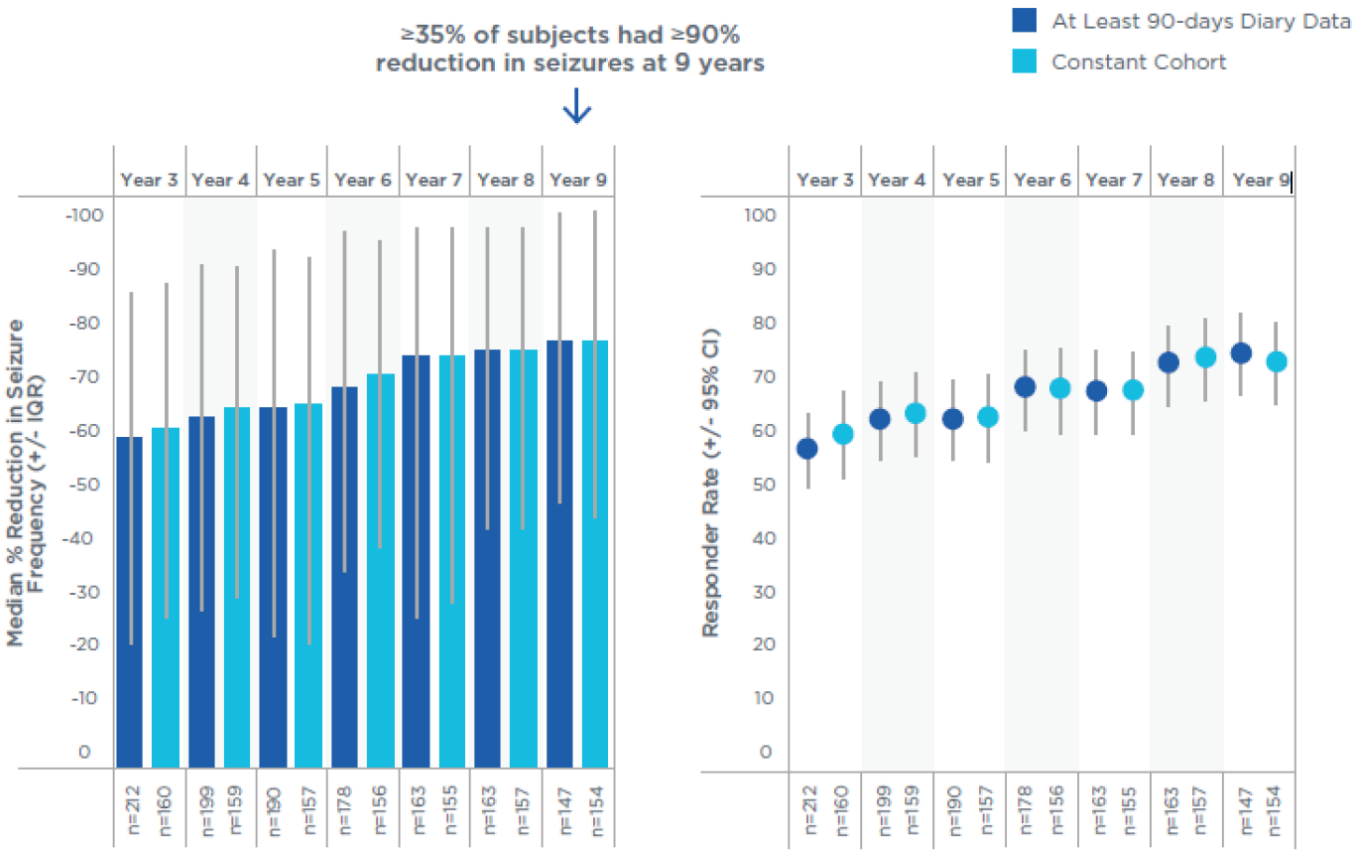
Bergey GK, et al. Neurology. 2015 Feb 24;84(8):810-7
Morrell et al. American Epilepsy Society. December 2016. Houston, TX.

- once subjects completed either the Feasibility or Pivotal study, they could continue in a follow-on Long-term Treatment (LTT) study.

- the study was ongoing as of the data cutoff on November 1, 2014.
- n=256
- at 7 years:
  72% median seizure reduction
  66% responder rate
  at least one seizure-free period lasting:
  ≥ 3 months - 39% of patients
  ≥ 6 months - 29% of patients
  ≥ 1 year - 16% of patients



- at 9 years (1895 patient years):
  75% median seizure reduction
  73% responder (≥ 50% seizure reduction) rate
  at least one seizure-free period lasting:
  ≥ 6 months - 28% of patients
  ≥ 1 year - 18% of patients
  no chronic stimulation-related adverse effects, no adverse cognitive or neuropsychological effects



- responder rate:
  - By seizure type
    - CPS 27%
    - GTC 65%
  - By ictal onset
    - Hippocampus 74%
    - Neocortex 37%

- effectiveness is similar for:
  - all ages and regardless of where the seizures started.
  - subjects with and without mesial temporal sclerosis (MTS), bilateral MTL onsets, prior resection, prior intracranial monitoring, and prior VNS*

    *mechanisms by which VNS and RNS act are likely quite different, suggesting that a failure to respond to one does not predict response to the other.

MEDICAL TREATMENT MONITORING

- typically, it takes many months to know whether a new AED will improve seizure control.
- electrographic data recorded by the RNS may be used to assess whether a new AED is likely to improve seizure frequency in as early as one month.

Clinical and electrocorticographic response to AED with RNS (correlations between device data and clinical seizure frequency)

Tara L. Skarpaas, Thomas K. Tcheng, Martha J. Morrell. Clinical and electrocorticographic response to antiepileptic drugs in patients treated with responsive stimulation. Epilepsy & Behavior 83 (2018) 192–200

- in patients with RNS, adding clobazam or levetiracetam gave higher clinical benefit (seizure reduction) than starting lacosamide or pregabalin – that correlated with change in interictal spike rate.

BIBLIOGRAPHY for ch. "Epilepsy and Seizures" → follow this LINK