Special Communication

Saudi Arabian Consensus Statement on Vagus Nerve Stimulation for Refractory Epilepsy

Khalid Alqadi[1], Hesham Aldhalaan[1], Abdulaziz Alghamdi[2], Fawzia Bamgadam[3], Amal Abu-Jabber[1], Saleh Baeesa[1,4], Ibrahim Althubaiti[1], Salah Baz[1]

[1]Department of Neurosciences, King Faisal Specialist Hospital and Research Centre, [2]Department of Neurosciences, Prince Sultan Military Medical City, [3]Department of Neurosciences, King Fahad Medical Centre, Riyadh, [4]Division of Neurosurgery, Department of Surgery, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Abstract

Vagus nerve stimulation (VNS) is an approved adjunctive therapy for refractory epilepsy and used in patients who are not candidates for resective epilepsy surgery. In Saudi Arabia, VNS device implantation is being performed since 2008 by several comprehensive epilepsy programs, but with variable protocols. Therefore, to standardize the use of VNS, a task force was established to create a national consensus. This group consisted of epileptologists, epilepsy surgeons and a VNS nurse coordinator working in comprehensive epilepsy centers and dealing with refractory epilepsy cases. The group intensively reviewed the literature using Medline, EMBASE, Web of Science and Cochrane Library, in addition to physician's manual. Evidence is reported as three stages: preimplantation and patient selection, a perioperative phase involving all stakeholders and post-operative care with specific programming pathways.

Keywords: Clinical practice, refractory epilepsy, Saudi Arabia, vagus nerve stimulation

Address for correspondence: Dr. Khalid Alqadi, King Faisal Specialist Hospital and Research Centre, MBC # J-76, P.O. Box: 40047, Jeddah 21499, Saudi Arabia.
E-mail: kalqadi@kfshrc.edu.sa

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INTRODUCTION

Epilepsy is a common neurological disorder that affects approximately 0.5%–1% of the world's population. The incidence of epilepsy is higher in developed countries.[1] In the Arab world, the prevalence of active epilepsy is about 6.5/1000 individuals, but this rate may increase in this fast-growing population.[2] The most common form of epilepsy in adults is partial (focal) seizure.[3] Notably, about 20%–40% of epilepsy patients have refractory epilepsy (also known as drug-resistant epilepsy).[3-5] The International League Against Epilepsy defines refractory epilepsy as failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug (AED) schedules, whether as monotherapies or in combination.[5]

Several surgical techniques are widely used to treat refractory epilepsy, including resection, disconnection or ablation of the epileptic zone. However, surgery may not be feasible in patients with a high risk of permanent postoperative functional deficits or with multifocal or hard-to-localize epileptic focus. Because of these limitations, alternative treatment approaches become necessary for refractory

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epilepsy patients. Currently, nonpharmacological therapies such as neuromodulations are being used to treat medically refractory epileptic patients, who are not suitable candidates for resective epilepsy surgery. Neuromodulation therapy uses electrical stimulation to inhibit brain excitability, with the aim to treat and prevent seizures.[6] One such therapy used for treating patients with refractory epilepsy is vagus nerve stimulation (VNS), which is considered a palliative therapy.[7-10]

VNS was approved in Europe in 1994 for the treatment of patients with generalized or focal-drug-resistant epilepsy. In 1997, the US Food and Drug Administration (FDA) approved VNS as adjunctive antiepileptic therapy for drug-resistant partial epilepsy patients aged >12 years.[11] Recently, the FDA also approved VNS as a safe treatment for refractory epilepsy patients aged 4–11 years.[12] Currently, VNS is offered to patients suffering from all types of refractory epilepsy.

Different studies have shown the effectiveness of using VNS in different types of epilepsy, including partial-onset (focal and multifocal), symptomatic and generalized epilepsy.[13-17] VNS has also been demonstrated to have robust efficacy against Lennox–Gastaut syndrome (LGS), which is a rare and severe form of childhood epilepsy.[18-20] Interestingly, VNS is also useful in reducing the problems of depression and mood swings associated with epilepsy.[21]

In Saudi Arabia, VNS was first introduced in 2008; however, only a limited number of tertiary centers used it when resective epilepsy surgery was not a viable treatment option.[22] Currently, an increased number of centers utilize VNS implantation to treat epilepsy, but with varying protocols. Therefore, the need to standardize the use of VNS was raised by a group of experts working in comprehensive epilepsy centers and dealing with refractory epilepsy cases. The purpose of this task force was to establish a national consensus statement applicable to all centers implementing the VNS program for patients with medically refractory epilepsy.

MATERIALS AND METHODS

In Saudi Arabia, VNS device implantation is indicated for children aged ≥4 years and for adults with refractory epilepsy to medical therapy and who are not candidates for other therapies such as resective epilepsy surgery.

A panel of experts in epilepsy – who are working in tertiary epilepsy centers across Saudi Arabia that accounted for >90% of the nearly 800 VNS implanted from 2008 to December 2019 (personal communication with LivaNova, the distributor of the VNS) – met over 2 days. This group consisted of epileptologists, epilepsy surgeons and a VNS nurse coordinator working in comprehensive epilepsy centers and dealing with refractory epilepsy cases.

The initial meeting of the task force highlighted the need for improving the current practice of VNS therapy for epileptologists, neurosurgeons and nurses in Saudi Arabia, Gulf countries and the Arab region. The panel decided to organize the VNS implantation therapy into three sequential parts, including preoperative and patient selection, perioperative and postoperative (device programming and follow-up) phases. The panel was divided into three groups and each was assigned to review the data of a particular phase in an open discussion to standardize the care for epilepsy patients suitable for VNS therapy.

Medline, EMBASE, Web of Science and Cochrane Library were searched for English literature published since inception up to March 2019. The following keywords were used in the searches: "vagus nerve stimulation therapy," "refractory epilepsy" "consensus," "guidelines" and "protocols." All obtained literature were discussed by each group. Papers that only reported the safety and efficacy of VNS therapy were excluded. The panel assessed the level of evidence of each phase using a modified version of the American College of Cardiology/American Heart Association Class of Recommendations and Level of Evidence, generating three categories for evidence: Level A (high-quality evidence from multiple randomized control trial or their meta-analyses), B (randomized and nonrandomized) and C (limited data and expert opinion).[23]

RESULTS

Based on the inclusion criteria, guidelines published from the UK and Canada were included along with an evidence-based guideline from the Guideline Development Subcommittee of the American Academy of Neurology and a consensus and guideline from the Brazilian League of Epilepsy and the Brazilian Academy of Neurology Committee of Neuromodulation.[8,21,24-26] The physician's manual and manufacturer's protocol were also included.[27] Overall, the search revealed comprehensive updates in the past 5 years,[28,29] including a meta-analysis by correlating the VNS device setting parameters and response.[30] However, the available literature was only of level C evidence, and this limited us from creating a comprehensive guideline. Therefore, for this consensus statement, detailed and tailored recommendations were created as a checklist for every phase of VNS to develop clear, measurable outcome

parameters that can be used for every patient at any epilepsy center. Most of the recommendations are the expert opinion of the authors unless specified otherwise or referenced.

Study Phase 1 (preoperative phase: selection criteria and presurgical workup)

The preoperative phase begins with the recommendation for VNS implantation to treat refractory epilepsy by epileptologists.

Selection criteria

The patients recommended for VNS therapy must meet one of the following prerequisites:

i. Symptomatic localized epilepsy with multiple and bilateral independent foci
ii. Cryptogenic or symptomatic generalized epilepsy with diffuse epileptogenic abnormalities such as LGS
iii. Failed intracranial epilepsy surgery with no feasible alternative surgical procedure
iv. Refractory epilepsy with contraindication to epilepsy surgery.

Presurgical work-up

i. Optimal candidates for VNS therapy should be referred to an epileptologist
ii. Before VNS implantation, seizure evaluation must be documented, including baseline seizure type, severity and frequency
iii. Every patient must have at least one documented seizure and should undergo a video-electroencephalography (EEG) recording for a minimum of 24 h
iv. Magnetic resonance imaging (MRI) of the brain (at least 1.5 Tesla) should be performed before VNS implantation to avoid any potential resective epilepsy surgery. Computed tomography scan of the brain might be used only if the MRI is contraindicated
v. Discussion on the cases of VNS candidates must be held in a multidisciplinary meeting, including, but not limited to, epilepsy and neurosurgery consultants
vi. The decision in the meeting should be documented in the patient's chart with the names of the attendees and the conclusion
vii. The concerns of the patients and caregivers should be addressed, and the details of the procedure must be explained to them
viii. It is imperative to discuss and set the expectation with the patients, their family and the caregivers concerning commitment to attend regular clinic appointments and also the expected response of VNS therapy within a realistic time frame
ix. Informative material should be provided to the patient [Supplementary Appendix 1].

Contraindications and precautions for vagus nerve stimulation implantation

i. Vagotomy

VNS therapy is not applicable for patients with bilateral or left cervical vagotomy.[12]

ii. Diathermy

Shortwave diathermy, therapeutic ultrasound diathermy should not be used on patients with VNS implantation. However, diagnostic ultrasound is not included in this contraindication.[12]

iii. Cardiac arrhythmia (Aspire SR® only)

The auto-stimulation (AutoStim) mode feature should not be used in patients with clinically significant cardiac arrhythmias. Moreover, patients with a pacemaker, implantable defibrillator, or those taking "beta-adrenergic blocker" medications, which interfere with normal intrinsic heart rate responses, are not eligible for the AutoStim mode feature.

Study Phase 2 (perioperative phase)

This phase begins as soon as the epilepsy patient management group approves VNS implant and it continues until the therapy has been initiated.

Preimplantation requisites for completing the necessary steps of the perioperative phase are as follows:

i. The device must be implanted by trained epilepsy neurosurgeon in VNS implantation
ii. Proper safety and precautions should be achieved through adequate communication and documentation (report of the epilepsy group) between multidisciplinary teams, preferably comprising VNS and epilepsy coordinator.

Preprocedure steps

i. The epilepsy team should document the discussion on VNS implantation in the patient's chart and should complete the preimplantation checklist [Supplementary Appendix 2] appropriately
ii. Following proper consultation with an epilepsy surgeon, the patients should be assured regarding the inclusion of the discussion for VNS placement in the chart
iii. Epilepsy surgeon should mention in their consult note that they had reviewed the documentation of the discussion made by the referring epileptologist with the patient and caregiver, in addition to the records of his or her dialogue
iv. VNS implantation might be performed as a same-day procedure or require a 1-day admission

v. Verification of the completion of all steps in the VNS procedure should be done using the checklist.

Immediate postoperative care

Postoperative wound assessment and potential removal of dressing should be performed before the device activation.

Study Phase 3 (postoperative phase and follow up)

Definition

This section of the recommendation proposes a step-by-step guide on the management of patients following VNS implantation.

First postimplantation visit

In the first 2 weeks following implantation, VNS device should remain switched off to allow the wound to heal and minimize chances of infection and postoperative complications. However, in certain situations, such as when a patient has ongoing seizures or when repetitive seizures are life-threatening to the patients, switching on the VNS device immediately after implantation should be considered, but only after a careful risk-benefit analysis has been carried out. In the first clinic visit, 2 weeks after VNS implantation, it is recommended to start with the settings labeled as titration number one in Table 1.

In each visit, including the first, faster titration should be considered and discussed with the patient and caregiver.

When the option of administering two doses in the same visit to ramp up the VNS settings is considered according to the recommended titration schedule in Table 1, a minimum gap of 30 min between the doses is recommended to test the ability of the patient to tolerate fast titration. The last titration [number seven in Table 1] should be completed in <6 months from the procedure over three or four visits, with a minimum 2-week interval between the visits.

The recommended titration is based on the patient's response and tolerability. It is advised to provide the patient and caregivers a detailed VNS card in Arabic explaining the consequences of VNS implantation.

Steps to follow in each subsequent visit

i. Interrogate the device and note the current parameters
ii. Following interrogation, adjust parameters as desired, based on the efficacy and the tolerability of the patient
iii. Perform system diagnostics once the device output current has been programmed
iv. Always interrogate the VNS generator as the last step before the patient leaves the clinic.

Patients should be referred to a tertiary epilepsy center experienced in dealing with VNS implanted patients for further adjustment when no satisfactory result is observed by the treating epileptologist or when high impedance is found.

Duty cycle

Duty cycle is defined as the amount of time the stimulation is being delivered in 24 h and is an essential element in VNS programming. Duty cycle is calculated as:

$$\frac{\text{On-time}}{\text{On-time} + \text{off time}} \times 100 .$$

Standard duty cycle is 10% when the basic settings consist of 30 s on and 5 min off [Table 2]. The duty cycle can be adjusted by manipulating the on and off times. The duty cycle reached by titration number seven is 16%. However, the maximum recommended duty cycle by LivaNova is 49%, which is typically achieved within 21 s on and 0.5 min off times.

If the duty cycle >16% is considered, it is recommended that the patient is referred to a tertiary epilepsy center.

Table 1: Recommended titration after vagal nerve stimulator implantation

Parameter	Titration number						
	1	2	3	4	5	6	7
Output current (mA)	0.25	0.5	0.75	1.0	1.25	1.5	1.5
Signal frequency (Hz)	20	20	20	20	20	20	20
Pulse width (us)	250	250	250	250	250	250	250
Signal ON time (s)	30	30	30	30	30	30	30
Signal OFF time (min)	5	5	5	5	5	5	3
AutoStim current (mA)	0.375	0.625	0.875	1.125	1.375	1.625	1.625
Autostim signal ON time (s)	60	60	60	60	60	60	60
Auto-stimulation pulse width (us)	250	250	250	250	250	250	250
Magnet current (mA)	0.5	0.75	1.0	1.25	1.5	1.75	1.75
Magnet on time (s)	60	60	60	60	60	60	60
Magnet pulse width (us)	500	500	500	500	500	500	500
HR detection	2	2	2	2	2	2	2
Threshold (%)	40	40	40	40	40	40	40

HR – Heart rate

Table 2: Duty cycle

On time (s)	Off time (min)								
	0.2 (%)	0.3 (%)	0.5 (%)	0.8 (%)	1.1 (%)	1.8 (%)	3.0 (%)	5.0 (%)	10 (%)
7	**58**	44	30	20	15	10	6	4	2
14	**69**	**56**	41	29	23	15	9	6	3
21	**76**	**64**	49	36	29	19	12	8	4
30	**81**	**71**	**57**	44	35	25	**16***	10	5
60	**89**	**82**	**71**	**59**	**51**	38	27	18	10

Avoid the duty cycles highlighted in bold. *The recommended duty cycle reached at titration number 7

The patients and caregivers should also be counseled regarding the potential worsening of the seizure frequency with these adjustments.

Use of magnet

The VNS magnet pack should be given to a patient at the time of activating the VNS device for the first time. The patient or the caregiver must activate the magnet stimulation immediately after the onset of an aura. If no aura is experienced, a caregiver can activate magnet stimulation instantaneously after the beginning of a seizure. The magnet stimulation mode results in an extra dose of stimulation being delivered at the onset or during the seizure. When needed, the device can be switched off by taping the magnet over the VNS generator.

Deactivation due to lack of efficacy

If VNS therapy has no beneficial effect at a therapeutic dose even after 24 months of implantation, in terms of seizure control or quality of life improvement, it is advisable to turn off the VNS generator after counseling the patient or the caregiver.

When the output current, magnet current and auto-stimulation are set at 0.00 mA, the VNS device is switched off.

We recommend monitoring the patient for 6 months for increased seizure frequency or severity. It is recommended to keep VNS device in place in case re-activation is required.

Magnetic resonance imaging scanning for patients with vagus nerve stimulation

MRI scanning of any patient with VNS implantation is feasible with the following precautions:

i. Avoid scanning between levels of C7 and T8 with a full VNS System implanted [Figure 1]
ii. If the patient has <2-cm lead remaining, a whole-body MRI can be performed
iii. Even after removal of the generator, a part of lead remains, MRI can be still performed using a transmit and receive coil.

Before MRI scanning, system diagnostics should be performed to ensure proper operation of the device, followed by an interrogation and generator settings.

The output current parameter should be programmed for normal mode, auto-stimulation and magnet mode as output current (mA) 0.0, magnet current (mA) 0.0 and auto-stimulation (Aspire SR® device) switched off.

After the MRI scan and once the patient leaves the magnetic area, the VNS device should be interrogated, and the setting parameters must be programmed to the last settings.

System diagnostics must be performed to check impedance, and the device must be interrogated to confirm successful programming.

Generator replacement

Generator replacement is required if there is an intensified follow-up indicator (IFI) warning message displayed upon interrogation.

IFI is displayed once the capacity of the generator reaches 8%–18% of its battery capacity. The end-of-service (EOS) warning message is seen when the capacity reaches 0%–8%, after which the generator will not provide stimulation, thereby urgently requiring replacement.

If case a replacement is required before the original generator has reached the EOS, the new generator can be activated shortly after surgery to minimize the effect of VNS therapy discontinuation. Immediately after surgery, the VNS device could be activated, to avoid any potential side-effects, we recommend decreasing all output parameters by 0.25 mA.

Antiepileptic drugs adjustment after implantation

No clear guidance or established evidence available on modifications of AEDs after VNS implantation. However, it is suggested to continue the same AEDs for at least 1-year postimplantation.

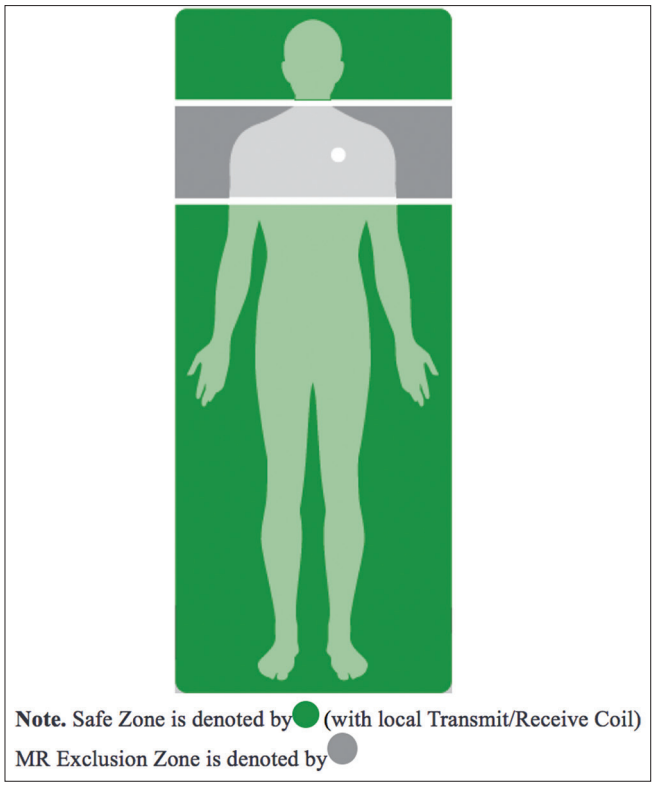

Figure 1: Magnetic resonance imaging safety zone in patients with vagus nerve stimulation

Toleration and side effects of vagus nerve stimulation implantation

The majority of patients tolerate the first visit stimulation of the device. However, in few patients, side effects may occur at the initiation of therapy or at the time of stimulus escalation. If a patient is unable to tolerate a pulse width of 250 μs, reduction of the output current by 0.25 mA is recommended. The pulse width and signal frequency could be decreased. If the side effects are not controlled despite the aforementioned measures, it is recommended to reduce the duty cycle by shortening the switched-on time. In Aspire SR®, increasing the auto-detection threshold by 10% to 20% might help in alleviating the side effects.

DISCUSSION

The available literature shows that VNS is an efficient and safe treatment option for both adult and pediatric populations suffering from refractory epilepsy and cannot undergo resective surgery or other medical and surgical management.[31] Patients with uncontrolled generalized epilepsy have limited nonpharmacological options and might benefit from VNS therapy.[32] Studies showed that the adjunctive VNS therapy in children with drug-resistant epilepsy results in a significant reduction of seizure frequency with no additional safety issues and also a dose-response correlation was detected for VNS in epilepsy patients.[33]

At the preoperative phase, an experienced epileptologist should evaluate the patients through brain MRI and a video EEG recording for at least 24 h to confirm refractory epilepsy, and only then VNS implantation is recommended.

Even though VNS implantation is a relatively safe procedure, risks are involved. Complications of VNS implantation are primarily associated with the surgical procedure, including infection at the site of implantation, fracture of the electrode, device dislodgment and battery failure.[22] The most common side effects of the VNS device are hoarseness, cough, paresthesia and shortness of breath. These side effects are usually transient and occur during the actual stimulation. However, if the side effects persist, they can be managed by adjusting the parameters. Other rare complications include bradycardia, laryngopharyngeal dysfunction, tonsillar pain and obstructive sleep apnea. Although rare, about 2% of such complications may cause significant suffering and can also be life-threatening.[7,34] If the side effects do not subside despite efforts, temporarily switching off the VNS device should be considered, and the patients must be referred to an epilepsy center proficient in dealing with VNS patients.

It is important that patients are completely aware of the risks and benefits of VNS therapy. Moreover, the patients must be informed that this therapy is unable to render them seizure-free and also complete discontinuation of all antiepileptic medications might not be possible; a resective epilepsy surgery is more likely to provide complete seizure relief than VNS. To decrease the seizure frequency and intensity, refractory epilepsy patients must continue with the AED regimen following VNS therapy.[32] Studies have shown that VNS implantation, along with multidisciplinary and multimodality treatment regimens and appropriate epilepsy surgery, would reduce seizure by 50% in >60% of the patients.[35] However, if the patient experiences continued seizure following this treatment regimen, it is recommended to refer the patient to a comprehensive epilepsy center for further evaluation and possible surgical procedure.[32]

CONCLUSION

For patients with refractory epilepsy, after a thorough evaluation by a neurologist specialized in epilepsy, an MRI of the brain and at least 24 h of video-EEG recording, VNS implantation can be considered, with a closely controlled perioperative phase and a monitored postoperative phase

and follow-up. Further evidence with a higher level of evidence is required to develop a guideline.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Appendix 1: Patient information material

All patients/family/caregivers considering VNS as a treatment for their epilepsy should be supplied with the information to make an informed choice. Information may be provided via leaflets, DVDs, consultation with the physician, epilepsy nurse and surgeon.

The following aspects should be covered:

- **What is VNS therapy?**
  - The vagal nerve stimulator (VNS) is used to treat intractable epilepsy
  - The generator automatically sends an electrical signal through the lead attached to the Vagus nerve
  - The stimulation causes a chemical reaction in the brain, which can improve seizure control.

- **How the VNS system is implanted**
  - The device is implanted by a surgeon who implants a small pacemaker-like generator on the left side of the chest wall and a stimulation lead (coil) around the Vagus nerve in the neck.

- **Associated risk of surgery**
  - Pain at the site of incision, infection, incision scarring, difficulty swallowing, vocal cord paralysis, which is usually temporary, but can be permanent

- **How the VNS generator is programmed**
  - The dosage is adjusted by using a handheld pre-programmed computer and wand system.

- **Increased outpatient appointments during the ramping up phase**
- **Adverse effects**
  - **Implant-related** adverse events reported during the pivotal study in ≥ 5% of patients are listed in order of decreasing occurrence: incision pain, voice alteration, incision site reaction, device site pain, device site reaction, pharyngitis, dysphagia, hypesthesia, dyspnea, nausea, headache, neck pain, pain, paresthesia and cough increased.
  - **Stimulation-related** adverse events reported during the acute sham-controlled study by ≥5% of VNS Therapy-treated patients are listed in order of decreasing occurrence: voice alteration, cough increased, dyspnea, neck pain, dysphagia, laryngismus, paresthesia, pharyngitis, nausea and incision pain.

- **Expectations of VNS Therapy**

The VNS can help reduce the rate and length of seizures for young people with epilepsy by preventing the electrical irregularities that cause seizures.

- **Antiepileptic medications use with VNS**

The patient should continue to use his regular antiepileptic medication as advised by his or her epileptologist.

- **Magnet use**

A special magnet to deliver another burst of stimulation, outside of the programmed intervals. It can help stop a seizure if applied over the device during seizures or preceded aura.

- **Potential improvement in quality of life**

The quality of life showed improvement after VNS implantation in some patients.

- **MRI compatibility**

MRI Brain should be obtained before VNS implantation, but if MRI needed after implantation, it could be done with special preparation.

- **Replacement of generator**

Battery service can be predicted before it ends with the current VNS model, which allow for elective generator replacement before the battery is fully depleted.

- **Potential lead fracture**

The lead fracture can occur over time while stimulation continues. Can potentially cause localized inflammation, pain and vocal cord dysfunction.

Supplementary Appendix 2: Vagus nerve stimulation preimplantation checklist

Checklist item	Yes/no
Refractory epilepsy was confirmed by epileptologist	
Video EEG recording for at least 24 h with documented seizure(s)	
MRI of the brain was performed	
Case was discussed in a multidisciplinary meeting and report was generated	
Patient concerns were addressed, and procedure was explained and documented	
Patient/family/caregivers informative material was given	
Patient was seen by epilepsy surgeon/neurosurgery	
Informed consent for the procedure was taken	
Date of the surgery confirmed	
Epilepsy surgeon/neurosurgery was informed about the admission	
Anesthesia consultation is completed	
Primary physician was notified before admission	
VNS type determined	
VNS device availability in stock (equipment checklist)	
Patient notified for all pre-implantation appointments	
Antiseizure drugs revised	
VNS dispensing company representative notified	
VNS diagnostics tested intra-operatively	
Heartbeat sensitivity calibration completed (only for Aspire SR 106)	
Procedure documentation completed by the surgeon immediately after the implantation	
VNS identification card handled to patient	
Follow-up postoperative appointments given to the patient	
VNS programming management form initiated in follow-up	
VNS interrogation checklist	
Review the patient's VNS card	
Interrogate the VNS device	
Adjust and titrate per clinical response	
Perform system diagnostics	

EEG – Electroencephalography; VNS – Vagus nerve stimulation