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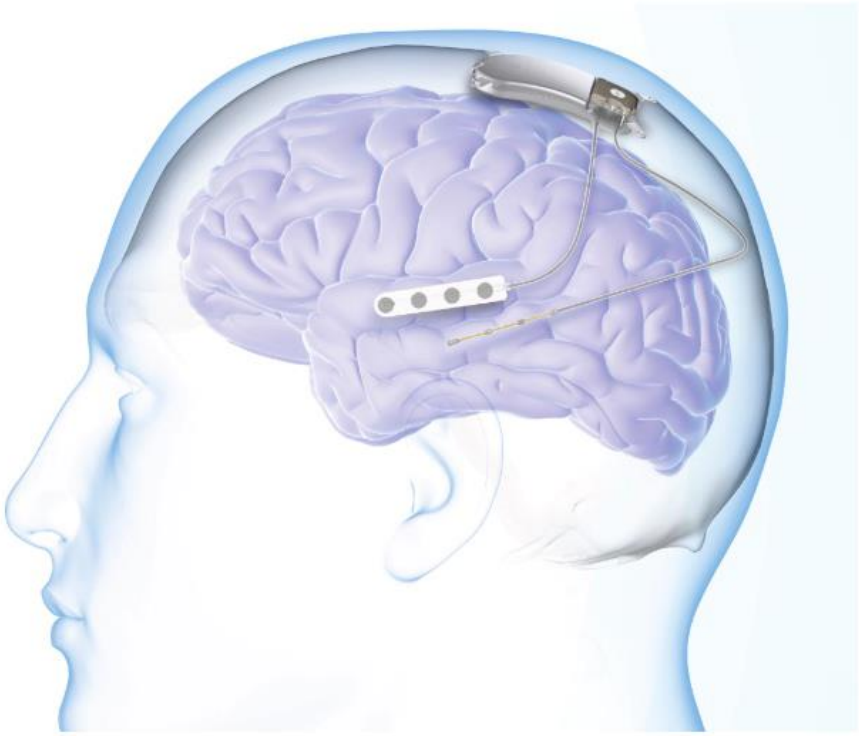
PRODUCT REPORT

NeuroPace RNS System – Neurostimulator Model RNS - 320



Pair 8

Aswathi Ravikumar - 151486337

Fizra Khan - 152177548

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1. Scope

Medical products are required to have documentation outlying its intended use, functionality, manufacturing methods, regulation conformations and safety measures, quality management system used and ethical considerations. These reports are critical to ensure that all the stakeholders (distributors, customers, users and regulatory bodies) have all the relevant information about the medical device. This product report features the Responsive Neurostimulation (RNS) system, a medical device manufactured by NeuroPace Inc, which is state of the art technology that has revolutionized epilepsy treatment. It is the world's first close looped brain responsive stimulation system that has minimal side effects and has proven to be effective in epilepsy treatment and management (1). Epilepsy is a debilitating and chronic condition that affects around 50 million people worldwide (2). Treatment methods include medication and tissue removal by brain surgery. The purpose of this report is to demonstrate the objective, functionality, operation, materials and manufacturing, processes, regulations and ethical consideration pertaining to the RNS system. Additionally, the purpose of this report is to serve as a learning opportunity to broaden our knowledge of the regulations a medical device needs to conform to, through reading as well as speculating.

2. Part 1 - Device Description

2.1 Manufacturer

NeuroPace Inc., manufacturer of the RNS system, founded in 1997 by David Fischell, specializes in implantable medical devices for neurological disorders. This company, based in Mount View California, Silicon Valley, USA generated $45.5M revenue in 2022 (3). The RNS system used to monitor and interfere with abnormal brain activity was first commercially introduced in 2014 by NeuroPace Inc. It has raised up to $247.3 million funding and has 16 investors including National Institute of Health (4). It has been awarded Most Promising New Product Award at the 22nd annual Phoenix Medical Device CEO Conference in 2015 (5).

2.2 General Information of the Device

Brand name(s)	NeuroPace RNS System, The RNS System, Neurostimulator model RNS-300M, Neurostimulator model RNS-320.
Generic device group	In-vivo active medical device
Market status	United States of America (USA)
Accessories	1. Cranial Prosthesis 2. Craniectomy Template 3. Connector Cover

	4. Connector plug 5. Ferrule and Ferrule Clamp 6. Lead Strain Relief 7. Torque Driver 8. Tunneling Tool, Tunneling Tool Tip, Tunneling Straw 9. Lead Cap 10. Stop Gauge 11. Suture Sleeve

Source (6)

2.3. Intended Purpose of the Device

Intended Use	To treat or manage the occurrence of epileptic episodes by detecting abnormal brain activity before the seizure develops and provides electrical stimulation to balance it.
Indications for Use	The RNS system is designed for the following patients: 1. over 18 years old having epilepsy disorder 2. have no more than 2 epileptogenic foci 3. have drug resistant epilepsy 4. who don't have less than 2 epilepsy episodes per month on average
Contraindications	The RNS system should not be used if there are: 1. Surgical complications 2. Coagulation disorders 3. Platelet count below 50,000 4. Another implanted medical device If RNS system is implanted, the following procedures can be lethal: 1. Diathermy 2. Electroconvulsive Therapy (ECT) *3.* Transcranial Magnetic Stimulation (TMS)
Nature of body contact, duration	The device is implanted in-vivo into the cranium. Duration depends on the use of the device. Based on the patient profiles during clinical trials, the neurostimulator proved to be viable for 2.6 to 4.6 years (estimated), depending on its usage.
Single use / reusable	Single use
Sterility	According to our knowledge, the device should be sterilized using FDA approved methods such as ethylene oxide (EO). It is compatible with electronic components and maintains the standard quality of the device. However, aeration must be used to remove the gas residuals. The implantable products are delivered sterile to the customer. They do not require any re-sterilization. The cleaning of the non-implanted components is done using single wipe with water. They should be placed in a sterile bag for later use.
User	1. Clinicians specializing in epilepsy

	2. Brain surgeons 3. Neurologists 4. Epilepsy centers *5.* Patients suffering from refractory epilepsy
Precautions and Warnings	1. Only NeuroPace leads or components are compatible with NeuroPace neurostimulators. 2. To prevent infection such as bacterial meningitis during the implant, anti-bacterial medication should be taken both pre and post operation. 3. Intracranial hemorrhage may occur if not implanted correctly 4. Side effects may include CSF leak, pain at the implant site, epidural or subdural hematoma or paralysis. 5. Allergic reactions may be possible 6. There is no scientific evidence of the effectiveness or adverse event in pregnant women. 7. Safety precaution while performing MRI or CT scan must be taken according to the manual guidelines to prevent any lethal consequences 8. Disconnect electric plug during cleaning or any contact with water otherwise may result in electric shock

Source (6)

2.4. Materials and manufacturing

The RNS system is comprised of the following components:

1. **Neurostimulator**: A device containing microprocessor and battery with 4 amplifying channels. It is attached to 2 leads and used to monitor, deliver and record the electrical activity of brain. The device is made up of titanium, is rectangular shaped, size under 60mm and weight 16 gm to avoid any disturbance to the patient and be biocompatible (6).

2. **Cortical Strip Lead and Depth Lead:** There are 4 electrodes with each lead having length under 35 cm. The leads are made up of silicone while the electrodes are platinum and iridium based (6).

3. **RNS Tablet:** The tablet is used to program the neurostimulator and visualize the recorded brain activity (6).

4. **Wand:** It is used as a communication device between the tablet and neurostimulator (6).

5. **Patient Data Management System (PDMS):** A software for maintaining and recording patient data (6).

According to our speculation, following methods can be used for manufacturing of the RNS system:

1. **Component manufacturing:** All the components such as wires, electrodes, batteries, microprocessor, Arduino/FPGA based motherboards boards, titanium or plastic casings can be acquired by FDA approved suppliers or manufactured individually in the same factory to make a neurostimulators wand.

    a. **Microprocessors:** Techniques such as deposition, lithography, etching and addition of capacitors and transistors are usually used to create microprocessors or microchips.
    b. **Casings:** Machining is usually used to create the casings of different components of the device.
    c. **Wires and Electrodes:** Techniques like annealing, hot extrusion, phase wiring is usually used to create wires etc
    d. **Battery:** Cathode formation and hermetic sealing methods are used to create a lithium-carbon monofluoride/silver vanadium oxide (Li-CFx/SVO) battery.
    e. **Motherboards:** It contains the main circuitry of the neurotransmitter such as microprocessor, transistors, capacitors. Hybridization is used to form the circuitry. Soldering and welding are used to combine the circuitry with a board.

2. **Assembly:** The device should be then assembled in a clean environment.

3. The motherboard and batteries are connected and put inside the casings with wires and sealed afterwards.

4. For RNS tablet, tablet can be acquired and developed software is installed on it to program the neurostimulator.

5. For software, developers can work Arduino IDE and other programming languages like Python, Java etc to develop user-friendly software to program the neurostimulator and maintain the patient record.

6. **Packaging:** We can use plastics like polypropylene that provide durability for long period storage. It is resistant to any impact that might occur during transportation and shelters from any kind of moisture especially during sterilization. Indication strips can be added to display successful sterilization. Each component can be covered with foam or bubble wraps to give extra protection. But it must be ensured that the packaging of individual components is not too tight so that when aerated after Ethylene Oxide sterilization, the air has enough space to flow and remove the Ethylene Oxide residue. Lastly, everything can be packaged in cartons that maintain the sterility of the device, protect the labelling and incorporate sealing features to ensure the device's integrity.

7. After the whole RNS system is manufactured, assembled, and packaged it can go to the storage facility for further distribution.

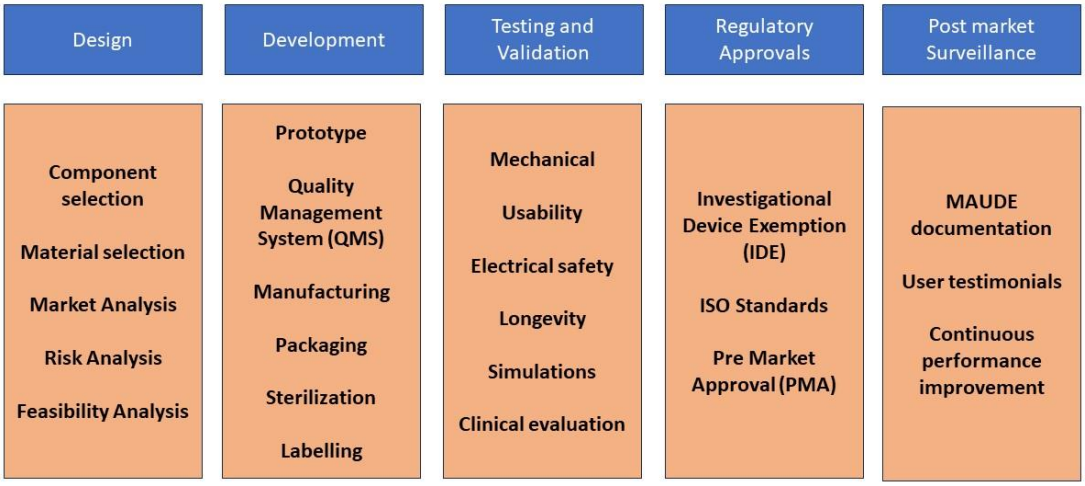

Fig (1) is a pictorial explanation of what we think are the possible stages that belong to the production of the RNS system.

We believe that sustainability is an important part to be considered during the entire process. It can be achieved in number of ways, in our opinion. A biodegradable material can be used instead of plastic or titanium casings while also considering its biocompatibility. We can also think about reducing the carbon footprint of the manufacturing and packaging sites by moving towards renewable energy solutions and proper waste disposal mechanisms. Transportation of the product to distributors or customers can also utilize renewable energy. Additionally, NeuroPace already requires the return of the device after explantation for proper disposal and the device is already compact, so it utilizes less material.

2.5. Main Principles of Operation

RNS system is designed to continuously monitor (even when asleep) and record the electrical activity of the patient's brain. Upon detection of abnormal electrical activity associated with seizures, it stops the seizure through electrical neurostimulation within milliseconds of detection. So, the main principles of operation are detecting electrical signals and responding via electrical stimulation while also recording the electrocorticorticography (ECoG) data and storing the data for future access (6).

The RNS Neurostimulator implant is surgically placed in the skull just under the scalp. The Cortical Strip Lead and Depth Lead are wires placed in the brain, the former on the surface of the brain and the latter in a deep region of brain tissue. These leads connect the neurostimulator to the areas of brain that are commonly identified as being responsible for abnormal electrical activity that give rise to seizures. For a short period of time following the implantation, the ECoG data is recorded by the neurostimulator without

any administration of electrical stimulation. As the electrical activity that give rise to seizures are not identical for all patients, the physician is able to program the neurostimulator more specifically to the patient's seizure related brain activity. Once the device is programmed for patient specific needs, the device is ready to provide electrical stimulation in response to the abnormal activity detected (7). Using the Wand (an external device the doctor moves over the neurostimulator), the data recorded by the neurostimulator is transferred to the RNS Tablet which is a computer device with the NeuroPace software. This data is managed by NeuroPace Patient Data Management System and is available exclusively to those who have user access to the data (generally the physician, patient, NeuroPace and a trusted member or loved one). Additionally, the RNS system is accompanied by a Medical Implant Identification Card for the patient that informs others of the patient's implant so any contraindications or harmful procedures can be avoided (8).

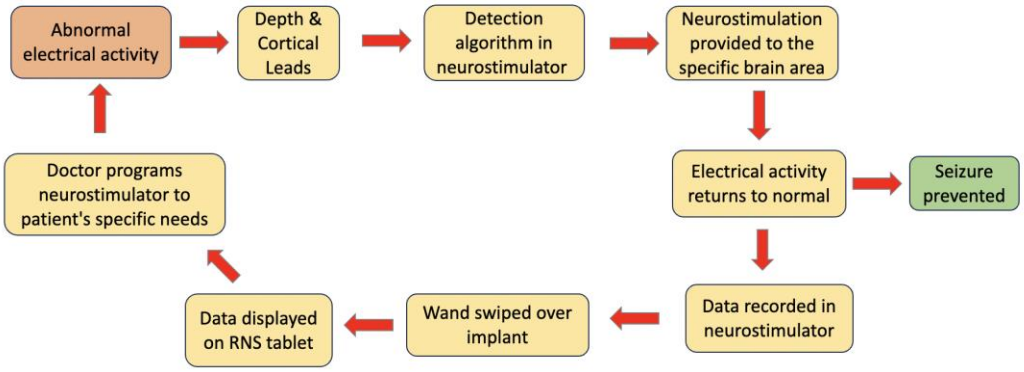

Fig (2) is a depiction of the basic principle of operation for the NeuroPace RNS System according to our understanding.

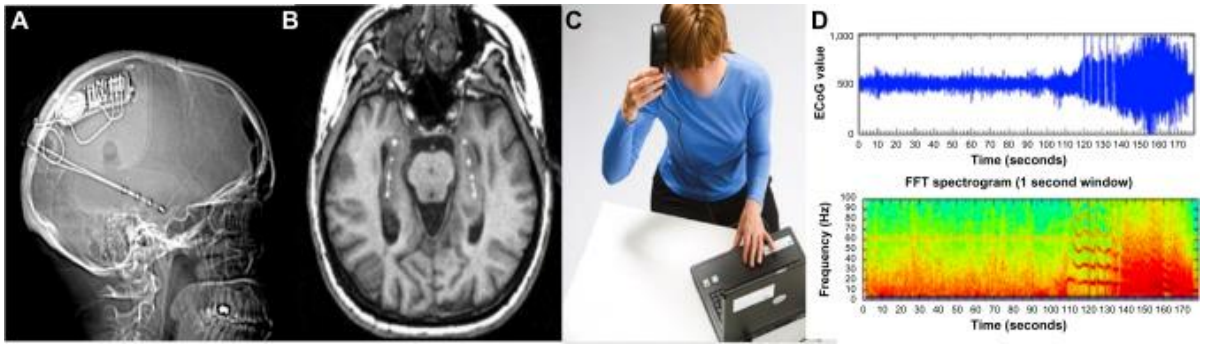

Fig (3) depicts the different components of the RNS system (9). (A) The RNS on skull X-ray. (B) Example of a bilateral hippocampal electrode implantation. (C) Interrogation of the device with the wireless wand and the programmer. (D) ECoG and time-frequency analysis from the device with detection of an epileptic seizure and stimulation delivered (vertical lines) (9)

2.6. Product Claims

We have categorized the product claims made by NeuroPace into consumer preference claims (commercial claims pertaining to patients or clinicians) and therapeutic claims (commercial claims pertaining to people who are more interested in clinical outcomes):

Consumer preference claims:

1. Fewer seizures and more seizure free days
2. Lower SUDEP rates (sudden unexpected death of someone with epilepsy, who was otherwise healthy)
3. Improved quality of life including better physical and mental health, less seizure related worry and improved cognition.

Therapeutic claims:

1. RNS system continuously monitors and responds within milliseconds to seizure-related brain activity
2. EEG data recorded for doctor to review and program the device to the patient's specific triggers.

The most important claims made by NeuroPace for the RNS system are the following:

- It continuously monitors and responds immediately to abnormal electrical activity in order to prevent seizures.

Continuous monitoring allows the detection of abnormal electrical activity in the patient's brain irrespective of the activity they are doing and so it deems to be more effective at detecting abnormal activity, and in the long term, preventing seizures.

- EEG data is recorded for the doctors to program the device to the patient's unique triggers (personalised treatment)

In epilepsy treatments, it is a challenge for the patients to find the right kind of therapy that suits them. For patients who cannot have surgery and/ or pharmacoresistant (resistant to the epileptic drugs), the RNS system provides the possibility of having personalized treatment and hence this claim is very important especially from a therapeutic perspective. Additionally, the brain activity data of the patient being made available to their physician will not only help the physician cater the treatment to the patient but also will provide insights into the condition of epilepsy itself by recognizing the more common patterns of electrical activity related to seizures in the population.

The best claims made by NeuroPace that convince the customers to buy the product are reduction in seizure frequency and improved quality of life from the physician's as well as the patient's perspectives.

This is because physicians are more likely to advise their patients of treatments that will reduce their stress about their disease and give them the time and space to live their lives more freely.

Main claims currently missing that should be emphasized is regarding the convenience of having the RNS implant. Although an invasive method (surgery) is required to initially place the implant, there is no regular maintenance or technical usage of the device that the patient really needs to worry about. Also, the implant is not visible outside, avoiding the stigma around epilepsy that the patient may have to encounter.

2.7 Competitive Products

DEVICE NAME	MANUFACTURER	INDICATIONS FOR USE	PRINCIPLE OF OPERATION
Percept PC System (DBS)	Medtronic	Bilateral stimulation of anterior thalamic nucleus (ANT) as an adjunctive therapy for Epileptic patients with partial-onset seizures, who are resistant to 3 or more antiepileptic medications and are aged 18 or above. Also indicated for other neurological conditions such as Parkinson's Disease, Essential Tremors and Dystonia (10).	Neurostimulator implant is surgically placed under the skin of the upper chest and is connected to the lead extensions that are implanted in the brain. It delivers controlled bilateral stimulation at regular intervals (programmed by doctor) to ANT (7).
Vercise DBS	Boston Scientific	Bilateral stimulation of subthalamic nucleus (SNT) as an adjunctive therapy to minimize some symptoms like tremors and movement associated with Parkinson's Disease in patients who are responsive to levadopa medication, where the symptoms are not controlled by the medications (11).	The basic operation is same as mentioned for Percept PC DBS System. But in Vercise DBS, Bionic Navigator software program is used by the doctor to adjust stimulation according to patient's specific needs. Also, the battery needs to be charged on a daily basis (12).
Infinity DBS	Abbott	Bilateral stimulation of SNT as an adjunctive therapy to minimize some symptoms like tremors and movement associated with Parkinson's Disease in patients who are responsive to levadopa medication, where the symptoms are not managed by the medications. Also, bilateral or unilateral stimulation of thalamic ventral intermediate nucleus (VIN) to reduce tremors in Essential Tremor patients, where the tremors are not managed by the medications (13).	The basic operation is same as mentioned for Percept PC DBS System.
SenTiva VNS (vagus nerve STIMULATION	Livanova	Adjunctive therapy to reduce frequency of seizures for patients with partial onset seizures, for patients aged 4 years and above, who are pharmacoresistant to antiepileptic medications (14).	Neurostimulator is implanted under the skin of chest which connects to the left vagus nerve in the neck. It delivers mild pulses to the brain through the vagus nerve to prevent or stop the onset of seizures. Can be programmed by doctor to fit patient's specific needs (12)

Monarch eTNS System	NeuroSigma	Non-invasive stimulation of Trigeminal Nerve as: - Monotherapy for patients with Attention Deficit Hyperactivity Disorder (ADHD), between ages 7 to 12, who are not under medications for ADHD. Additionally, as we understand it, the patient must have an adult who is aware of the methods and trained to operate the device efficiently (15), - Adjunctive therapy for Epileptic patients with partial-onset seizures, with or without secondary generalization, who are resistant to 2 or more antiepileptic medications and are aged 18 or above. Approved by FDA as of 2022 (16).	Electrical stimulation of Trigeminal Nerve through the skin provided by the electrical patches attached to the forehead of the patient (by their caregiver if young) at night. Stimulation is administered every night for 7-9 hours as the patient sleeps (15).

2.7.1 Competitive advantage

NeuroPace RNS system is one of its kind. The other competing devices like DBS, VNS and eTMS have similar technologies, however, the best therapeutic neuromodulation device for Epilepsy on the market is NeuroPace RNS system (17). This is because it is a continuously monitoring, closed loop responsive system which means it can detect the problem (abnormal electrical activity) irrespective of what the patient is doing (eg., sleeping) and immediately respond to mitigate seizures, unlike DBS devices which administer continuously administer pulses at intervals. The latest models of VNS can detect changes in the patient's heart rate associated with seizures and stop the seizure in its early stage, but this is not accurate. RNS also records and provides EEG data to the doctor to program the neurostimulator to respond to the patient's unique triggers. Although the other devices also have the mechanism of personalised treatment through programming the device, the data is more accurate and closely related to the seizures in RNS system. The RNS system requires very low maintenance from the patient. The patient does not have to do anything to handle the device itself; they only need to visit the doctor for regular follow ups. This is not the case for DBS which requires daily charging, and VNS device which may cause difficulty with speaking as well as lead to throat irritation and coughing due to the neck implant. A major selling point for the RNS device that is not clinically relevant is that it is not visible outside on the patient which avoids judgements made on the patients due to the negative stigma around Epilepsy.

The main drawbacks of the NeuroPace RNS system where it loses its competitive edge is its high invasiveness as it requires a brain surgery to place the implants. Brain surgery itself poses a big risk to the patient, however, additionally there is also the risk of postoperative infections. Also, in the case of an error or defect in the function of the device post-surgery, the patient would have to undergo another surgery to check for the issue. The newly FDA-approved eTNS therapy for reducing seizures, is non-invasive as it only requires the patient to attach skin patches onto their forehead. Therefore, we think eTNS would be much safer for the patients. even though there is the extra effort of adhering the electrical patches.

3 Part 2 – Research and Development

3.1 State-of-the-Art Review

Epilepsy is a chronic condition that causes the brain to lose its primary functional capacity for a short period of time in the form of seizures. It affects a person's quality of life on a large scale and may be lethal in some cases (2). Treatments for epilepsy included medications and ablation surgery, however, in many cases drugs or medicines are not effective (18). Neuromodulation is an approved technology that assists these patients in managing their disease to improve their daily life. A medical device company, NeuroPace Inc., has introduced a Responsive Neurostimulation (RNS) system that monitors, detects and regulates the brain activity that causes seizures by providing electrical stimulation to the seizure area(s), also called closed loop brain responsive system. It has two kinds of components; implantable such as neurostimulator and two electrical leads, and non-implantable, wireless telemetry device and programmer. The neurostimulator takes information from the electrical leads, checks for abnormal activities in neurons then responds to it by providing appropriate electrical stimulation.

The novel mechanism allows the patient to receive personalized treatment at the targeted location without damaging or altering any other parts of the brain. In addition, the neurostimulator records the brain activity i.e., iEEG and other parameters which helps physicians make informed decisions about the treatment (17). iEEG can also help in producing large dataset on seizure patterns that can help in further investigations and producing novel technologies. It improves quality of life including mental health, physical health and cognitive function. It has been proven to reduce the occurrence of seizures up to 75% over the time and reduced the unexpected deaths in epileptic patients (19). It is important to note that it poses some risks such as post-surgery infections, hemorrhage and other complications due to brain surgery.

Other similar devices for treating neurological conditions include Deep Brain Stimulation (DBS) and Vagus Nerve Stimulation (VNS). These devices use the same neuromodulation technique but pose practical complications. They provide continuous stimulation to the whole affected area, without localizing the seizures, for longer periods of time which can alter crucial brain functions such as cognitive impairment, memory loss, and speech impairment (17). These devices are only customizable based on the treatment response such as recovery or symptom relief, rather than patient's seizure patterns.

The RNS system has undergone 4 FDA approved clinical studies (19) (20). It has acquired the Premarket Approval (PMA) to commercialize the product in the United States (17). The effectiveness and efficacy are not yet evaluated in children, pregnant women or people having comorbidities (6). Post-market surveillance that included testimonials and stories has shown positive feedback from patients, epileptic centers and clinicians (21), (22). Even though it is primarily used for epilepsy treatment, we think further

investigations can be conducted to demonstrate its efficacy for other neurological disorders such as multiple sclerosis, schizophrenia, bipolar disorder etc.

3.2. Preclinical Studies

Features we think should be tested during developmental stage before clinal use:

- **Biocompatibility** of the implantable components of the RNS system such as neurostimulator, the Cortical Lead and the Depth Lead (extensions and electrodes). The material that the implants are made of or are coated with must not cause any toxic reactions in vivo and must be bioinert.
- **Electrical Safety** to ensure the efficiency and accuracy of the chosen leads receive and send electrical signals, the connectivity within the circuit, the battery of neurostimulator implant, and the insulation to eliminate possibility of electrical shorts.
- **Electromagnetic compatibility** with other electrical implants or devices the user may come in contact with.
- **Mechanical and Biomechanical properties** of the implant to test its response to pressure, mechanical forces (movement of implant within brain), different temperatures and moisture, and to test for device under simulated biological conditions to ensure secured placement of leads.
- **Usability of the device** - The signal or wireless connectivity of the implant to the external components such as the Wand and PDMS software must be effective; the PDMS software needs to be tested for its function; the user interface must be tested for its comprehensibility and convenience.
- **Shelf-life** as well as the effects of exposure to various environments such as high or low temperatures and pressures of the device must be tested to predict any damages that may occur during transportation or storage.
- **Packaging and Sterilization –** Due to the electronic nature of the device, it will have to undergo Ethylene Oxide sterilization method. So, the packaging must be done accordingly to ensure the device is sterile and will not cause any infection to the patient.
- **Functionality of the device in-vivo** – Animal studies to test how the device functions within a living organism.

Preclinical studies performed on the RNS system as part of the developmental process:

1. Laboratory studies for implant components:

- RNS neurostimulator was tested for its electrical output functions, circuit function, electrical safety, battery safety and longevity, function under environmental conditions like temperature changes, pressure changes and vibrations, functionality after being dropped and x-ray

interaction. Standards used – ISO 14708, EN 45502, IEC 60068, IEC 60601, ASTM D 3332-99 and ASTM D 4169-99 (23). We think that ISO 14708 was used because it outlines specifications for implantable neurostimulators in terms of safety measures related to biocompatibility, safety and reliability. EN 45502 complements ISO 14708 and is helpful in receiving the CE mark in Europe so in the future, the RNS system can go to the European market. ASTM D 3332-99 and ASTM D 4169-99 test for mechanical properties and fragility of products and effects of transportation on the product to avoid damages. IEC 60068 and IEC 60601 ensure that electrical safety standards of the device are met, and that different environmental exposure does not damage the electronics.

- The Depth lead and Cortical lead were tested for ideal design dimensions, electrical safety, connectivity, environmental factors, tensile strength, conductivity and release of particles into surrounding tissue (23).

2. Laboratory studies for external components:

- Software development and verification tests were done for NeuroPace Programmer, Wand, Remote Monitor and PDMS software, adhering to FDA standards. Mechanical and environmental factors were also tested. Standard used- IEC 60601 (23). We think this standard was used because it specifies requirements for electrical equipment and devices.

- Electromagnetic compatibility was tested according to the IEC 60601 standard and the wireless technology was tested according to United States FCC CFR and also adhered to the ISO 14708 standard for implantable neurostimulators (23).

- Sterility validation studies were performed according to the standards ISO 10993-7 and ISO 11135-1 (23).

- Studies to validate packaging and shelf life were carried out according to the ISO 11607 standards (23).

- All the components that will come in physical contact with the patient were tested to see if they were biocompatible once they were sterilized. ISO 10993-part 1 (which assesses the biocompatibility of medical products) standard was used (23).

3. Animal studies

- Acute and long-term local and systemic effects as well as possibilities of neurotoxicity of the RNS implantation in rabbits were studied, adhering to the ISO 10993 standard recommendations for carrying out clinical studies (23).

- To assess the safety of the depth and cortical leads, studies were performed on sheep by implanting the leads and testing their function under simulated conditions (23).

- The detection algorithm was tested and validated using studies based on which the FDA granted the RNS device IDE (Investigational Device Exemption) and approved it for clinical studies (23).

Preclinical tests that we think are required to verify each product claim:

- To support the claim that the device provides a personalised treatment, there needs to be evidence backing a high-quality detection system and evidence that the data can be recorded efficiently and can be used to program or tune the device for the patient's unique seizure related electrical activity. Studies to test the detection algorithm of the NeuroPace RNS device were done using artificial ECoG waves and also to test how effectivel the detectors can be tuned to a particular patient using archived patient ECoG records. This is also applicable for the claim that RNS responds quickly.

- Continuous use of the device to monitor the brain activity of the patient can be indirectly extrapolated from the long-term implant test done on sheep to test for neurotoxicity. These tests were 33 - 200 days long. However, there is no separate preclinical study for this objective alone and hence no strong empirical evidence backing the claim.

- Recording and displaying patient data can be tested using studies that test software efficacy and programming aspects.

- Improved quality of life cannot be tested preclinically as it is to do with patients. This has to be studied during clinical trials through qualitative research studies.

3.3. Clinical Evaluation

Evaluation of the medical device's clinical performance during the product development phase is critical to validate the device's operability as intended and to ensure patient safety. To evaluate the clinical performance of NeuroPace RNS system, data from preclinical studies performed (as discussed in section 1.2) in addition to existing literature about similar device functions and adverse events (DBS & VNS)

should have been used to analyse the efficacy of the RNS system itself. The data could have also helped recognize gaps, ask questions and create hypotheses for clinical investigations. NeuroPace should have ensured that according to the preclinical data, the RNS system conforms to the general safety and performance requirements by FDA and also functions according to the intended use. Data suggesting side-effects and adverse effects also would have been submitted. Since the RNS system was a novel device, when it was developed, Clinical investigations must have been a necessary step. Clinical studies could have aided in assessing how well the device works in the treatment of epileptic seizures, the user experience and patient safety. Additionally, post-market follow-up would have been required to fill any gaps in the data or test new technologies or deploy any new safety measures.

Clinical studies pertaining to the NeuroPace RNS system would have been performed to obtain data that will test the efficacy of the medical device in clinical settings, will help narrow down and establish indications for use and test the safety requirement protocol as recommended by CFR (Cide of Federal Regulations) for class III devices. Our speculation on the types of clinical studies that should have been performed on NeuroPace RNS system following the IDE (Investigational Device Exemption) are:

- **Pilot studies** to test that the preclinical data matches the data obtained from real patients. This is usually done using small cohort size as it is used as a base to carry out bigger clinical trials. These studies are also used to establish the indications for use of the device. For instance, one study could have had multiple groups of patients, each group belonging to a particular age. The RNS system could have been trialed on them to see which age groups found it to be most effective. This data would largely contribute to the indications for use.

- **Feasibility studies** to test the safety and practicality of using the RNS device on real patients as well as other logistics that surround the usage of the device in clinical settings. These studies are done using small cohort size because the purpose of these studies is to collect data about the process of using the device (hows) and not technical or medical data pertaining to the device itself. The data from these studies could aid in adding to the user manual documentation.

Pilot and feasibility studies can also be combined to obtain both technical as well as logistical data from the same set of studies if time or resources are scarce. In this case for NeuroPace RNS, this could have been a possibility too.

- **Randomized control trials** as part of pivotal studies to test the outcome of the RNS system as a treatment against control groups comprising participants who have epilepsy and are using other treatments or methods to manage their seizures. The data from these studies will establish the efficacy of the device in comparison to other existing treatment options for epilepsy.

- **Long-term treatment studies** and **observational studies** to study the duration required by the RNS system to take into effect and what factors affect this. These studies could have helped test for the outcomes of personalised treatment as mentioned by NeuroPace RNS system.

- **Studies to test for RNS system as an adjunct therapy** to other therapies for epilepsy such as various pharmacotreatments, resective surgery etc., to refine the indications for use. It is currently indicated that RNS system is ideal for patients who are pharmacoresistent. These studies could have helped with this indication.

Our estimation of clinical studies that have been required to support the product claims made by NeuroPace RNS:

- To test the claims that RNS would lead to 'lower SUDEP rates', result in 'fewer seizures and more seizure free days', 'RNS system continuously monitors and responds within milliseconds to seizure-related brain activity' and 'EEG data recorded for doctor to review and program the device to the patient's specific triggers'; long term treatment studies and randomised control trials would be required. As it takes at least up to 1 year for the positive outcome of RNS treatment to be observed in the patient, a short study will not provide empirical data. Therefore, long-term treatment studies will be ideal to test the functioning of the device in real patients as well as the user experience. Randomised control trials where the control group comprises of Epileptic patients who are not exposed to RNS therapy but are taking medications or another form of therapy to manage seizures could provide data to compare the outcomes of RNS against other treatment options.

- In order to back the claim of 'improved quality of life', studies using qualitative research methods would be more helpful because there are a lot of vague variables like 'level of happiness' or 'mood' that cannot be quantised. Health-Related Quality of Life (HRQoL) surveys and longitudinal observational studies can be used. Additionally, a survey to measure quality of life can be added to the randomised control trials testing the function of RNS device.

4 Part 3 – Classification, Safety and Risk Management

4.1 Classification of your device.

The regulation strategy of any device depends on its intended use and product claims by the manufacturer. The intended use of the RNS system is to treat and manage a medical condition in humans called epilepsy and provides improved quality of life with this personalized treatment, as claimed by the manufacture. Parts of the RNS system such as neurostimulator and electricals leads are implanted into the brain surgically. Therefore, it qualifies as a medical device.

In the EU, Medical Device Regulation (MDR) is a regulatory body for all medical devices that replaced Medical Device Directive (MDD) to pose stricter regulations for better patient safety and providing quality treatment. It requires technical documentation, certification of notified bodies, conformity assessment and CE marking, assessment of quality management system, evidence of clinical evaluation among other things. Therefore, the RNS system falls under MDR, and requires its approval along with EUDAMED registration. It classifies as Class III medical device under this regulation because it is an invasive and active device, is implanted for a longer duration of time i.e., at least 5 years and the procedure pose high potential risks to the patient. In the US, the regulatory body is Food and Drugs Administration (FDA) for all medical devices. The RNS system falls under this and requires pre-market approval (PMA) because it is a Class III medical device under FDA regulations.

Market area	**Regulation**	**Risk Classification**	**EU Classification rule / FDA Product code**
EU	MDR	Class III	NA in EU
USA	FDA	Class III	PFN

4.2 Applied Standards

Most applicable standards that NeuroPace RNS system has been tested against are:

- ISO 13485 – QMS for design and manufacturing of medical devices.
- ISO 10993 – Assessing the biocompatibility of medical devices.
- IEC 60601 – Medical electrical equipment safety standards.
- IEC 62304 – Development, maintenance, risk management, configuration management and problem management of software in medical devices.
- ISO 14971 – Risk management for medical devices (Process to identify hazards; tests safety of product during its life cycle).
- FDA 21 CFR Part 820 – Quality System Regulation for all medical devices manufactured within the USA to ensure safety.

- ISO 11607 – Validate shelf-life and packaging; required in EU for CE mark; FDA recognized (23).

From our perspective, the most applicable standards that NeuroPace RNS system has been tested against are:

- FDA 21 CFR Part 820 – Title 21 CFR Part 820 is a set of regulations outlining good manufacturing practices of Medical Devices manufactured and marketed within the US. As NeuroPace RNS is a medical device made available in the US market, it is required to adhere to the country-specific regulatory standards which are put in place by FDA.
- ISO 13485 – This is the most applicable standard to conform to for any company (including NeuroPace) designing, producing, manufacturing and servicing medical devices as it is an internationally recognized quality management system. This means that if a company wishes to introduce their medical device to a new market, they have the documentation of this standard to prove the quality and safety of the device. Additionally, adhering to QMS also provides a competitive edge for the company among customers.

- ISO 10993 – As the RNS system comprises of a neurostimulator implant that needs to be placed within patient's body, the biocompatibility of the materials used to manufacture the implant components become very significant. Their biocompatibility needs to be tested and ensured. For this reason, this standard is very important for the RNS system.

- ISO 14971 – Reducing and managing the risks is significant for any medical device because of the dire consequences it can have when things go wrong. But especially as the RNS system is dealing with patient's brain which is a very delicate organ, it is critical to identify possible hazards, take measures to mitigate or prevent them and ensure the safety of the device.

4.3 Risk Assessment and Risk Control

Hazard (Known and foreseeable sources of harm and how the patient is exposed to the hazard)	**Harm** (Physical injury or damage to health)	**Risk Control** (Protective measures in medical devices or manufacturing process)
Leakage from Lithium-carbon monofluoride/silver vanadium oxide (Li-CFx/SVO) battery. This could be caused by over discharge of the battery	Chemical leakages can cause brain damage	To prevent over discharge, a limit is placed on each cell within the battery where the control circuit cuts the current path off at the limit.
Temperature rise from constant powering of the neurostimulator implant	Can cause burns to the tissue surrounding the neurostimulator implant	- Laboratory tests are done to ensure that the temperature rise is within the acceptance criteria which is within the safe operating range. - Thermal sensors that constantly monitor the temperature of the implant and send real-time data and alerts to the control system are integrated into the implant. - Feedback temperature may be incorporated where the implant device is programmed to reduce its power when it reaches the temperature threshold, consequently reducing the temperature.
Malfunctioning of microprocessor in the neurostimulator	Stimulation shock/ over stimulation to the brain if the stimulations are not detected and regulated correctly	- A redundant microprocessor is installed to act as an automated backup if the main microprocessor fails or malfunctions. - Failsafe mechanisms that lead to the device shutting down or sending alarms to the control system in case of malfunction.
Electrical leads: A) breaking off inside the patient's brain B) causing electrical short	A) can cause tissue damage B) can cause brain damage or other neurological symptoms	- To avoid lead breakage, biocompatible and flexible material like silicone is used in manufacturing the leads - Design of the connectors is ensured to be durable and reliable. This reduces the risk of leads breaking and electrical shorts. - Built-in strain relief mechanisms like coils are incorporated to absorb mechanical stress. This reduces the risk of breakage, as well as the risk of damage to insulation which can otherwise cause electrical shorts.
Interference of neurostimulator with other electrical devices that the patient may encounter	Interference may affect the functioning of the neurostimulator and result in erratic or abnormal stimulation of the patient's brain leading to adverse effects.	- Electromagnetic compatibility tests are done to test the susceptibility of neurostimulator to interfere with other electrical devices. - Frequency band range for neurostimulation is selected so interference does not happen with common electrical appliances and devices. - Clear instructions and warnings provided in the product labelling for patients.

4.4 Reported Hazardous Situations in FDA Database

Database	Number	What is the most typical reason for report/warning
MAUDE (Manufacturer and User Facility Device Experience database)	25	The most typical reason was post-operative infections near the implanted site
FDA Warnings Letters (may be also company specific)	1	The reason for the warning was not acquiring a pre-market approval before commercializing and marketing of a NeuroField Inc. device

While browsing through the MAUDE, we found 25 reported events with the brand name RNS System or NeuroPace RNS System with the NeuroPace Inc, as the manufacturer. We found that all hospitalizations either during or post RNS implantation were considered an event. Most of the events were surgical and post operations such as infections or skin erosion at the implanted site. The other events included leads breakage due to seizure related head trauma or the reason was unknown. One event reported a psychotic episode due to the surgical complication and the other reported hospitalization due to suicide ideation.

There were no warning letters available for NeuroPace RNS System. However, a similar company named NeuroField Inc., was issued a warning letter by FDA. The company produces neurostimulation and electroencephalogram (EEG) monitoring devices. The warning letter mentions that the company does not have pre-market approval or evidence of investigational device exemption (IDE) to produce, commercialize and market their products. They also mention that the company has only registered the devices as biofeedback devices (Class II) under FDA regulations, but the scope of these devices is more than that (Class III) as claimed and marketed by the company on their website and social media. Furthermore, the company does not follow the standard good manufacturing requirements for manufacturing, packing, storage or installation. Therefore, the company is directed to cease all activities and submit an application for adequate approval from FDA (24).

5 Part 4 – Ethical Aspects

1. **Risk-benefit analysis:** Brain surgery for the implantation of neurostimulator poses a great risk to the patient. So, it is important to ensure that the outcome of using the RNS system is truly greatly beneficial for the patient. The need for this device for the patient must be thoroughly evaluated by the doctor and the patient must be involved in making this decision after being fully informed about the risks and benefits. This also involves the responsibility of NeuroPace to adhere to safety standards, carry out risk assessments and provide documentation in the form of manuals to the patients, distributors, hospitals and doctors with clear indications for use so patient safety is

not compromised. RNS system takes time to show results in reduction of seizure frequency in patients and during this time, the patient will still have seizure occurrences. It is over one or two years, that the outcome of the therapy can be observed. This must be considered as a cost weighed against the future benefit. The safety of the

2. **Informed consent:** It is extremely important to make sure that the patient or research participant understands the risks that they will or might encounter before they agree to the procedure. They should be aware of the details of procedure, products or device to be used, risks, benefits, warnings, precautions, side effects, and post implantation care. Participants should not be pressurized to go through the procedure even if the physician/clinician thinks that it is the best and beneficial thing for them. They should merely be presented with all facts and information in an objective way and the ultimate decision should always be made by the patient.

3. **Transparency in results:** It is imperative to report all kinds of incidents and potential harm caused by the device. If any adverse event is encountered for any user, it should be reported clearly and as it is. It allows other clinicians and users to be aware of that fact and proceed accordingly. Moreover, any potential or unforeseen fault/bug in the device or its software should be addressed, and others should be made aware. During the research process, the evidence provided for the device's effectiveness and efficacy should be stated clearly and accurately so as not to mislead the entire community.

4. **Inclusivity, accessibility and equity (gender, age, economic background, race):** One of the main ethical considerations is making the device inclusive of all user groups e.g. differently abled people. The pricing of the device should be fair for it to be accessible to low-income groups. Research of this device should include different kinds of user such as male, female, young, old, different races, queer to determine its effectiveness for different people, something that works for one group of users might not work for other groups. Additionally, equity should also be considered in the workplace of NeuroPace Inc.

5. **Confidentiality and integrity**: The software and protocols should be made in a way that they protect the confidentiality and privacy of the patient when it is recorded in the PDMS software or even during research studies. Generally, patient data access is provided to the patient, their physician, caregiver or loved one (if permitted by the patient) and NeuroPace would have a record of all patient data. In terms of integrity of the manufacturer, in the case of a malfunction device or device components, it is important for NeuroPace to reimburse the user/buyer and replace the defective device.

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