The Genio® System 2.1

Technical Sleep Lab Manual

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List of Abbreviations

AC	Genio® Activation Chip (Activation Chip), model #2364
AHI	Apnea Hypopnea Index
AIMD	Active Implantable Medical Device
App	Application
BLE	Bluetooth Low Energy
BMI	Body Mass Index
CU	Genio® Charging Unit (Charging Unit), model #2238
DC	Duty Cycle
DISE	Drug-Induced Sleep Endoscopy
DP	Genio® Disposable Patch
EMC	Electromagnetic Compatibility
ES	Genio® External Stimulator
FCC	Federal Communications Commissions
ID	Identification
IS	Genio® Implantable Stimulator
IFU	Instructions for Use
MRI	Magnetic Resonance Imaging
OSA	Obstructive Sleep Apnea
PAP	Positive Airway Pressure
PCB	Printed Circuit Board
PS	Power Supply (also referred to as Power Adaptor)
PSG	Polysomnography
RTC	Real Time Clock
RF	Radiofrequency
RFID	Radiofrequency Identification
SN	Serial Number
SW	Software

1 Introduction

Sleep apnea is a respiratory sleep disorder characterized by recurrent episodes of partial or complete upper airway obstruction during sleep, resulting in disrupted sleep patterns and excessive daytime somnolence as well as other medical co-morbidities. The most common type of sleep apnea is Obstructive Sleep Apnea (OSA). One of the major causes of OSA is the inability of the tongue muscles to resist negative inspiratory pressure in the pharynx due to the sleep-related loss in muscle tone. As the tongue is pulled backwards, it obstructs the upper airway, decreasing ventilation and lowering lung and blood oxygen levels. Stimulation of the hypoglossal nerve causes the tongue muscles to contract, thereby maintaining an open, unobstructed airway.

This Manual describes the set up and the use of the Genio® System 2.1, a bilateral hypoglossal nerve system developed for the treatment of OSA.

1.1 Therapy Overview

The Genio® System 2.1 comprises of a bilateral Implantable Stimulator (IS), which is implanted via a minimally invasive surgical procedure and positioned over the genioglossus muscle with its electrodes facing both left and right hypoglossal nerve branches. Stimulation of the hypoglossal nerve causes the tongue muscles to contract with the intention to maintain an open airway. The IS receives energy pulses transmitted by an Activation Chip (AC) which is attached to an adhesive Disposable Patch (DP) and placed on participant's skin under the chin. The AC, containing the participant's stimulation parameters and a rechargeable battery, is programmed and adjusted using a Genio® Sleep Lab Application (App) via wireless Bluetooth communication. The DP, connected to the AC, is placed by the participant under the chin every night before going to sleep and removed in the morning, to activate and discontinue the stimulation, respectively. The battery of the AC will be recharged during the day using the Charging Unit (CU).

During the implant procedure, an External Stimulator (ES) is used to enable the surgeon to activate the IS in order to verify its functionality and optimal placement.

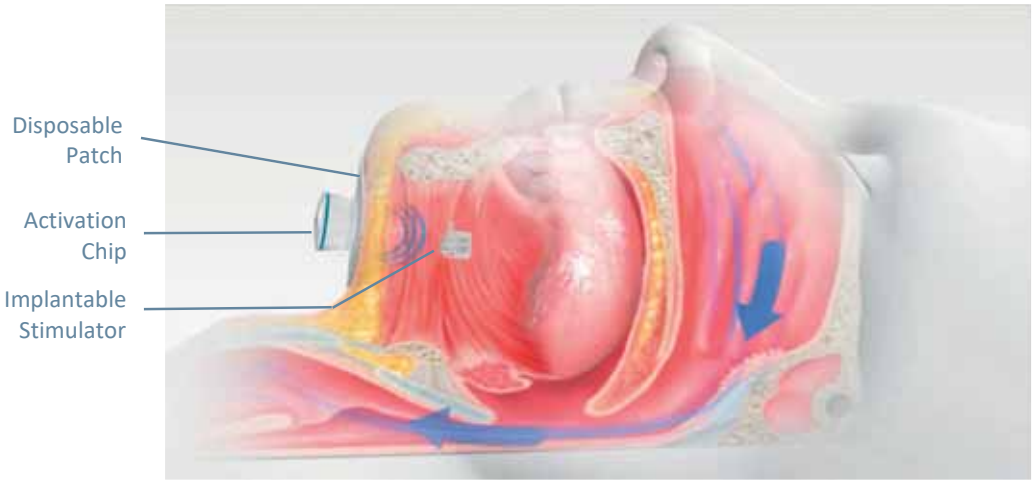


Figure 1: Genio® System 2.1 therapy overview

2 Safety Information

2.1 Intended Use

The Genio® System 2.1 is used to treat subjects suffering from moderate-to-severe Obstructive Sleep Apnea (OSA) (Apnea-hypopnea Index [AHI] of greater or equal to 15 and less than or equal to 65). The Genio® System 2.1 is used in adult subjects who have not tolerated, have failed or refused Positive Airway Pressure (PAP) treatments. PAP failure is defined as an inability to eliminate OSA (AHI of greater than 15 despite PAP usage) and PAP intolerance is defined as:

a) inability to use PAP (less than 5 nights per week of usage; usage defined as 4 hours or more of use per night); or

b) unwillingness to continue to use PAP (for example, a subject returns the PAP system after attempting to use it).

2.2 Contraindications

The Genio® System 2.1 is contraindicated for:

- Subjects below 22 or above 75 years old
- Subjects with a Body Mass Index (BMI) above 32 kg/m^2
- Subjects with an Apnea-Hypopnea Index (AHI) below 15 or over 65 events/hour
- Subjects with combined central and mixed AHI > 25% of the total AHI
- Pregnant/breastfeeding women or women planning to become pregnant
- Subjects with any functional or structural problem that would impair the ability of a hypoglossal nerve stimulator to treat OSA
- Subjects with any medical illness or condition that contraindicates a surgical procedure under general anesthesia or that would prevent the implantation of the Implantable Stimulator or the placement of Activation Chip/Disposable Patch
- Subjects with coagulopathy or requiring anticoagulant medications (such as warfarin, clopidogrel (Plavix) or similar; prophylactic aspirin not exclusionary) that cannot be safely stopped in the perioperative period
- Subjects with major head and neck abnormalities narrowing the airway or the implantation site
- Subjects with hypersensitivity to any material of system components

2.3 Warnings

2.3.1 Training

Only trained clinical staff who underwent training by Nyxoah can configure the Genio® System 2.1.

2.3.2 Pediatric Use

Safety and effectiveness of the use of the Genio® System 2.1 has not been established for children.

2.3.3 Components

The use of components not provided by Nyxoah may result in device malfunctioning, damaged devices or increase the risks to the users.

Changes or modifications not expressly approved by the party responsible for compliance could void the user's authority to operate the equipment.

2.3.4 Interaction with Other Active Implantable Medical Devices (AIMD)

Subjects with other Active Implantable Medical Devices (AIMD) should not be implanted even if the devices can be temporarily turned off as it may interfere with the Genio® Implantable Stimulator, i.e. the potential for interference has not been studied.

2.4 MRI Safety Information

The Genio® Implantable Stimulator (IS) is a Magnetic Resonance (MR) Conditional device which means that the implant is safe in the MR environment within certain conditions.

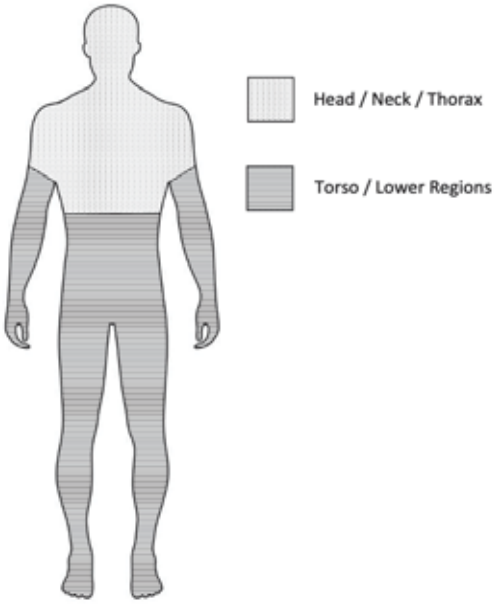
This section contains important information regarding the Genio® IS and the conditions in which a patient implanted with the Genio® IS can safely undergo an MR scan. MR scans must be performed only as described in this section.

2.4.1 MR Scan Conditions

Non-clinical testing has demonstrated the Genio® IS is MR Conditional. A patient with this device can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 1.5 Tesla and 3 Tesla, with:
    - Maximum spatial field gradient of 2000 G/cm (20 T/m)
    - Maximum switched gradient slew rate per axis of 200 mT/m/ms
    - Maximum switched gradient amplitude per axis of 45 mT/m
    - Maximum scan duration:

Landmark Position	Scan duration	Maximum SAR
Head/Neck/Thorax	<15 minutes continuous scanning	Whole body averaged specific absorption rate (SAR) of 1 W/kg or head averaged SAR of 1.6 W/kg (Normal Operating Mode)
Torso and Lower regions	<15 minutes continuous scanning	Whole body averaged specific absorption rate (SAR) of 2 W/kg (Normal Operating Mode)



Under the scan conditions defined above, the Genio® IS is expected to produce a maximum temperature rise of less than 5^{o} C of continuous scanning.

In non-clinical testing, the image artifact caused by the device extends approximately 5 cm from the Genio® Implantable Stimulator when imaged with a gradient echo pulse sequence and a 3 Tesla MR system.

2.4.2 MRI Technician warnings and precautions

- Caution: In some instances, a stimulation of the tongue muscles can occur leading to uncomfortable sensation.
- Genio® System 2.1 external devices (such as the Genio® DP or AC) shall not be brought by the patient to the MR scan room and used during the MR scan. The use of the Genio® DP and AC during an MR scan is prohibited.
- Do not scan patients with fever.
- During the MR scan, continuously monitor the patient, notice any signs of anxiety and/or discomfort.
- The device may move and thus cause discomfort and/or pain when used in the scanner.
- The patient may feel discomfort during part or all of the MR scan. If the patient feels uncomfortable pain or heating during the MR scan which is intolerable, the scan should be terminated.
- The MR scan should be conducted at least 6 weeks after patient implantation or revision surgery.

2.4.3 Potential risks associated with MR scans

The Genio® IS device has been designed to minimize the potential adverse events that could result in patient harm.

The potential MR scan-related adverse events are listed below:

- Implant heating causing damage to tissue in contact with the implant
- Implant migration causing damage to tissue in contact with the implant
- Implant migration causing the implant to be surgically removed (and replaced)
- Unintended over stimulation causing damage to tissue in contact with the implant
- Unintended stimulation causing discomfort due to electrical stimulation
- Device malfunction causing the implant to be surgically removed (and replaced)
- Diagnostic problems due to artifacts - shadowing on the MR image in the vicinity of the implant causing loss or disturbance of diagnostic information

2.5 Precautions

2.5.1 Pregnancy

There might be unknown risks to pregnancy and breastfeeding if the implanted device is used while pregnant. For this reason, a pregnant/breastfeeding participant or a participant planning to get pregnant should not be implanted. If the participant becomes pregnant after implantation of the device, the device should remain inactive until the participant stops breastfeeding.

Female participants are strongly advised to use effective contraception during the course of the study.

2.5.2 Treatment with Therapeutic Ionizing Radiation

Participants should not undergo treatment with therapeutic ionizing radiation after the implantation of the Implantable Stimulator. If such therapy is required, then according to the radiation therapy type, the device may be either explanted or there will be a need to shield the device and confirm its function after treatment.

2.5.3 Hyperbaric Chambers

There may be possible safety hazards associated with hyperbaric chambers.

2.5.4 Entering Special Areas

Participants implanted with the Genio® Implantable Stimulator should seek medical guidance before entering environments that are protected by a warning notice preventing entry by participants fitted with an Active Implantable Medical Device (AIMD) such as a pacemaker.

2.5.5 Defibrillation/Cardioversion

When a participant is in ventricular fibrillation or atrial fibrillation, the first consideration is the participant survival. It is recommended to remove the AC-DP prior to the use of defibrillation or cardioversion. After defibrillation or cardioversion, the physician should confirm The Genio® System 2.1 is working as intended. Please note that possible interaction between The Genio® System 2.1 and cardiac devices (implantable defibrillators) has not been investigated.

2.5.6 Metal Detectors

Interactions with metal detectors are unlikely to damage the Implantable Stimulator or cause clinically significant symptoms. However, the Implantable Stimulator contains metal parts that might possibly set off metal detector alarms. The participant must tell security personnel that they have an implanted device in the chin area and always have their Participant Card with them. Security wands should not affect the device.

2.5.7 Theft Detector, RFID systems and Security Screening Devices

Participants must use care when approaching theft detectors, RFID systems and security devices (such as those found in airports, libraries, department stores, and government buildings). When approaching these devices, participants are advised to do the following:

1. Show the security personnel the Participant Card and notify them that they have an implanted medical device in the chin area.
2. If they must pass through the theft detector or security screening device or in proximity to RFID systems, they are advised to proceed through the security device and keep as far from it as possible. They should not linger near or lean on such devices.

Note: Some theft detectors might not be visible.

2.5.8 Therapeutic Ultrasound

Participants should consult their doctor prior to undergoing treatment with ultrasound therapy as it might damage the Implantable Stimulator and/or might cause damage to the tissue.

2.5.9 Radio-Frequency or Microwave Ablation

Participants should not be exposed to radio-frequency of microwave ablation. The electrical current may cause heating resulting in device and/or tissue damage.

2.5.10 Water and Humidity

Keep the Genio® external devices away from extremely humid areas and sources of water. Failure to keep the devices dry may result in device malfunctions.

2.5.11 Cleaning of the devices

The devices should be kept in a clean environment. The Activation Chip should be kept in the provided protective cover when it is not in use or not being charged. Do not clean the devices. If functionality is compromised, contact your physician.

2.6 Risks

2.6.1 Risks Associated with the Implantation Procedure

For the purpose of device implantation, the participant will undergo a surgical procedure under general anesthesia. Whilst anesthesia is generally very safe nowadays, there is always the possibility of some risks associated with anesthesia. The commonly known adverse events associated with anesthesia are listed below. Most of these anesthesia-related events are uncommon and are generally resolved quickly. The risk of brain damage or death due to anesthesia is very low.

The risk of problems from anesthesia increases for people who have frequent surgical procedures within a short timeframe and participants with other high-risk diseases.

From prior clinical trial experience, the average implantation of the IS was 134±43 minutes. Exposure to general anesthesia for the implantation is similar to other surgeries and is expected to take on average 200 minutes. The anesthesia and implantation surgery may involve the following risks:

Very common risks (which may affect more than 1 in 10 participants):

- Post-surgical discomfort
- Post-surgical numbness, tingling or other sensory changes related to the skin incision
- Post-surgical mild to moderate swelling or bruising around the incision site
- Post-surgical mild to moderate pain, stiffness or tenderness at the incision site
- Impaired or painful swallowing
- Impaired or painful speaking due to the procedure
- Paresthesia (sensation of ticking or itching)
- Bleeding (including hematoma)
- Abnormal scarring
- Pain or irritation in the throat or nasal passage from intubation
- Feeling unwell or vomiting
- Dry mouth
- Post-surgical hoarse voice due to anesthesia
- Bruising at the site of injections

Common risks (which may affect between 1 in 10 and 1 in 100 participants):

- Post-surgical headache, dizziness
- Damage or trauma to nerves, blood vessels or muscles
- Transient tongue weakness
- Local skin irritation
- Post-surgical diarrhea
- Tongue fasciculations (twitching of tongue)
- Tongue muscle weakness or soreness
- Muscle or skin tightness
- Post-surgical back pain due to lying on the table during the procedure
- Infection

Uncommon risks (which may affect less than 1 in 100 participants):

- Temporary lip weakness
- Post-surgical fever
- Superficial skin infection
- Impaired sense of taste
- Tongue may get larger or smaller
- Persistent pain at the implant site
- Post-surgical irritability, nervousness, confusion
- Post-surgical sleep problems like insomnia or sleepiness
- Post-surgical respiratory complications requiring ventilation
- Aspiration (i.e., food/fluid directed to windpipe when swallowing)
- Allergic reaction to anesthetics or other medications used before, during, or after the surgery

2.6.2 Risks Associated with the Devices and the Use of the Devices

The potential device-related adverse events are listed below:

Very common risks (which may affect more than 1 in 10 participants):

- Discomfort due to electrical stimulation
- Mild tongue abrasion
- Temporary local skin irritation
- Abnormal scarring
- Tongue fasciculations (twitching of tongue)
- Paresthesia (sensation of tickling or itching)
- Impaired or painful swallowing due to the device

Common risks (which may affect between 1 in 10 and 1 in 100 participants):

- Dry mouth
- Temporary tongue muscle weakness or soreness
- Temporary usability or functionality issues with an external device leading to temporary delay of treatment
- Permanent usability or functionality issues with an external device leading to no therapy
- Usability or functionality issues with the implanted device
- Increased or continued snoring
- Mouth blisters (due to tongue rubbing against teeth during stimulation)
- Pain or irritation in the throat or nasal passage
- Post-surgical mild to moderate pain, stiffness or tenderness at the incision site
- Implant may need to be surgically removed (and replaced)
- Infection

Uncommon risks (which may affect less than 1 in 100 participants):

- Allergic and/or rejection response to the implanted device
- Damage to tissue in contact with the implant
- Damage to tissue in contact with external devices
- Persistent pain at the implant site
- Impaired or painful speaking due to the device
- Damage or trauma to blood vessels/nerves in the vicinity of the implant
- Clinically significant implant migration (device moving from implanted location)
- Change in salivary flow

2.6.3 Risks Associated with the Revision Procedures

If an additional surgery is performed in order to have the implant removed, repositioned or replaced, the risks detailed above, along with some new risks, would apply to the surgery. The risks of a revision surgery are higher because scar tissue builds up around the implanted device, and there is a higher risk of infection from the surgery. Additional injury to the nearby nerves, blood vessels or tissues could occur.

2.6.4 Risks Associated with Sleep Studies

The Polysomnography (PSG) itself is a non-invasive, painless test but may be uncomfortable. Complications are rare. The most common side effects are as follows:

- Inability to sleep in the sleep lab causing fatigue the next day and loss of productivity
- Local irritation or bleeding of the skin where external electrode sites are attached
- Bruising, bleeding or soreness from external electrode removal

2.6.5 Risks Associated with Drug-Induced Sleep Endoscopies (DISE)

Administration of sedative medication (Midazolam and/or Propofol) in DISE is known to induce muscle relaxation which is an intended effect of this drug in this study. The participant may experience general fatigue, somnolence or even start sleeping after the injection, which is normal and somewhat expected.

The dose for the DISE procedure is rather low compared to doses usually administered to participants receiving these drugs (Midazolam and/or Propofol) in the frame of their normal medical care.

Therefore, side effects rarely observed with these drugs at higher doses or after repeated administration are quite unlikely to be seen in this study. These known side effects are:

- Bradycardia (the heart beats more slowly)
- Visual disturbances
- Dry mouth, gastrointestinal disturbances
- Headaches, confusion
- Paradoxical reactions (e.g., aggressive behavior, hostility, hallucinations, disinhibition, excitation, irritability and increased anxiety)
- Slowing down of breathing (respiratory depression)

Intravenous injection can also cause local irritation of the skin at the injection site, which can result in red and itchy areas of the skin.

Propofol used in DISE contains egg lecithin, soybean oil, and glycerol, and the risk of allergy is particularly high if the participant is allergic to these.

Other side effects associated with DISE include the following:

- Nose bleeding
- Trauma to the upper airway
- Suspension of breathing episode
- Light-headedness
- Pain or irritation in the throat or nasal passage

2.6.6 Risks Associated with Pregnancy

The general anesthesia performed for the implantation surgery may present risks for the embryo if the participant is pregnant. In addition, the effects of the Genio® System 2.1 on the unborn child and on the newborn are not known. Because of this, a participant cannot be implanted if pregnant, trying to become pregnant, or breast-feeding.

If a participant gets pregnant after being implanted, the device should remain OFF until the participant stops breastfeeding.

2.7 Storage and Handling

2.7.1 Storage Temperature

External system components should be stored in a clean area with room temperature of approximately +15 °C to +27 °C / +59 °F to +81 °F.

Do NOT expose the products to direct sunlight.

2.7.2 Humidity

Keep the Genio® external devices away from extremely humid areas and sources of water.

2.7.3 Expiration Date

The Disposables Patches should not be used after the expiration date. Expiration date is indicated on component's packaging labels.

2.7.4 Handling

The components of The Genio® System 2.1 should be handled with care.

- The metal connectors at the bottom of the Activation Chip should not be in contact with any surface but the Disposable Patch, the Charging Unit docking area or the Activation Chip protection cover.
- The devices should not be placed on any metallic surfaces.
- Make sure to close the zipper of the bag containing the new Disposable Patches, to avoid any moisture/humidity that may affect the adherence properties of the patches.

2.7.5 Transportation of Device

Respect the following package and transport conditions of the different components:

- Always transport the Activation Chip in its protective cover
- Do not fold the Disposable Patches before use
- Disconnect the Charging Unit from its adapter
- Disconnect the Repeater from its adapter

2.8 Wireless communication

Communication Interference between the repeater and the activation chip may be temporarily disturbed by other wireless devices or proximity of the Genio® system components to large metallic surfaces. To reduce or stop interference, move the Repeater and Genio® AC away from the source or the metallic surface. The effect is temporary and will not damage the system.

This device complies with part 15 of the FCC Rules (FCC ID: 2A6HG-NX-ASM-002325). Operation is subject to the following two conditions: (1) This device may not cause harmful interference, and (2) this device must accept any interference received, including interference that may cause undesired operation.

NOTE: "Harmful interference" is defined in 47 CFR §2.122 by the FCC as follows: Interference which endangers the functioning of a radionavigation service or of other safety services or seriously degrades, obstructs, or repeatedly interrupts a radio communication service operating in accordance with the [ITU] Radio Regulations

3 Description of the Genio® System 2.1

The Genio® System 2.1 is an implantable neurostimulation system comprised of one implanted device, the Implantable Stimulator (IS), and of the following external devices:

- The Genio® External Stimulator (ES)
- The Genio® Activation Chip (AC), model #2364
- The Genio® Disposable Patch (DP)
- The Genio® Charging Unit (CU), model # 2238
- The Genio® Smartphone App (Optional)
- The Genio® Sleep Lab Application (running on a Raspberry-Pi mini-computer (Repeater))

Figure 2 below provides a schematic illustration of the relationship between The Genio® System 2.1 components.

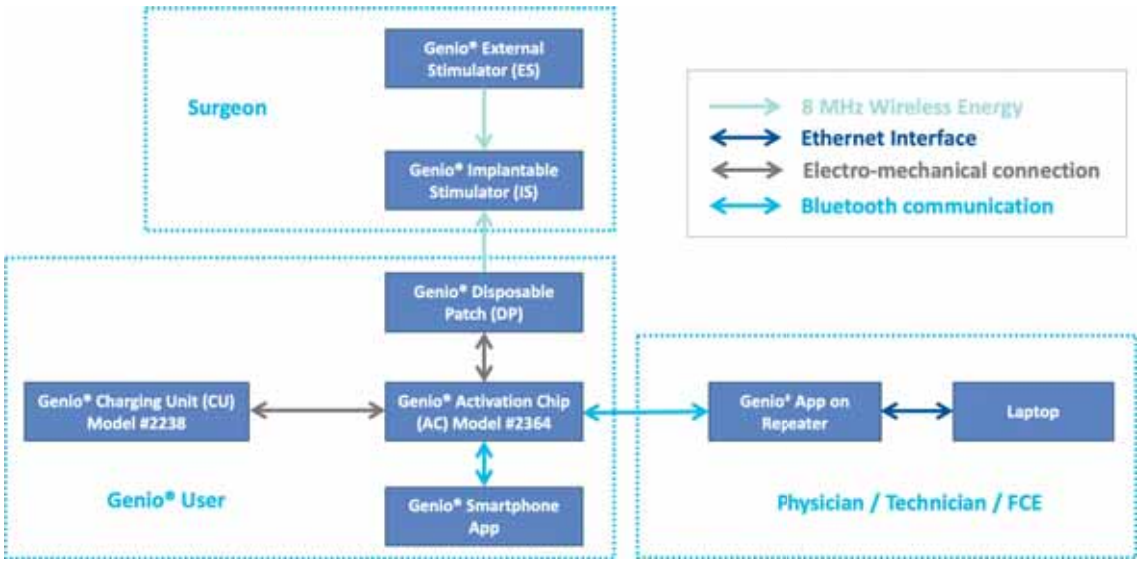


Figure 2: Relationship between Genio® System 2.1 components and users

The IS is a neurostimulation device implanted in the chin area via a minimally invasive surgical procedure and positioned over the genioglossus muscle with its electrodes facing both left and right hypoglossal nerve branches. Stimulation of the hypoglossal nerve causes the tongue muscles to contract with the intention to maintain an open airway. During the implant procedure, the ES is used to enable the surgeon to activate the implant in order to verify its functionality and optimal placement.

In order to stimulate the nerve, the IS receives energy pulses transmitted by the AC which is attached to an adhesive DP placed under the chin of the participant. The AC contains a rechargeable battery and the participant-specific stimulation parameters. The battery of the AC is charged on a daily basis using the CU. Users can also control their treatment and access some usage data using their Genio® Smartphone App.

The Genio® Sleep Lab Application is used in the sleep laboratory by a Nyxoah FCE under the direction of the Investigator. The software is used to change the stimulation parameters set on the AC, installed

on a Repeater, and communicating with the AC via Bluetooth. The repeater, positioned close to the participant, is connected via Ethernet cable to a laptop to enable the user to configure the AC from a distance (for example, from the control room during sleep studies).

Prior to going to sleep, in order to activate the stimulation, the participant places the DP, connected to the AC, under the chin (see Figure 3.a). In the morning, the participant discontinues the stimulation by removing the DP and the attached AC (see Figure 3.b). The participant is instructed to save all used patches in a re-sealable zipper storage bag for return at the next doctor's visit and to place the AC in the CU for daily charge.

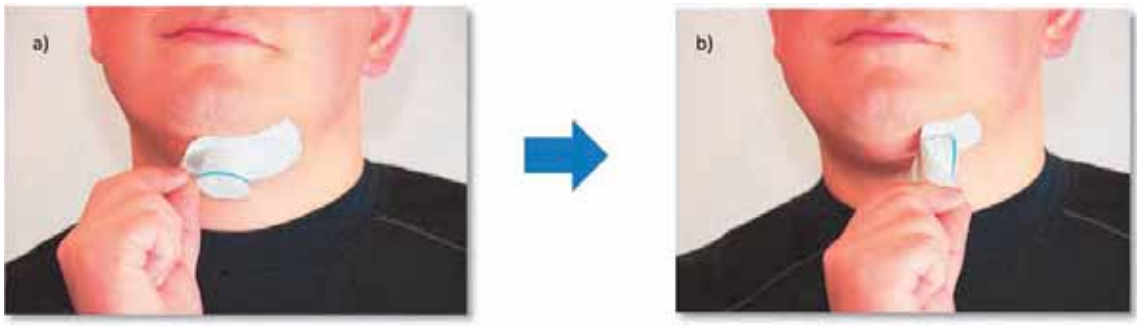


Figure 3: Daily use of the Genio® System 2.1

3.1 Genio® Implantable Stimulator

The IS (see Figure 4) is a small bilateral implant that consists of two pairs of stimulating electrodes (one on each side of the device), electronics, a receiving antenna in the center and 4 suturing pads positioned on the IS legs. The IS does not include a battery.

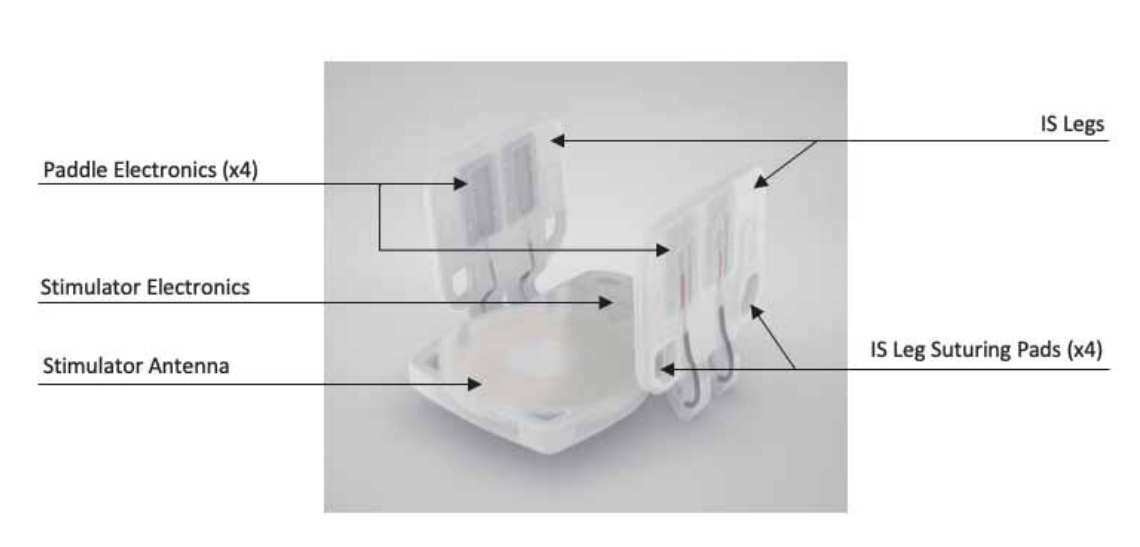


Figure 4: Genio® Implantable Stimulator

The IS is provided sterile and is the only implantable component of the Genio® System 2.1. This device is coated with a medical grade silicone material and the entire coating is sealed with Parylene to prevent

damage to the device from biological fluids. The electrodes' aperture area is purposely left uncoated to ensure good transmission of stimulation energy to the tissue.

3.2 Genio® External Stimulator

The ES (see Figure 5) is a single-use, sterile accessory that is used only during the implantation procedure. This device is comprised of a power button, a stimulation indicator, a retraction mechanism to adapt the IS-ES distance, an antenna, Li-Ion battery and electronics for electromagnetic power transmission.

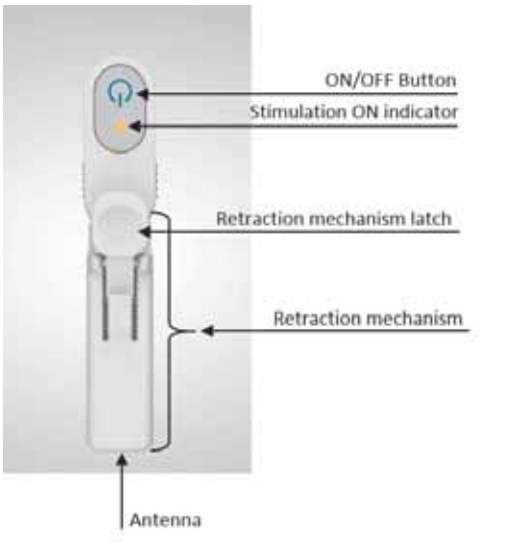


Figure 5: Genio® External Stimulator

3.3 Genio® Activation Chip (Model #2364)

The AC (see Figure 6) is a microprocessor that stores the participant-specific stimulation parameters programmed by the sleep physician. The AC contains a rechargeable Li-Ion battery, electronics for Bluetooth communication and electromagnetic power transmission and memory for storage of stimulation parameters.

Figure 6: Genio® Activation Chip, model #2364

3.4 Genio® Disposable Patch

The DP (see Figure 7) is a single-use biocompatible adhesive patch that is placed each night by the participant under the chin above the implant's incision site prior going to sleep. The AC fits onto the DP and allows the activation of the IS by transferring energy wirelessly.

The DP is comprised of a flexible Printed Circuit Board (PCB) (the antenna) and an adhesive patch made of porous, highly breathable, elastic multilayer polyurethane/synthetic nonwoven material coated on one side with a hypoallergenic, pressure sensitive adhesive.

Figure 7: Genio ® Activation Chip and Genio® Disposable Patch

3.5 Genio® Charging Unit (model #2238)

The CU (see Figure 8) and its power adapter are used to charge the AC during the day, in order to be ready for the next night. The CU is comprised of a docking area to plug the AC in, a power LED indicator and a micro-USB port to connect the power adapter. It is powered by 100V-240 V/50-60 Hz and provides a regulated 5 VDC output.

Figure 8: Genio® Charging Unit with Activation Chip

3.6 Genio® Sleep Lab Application

The Genio® Sleep Lab Application is used in the sleep laboratory by a Nyxoah Field Clinical Engineer (FCE) under the direction of the Investigator to configure the AC stimulation parameters. This remote application, called Genio® Sleep Lab Application, runs on a small mini-computer (called Repeater) and uses low energy Bluetooth protocol to enable the operator to configure/customize the AC stimulation parameters from a distance.

Once the AC is connected to a DP, the Genio® App can be used to perform AC check-ups, to read usage data stored in the AC and to program/adjust the stimulation parameters.

4 Titration Procedure

Activation Visit

After approximately eight weeks of wound healing post-surgery, the participant will return to the hospital for implant activation. The AC will be configured while the participant is awake, to validate comfortable stimulation parameters. During this visit, the participant will receive a Patient Kit and will be trained to use the Genio® System 2.1 according to the Participant Manual (Doc ID: LAB-0001673). This Patient Kit contains an AC, a CU, DPs, a Participant Manual and a Quick Set Up Guide. At the end of this activation visit, the device will be programmed with the participant's parameter settings defined during the wakeful titration. The participant will be sent home and will be asked to use the device during the day and/or night in order to get used to the stimulation.

Titration Visit(s)

In order to optimize participant's therapy, the participant will return to the hospital for titration visit(s) as per protocol. The stimulation parameters will be refined during wakeful and/or asleep (during sleep study, namely polysomnography (PSG)) sessions until reaching the settings that do not wake the participant and maintain upper airway potency, oxyhemoglobin saturation, and sleep continuity.

First, a **wakeful titration** is performed according to the Therapy Optimization Guidelines while the participant is awake. The goal of the wakeful titration is to identify the following stimulation thresholds:

- Motor threshold – when motion of the muscle/tongue is first noted by the physician,
- Uncomfortable/Pain threshold – when stimulation becomes unpleasant or even painful.
- Lower and upper amplitude limits – Allowing the patient to adjust the intensity of the stimulation using their Smartphone application.
  Note: Lower and upper amplitude limits are for use in the user's Smartphone application.

For a **PSG titration**, the PSG equipment will be setup and the participant sent to bed following which the recording starts. The stimulation will start after the participant is asleep. The electrical stimulation parameters will be refined according to the Therapy Optimization Guidelines until reaching the settings that do not wake the participant and maintain upper airway potency, oxyhemoglobin saturation, and sleep continuity. Once done, these optimal settings will be maintained over the entire night and PSG and respiratory parameters will be recorded until participant's final wake-up. During the night, it may be necessary to perform further adjustments of electrical stimulation parameters. In the morning, the device will be programmed with the participant's optimal stimulation settings and the participant will be sent home to use The Genio® System 2.1 during sleep.

For wakeful and PSG titrations, The Genio® System 2.1 needs to be set up in order to program and modify AC stimulation parameters. These steps are detailed in the following.

4.1 Genio® System 2.1 Set Up

The Genio® System 2.1 set up includes different steps, all being described in the following sections (4.1.1 to 4.1.4):

1) Charging of the AC
2) Set up of the Repeater
3) Set up of the AC/DP
4) Start-up of the Genio® Sleep Lab Application

An overview of the system set up is presented on Figure 9.

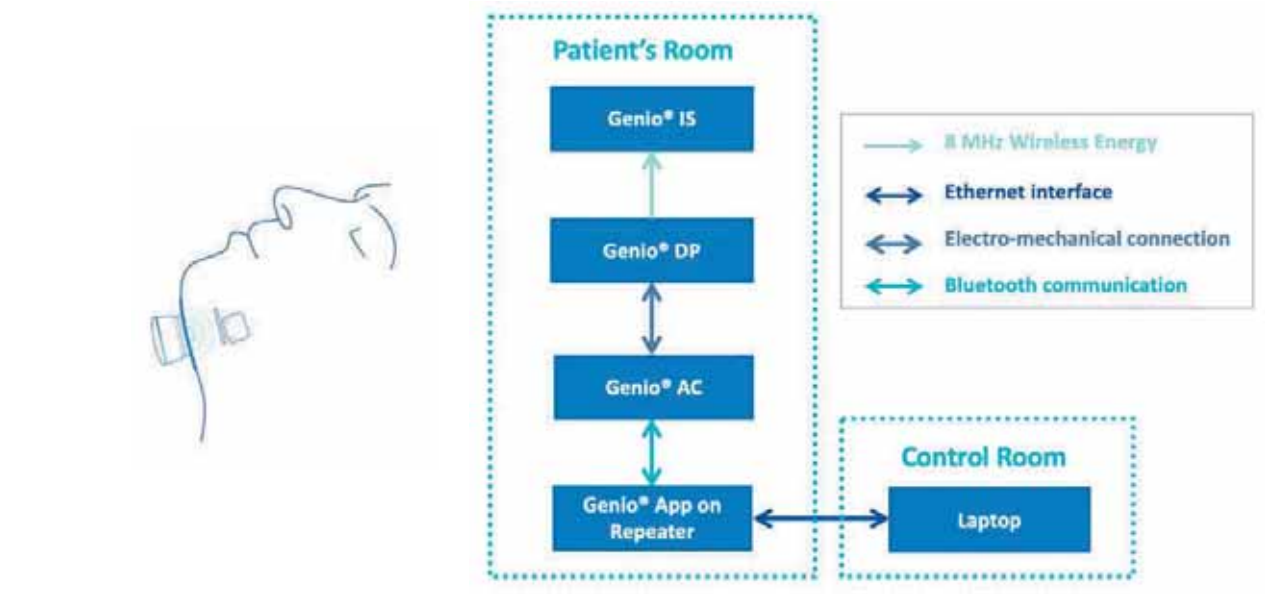


Figure 9: Overview of the Genio® System 2.1 set up for a titration session

Prior to the participant's arrival, verify the following equipment is ready, charged as required and available (this list includes back-up devices):

- 2 Repeaters and their power cord
- 2 Laptops and their charger
- 2 Ethernet adapters[1]
- Repeater/Application password list
- 4 Ethernet cables of appropriate length
- 2 CUs and their chargers
- 1 box of 15 DPs
- 1 Technical Sleep Lab Manual
- 2 ACs[2]

4.1.1 Charging of the Activation Chip

For an activation visit or if a new AC needs to be supplied to the participant, the physician/technician needs to fully charge the AC prior to participant's arrival by following the steps described in this section. For a titration visit, the participant will be asked to bring their fully charged AC. At participant's arrival, the AC battery level using the Genio® Sleep Lab Application is verified (see section 4.1.4).

In order to charge the AC:

[1] If the laptops do not include an ethernet port, specific adapters should be used.
[2] AC is provided in the Patient Kit as a standard component. Nevertheless, it is advised to have two back-up ACs.

1) Connect the appropriate country specific supplied plug to the CU power adaptor (see Figure 10).

Figure 10: Charging Unit, Charging Unit adaptor and country-specific plugs

2) Carefully connect the CU to the power adapter supplied by Nyxoah and place it on a firm surface.

⚠ Battery Precautions: (1) Use ONLY the supplied Nyxoah charger and its power adapter. Any other power supply may damage the devices. (2) Do NOT use/store the devices nearby heating sources or under the blazing sun. (3) Do NOT open device housing.

3) Connect the power adapter to a power outlet. The lights on both the adapter and the CU should turn green upon connection to power (see Figure *10*).

Note: If the adapter (CU) LED does not turn ON, it means that the adapter (CU) may not be properly connected to the power outlet (power adapter).

Figure 11: Charging Unit and power adapter light upon connection to power

4) Remove the AC from the protective cover by gently pushing down one of the three tabs using one hand and pulling out the AC with the other hand (see Figure 12).

⚠ Do NOT touch the metal pins on the bottom of the Activation Chip and do NOT place these metal pins on any surface.

Figure 12: Removal of the AC from its protective cover

5) Place the AC in the docking area of the CU.

⚠ Do NOT use excessive force when inserting AC in the CU or when removing it.

6) Verify the AC green LED flashes (see Figure *13*, indicating that the AC battery is charging. Charging may take up to three hours.

Figure 13: Blinking Activation Chip LED upon connection to the Charging Unit, indicating charging.

Note:

- *If the AC green LED stays constantly ON, it means that the AC battery is fully charged.*
- *If the AC LED does not turn ON even though the CU LED is ON, it may indicate that the AC is malfunctioning. In this case, contact Nyxoah.*

7) Once the AC is fully charged, its green LED turns constantly ON (see Figure 14), indicating that the AC is ready for use.

⚠ Do NOT touch the metal connectors on the bottom of the AC and do NOT place these metal connectors on any surface.

⚠ In case the AC was dropped, check if any damage is observed. If damaged, contact Nyxoah.

⚠ When the AC is not in use, place it either in its protective cover or in the CU docking area.

Figure 14: Constant Activation Chip LED upon charging completion.

Note: For more detailed information regarding the AC, CU and power adaptor LED indications, see Appendix A, Table 4, Table 5, and Table 6, respectively.

4.1.2 Set Up of the Repeater

To configure the AC parameters, an application (Genio® Sleep Lab App) is needed. The Genio® Sleep Lab App is installed on a supplied mini-computer called a Repeater, that is connected via an ethernet cable, to a laptop. The laptop serves as a screen for the Repeater.

Follow these steps to set up the Repeater:

1) Connect an Ethernet cable to the (see Figure 15).

Figure 15: Repeater connected to Ethernet cable

2) Connect the Repeater to the laptop using one or two Ethernet cables depending on the sleep lab configuration:
   (a) **With one Ethernet cable**; the length of the cable should accommodate the distance between the participant's room and the control room. Connect one end of the Ethernet cable to the laptop (using an adapter if applicable) and the other end to the Repeater.
   (b) The other option is to use the **Ethernet wall network**. For this set up, two Ethernet cables are needed. Connect one end of the first Ethernet cable to the laptop and the other one to an Ethernet wall plate in the control room. Connect one end of the second Ethernet cable to the corresponding Ethernet wall plate in the participant's room and the other to the Repeater Ethernet port. **If available, this option should be preferred as it avoids having a cable going from the control room to the participant's room.**

3) Connect the supplied Repeater to the power outlet (see Figure 16). It will take approximately 2 minutes for the repeater to be ready for use.

Figure 16: Repeater connected to Ethernet cable and power cable

Note: If more than one participant is in for a PSG titration during the same night, the operator can connect more than one Repeater to a single Laptop using an Ethernet switch. For more detailed information, see Appendix B.

4) Connect the laptop to the power outlet using its charger and turn laptop on.

4.1.3 Set Up of Activation Chip and Disposable Patch

The steps to set up the AC and DP are listed below:

1) In order to reset the AC, place it in the CU docking area while the CU is connected to the power outlet and remove it. Once removed, the red/yellow/green LED of the AC blink sequentially, indicating that it has been reset and is ready to be used.

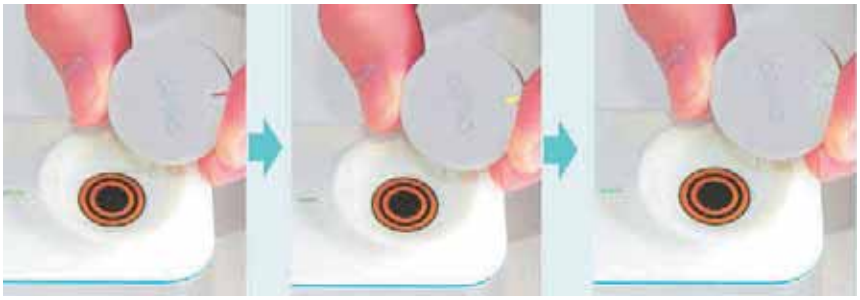


Figure 17: Red/Yellow/Green LED Indications on the Activation Chip following reset in the Charging Unit

Note: For more detailed information regarding the AC, CU and power adaptor LED indications, see Appendix A, Table 4, Table 5, and Table 6, respectively.

2) The Activation Chip light will then start blinking as follows until a Disposable Patch is connected:
    A. If the blinking light on the AC is green (see Figure 18.1), it means the AC is charged and ready to be connected to a Disposable Patch.
    B. If the blinking light on the AC is yellow (see Figure 18.2), it means the battery of the AC is low and needs to be re-charged before being used for an entire night.

C. If the blinking light on the AC is red (see Figure 18.3), it means the AC is malfunctioning. The Genio® system cannot be used before the chip is replaced. If this occurs, contact Nyxoah as soon as possible.

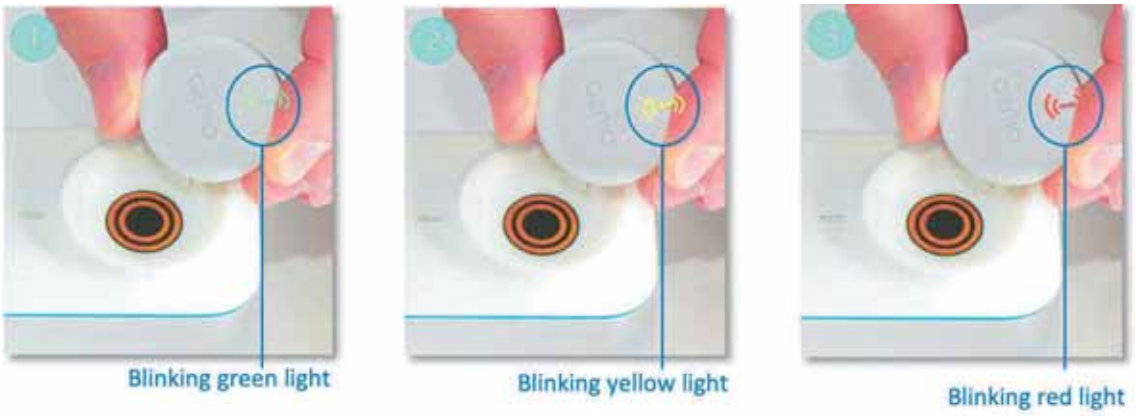


Figure 18: Different blinking AC LED scenarios following AC reset

3) Place the DP on a firm surface and connect the AC to the DP.

⚠ Do NOT place the DP on a metallic surface or near any type of metal. Attempting to attach the AC while the DP is close to a metal may cause device malfunction.

Do NOT use excessive force when connecting the AC to the DP.

Note: The connection between the AC and the DP must be performed within 5 minutes after the AC reset (while the AC green LED is blinking), otherwise, it should be reset again according to step 1.

4) Verify that the AC LED turns ON for about 5 seconds when connecting the AC to the DP, indicating they are properly attached.
   a. If the AC light is green (see Figure 19.A), it means the AC battery is charged and ready for a full night of use.
   b. If the AC light is yellow (see Figure 19.B), the Activation Chip battery is low and needs to be charged to ensure operation throughout the entire night.

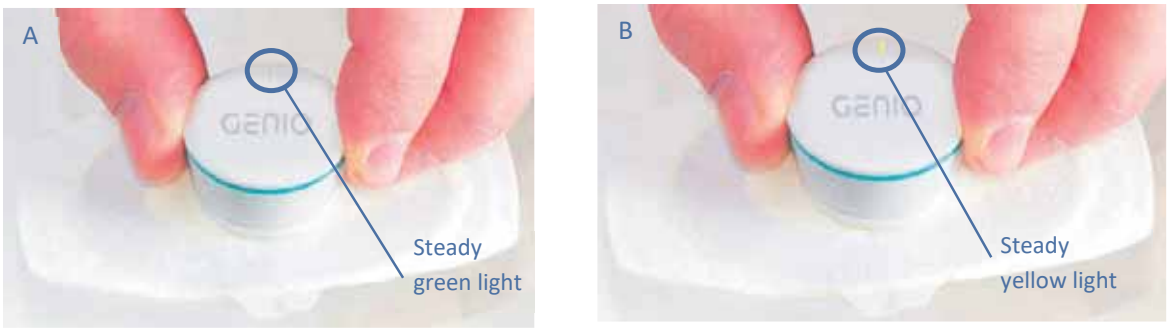


Figure 19: Constant green or yellow AC light displayed upon DP connection

Note: If the AC light does not turn ON when connecting it to the DP, reset the AC by placing it in the docking area of the CU and remove it. The AC red/yellow/green LEDs should blink sequentially. If not, verify that the AC is fully charged. If problem remains, contact Nyxoah.

4.1.4 Start-up of the Genio® Sleep Lab Application

Once the system is set and the participant is ready:

1) Open the Laptop and launch the Chrome browser.
2) The repeater, and therefore the Genio® Sleep Lab Application, can be accessed using one of the following options:
   - In the browser's address bar, by typing in the following address (see Figure 21): http://AAA.BBB.CCC.DDD:8000

Note: AAA.BBB.CCC.DDD refers to the IP address specific to each repeater and provided with it (see example on Figure 21).

Figure 20: Chrome browser (Example for a specific repeater with IP 169.254.109.162)

   b. By clicking on the Genio® Sleep Lab Application bookmark, saved beforehand in your browser.

Note: In order to add a shortcut to the Genio® Sleep Lab Application in your browser, click on the Bookmark icon in your Chrome browser (see Figure 22). ***Note that this bookmark will be specific to the repeater in use.***

Figure 21: Bookmarking the Genio® Repeater for quick access

3) The Genio® Sleep Lab Application login screen will be displayed.
4) Enter the supplied application password (see Figure 23) and press "Submit".

Figure 22: Enter application password tab

Note: When refreshing the Genio® Sleep Lab application window, session will be terminated and will require entering the application password and restarting the session.

5) Enter the operator's name (see Figure 24) and press "Next".
Note: If not used for the first time, the App automatically suggests the last operator's name entered under the "Next" button (see Figure 24).

Figure 23: Enter operator name tab

6) Select the site code and press "Select" (see Figure 25).

Figure 24: Site selection tab

Note: If the desired site code is not available in the predefined list, create a new site by clicking "Create New Site", typing in a site code in the opened pop-up message, and clicking OK (see Figure 26). The new site will be added to the Site List (Figure 27). Select the relevant Site number and click "Select".

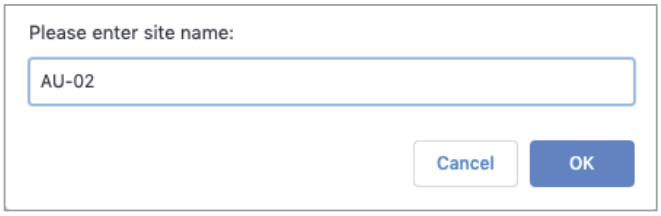


Figure 25: Creating a new site

Figure 26: New site added

Note: A "Test Mode" button is also available, allowing the operator to skip the steps of selecting a site code, participant number, and a visit (steps 7, 8, and 9 below). This test mode can be used for testing purposes, not in a formal clinical session.

7) Select the participant number in the predefined list and press "Select" (see Figure 28).
Note: If the desired participant number has not been created yet, click on "Create Patient" (see Figure 28). Enter the patient number in the new patient window (see Figure 29) and confirm your selection. The new Patient ID will be added to the patient's list (Figure 30). Select the relevant patient ID and click "Select" to continue.

Note: Participant number has to be composed of numerical values (between 1 and 999) otherwise an error message appears.

Figure 27: Choose participant

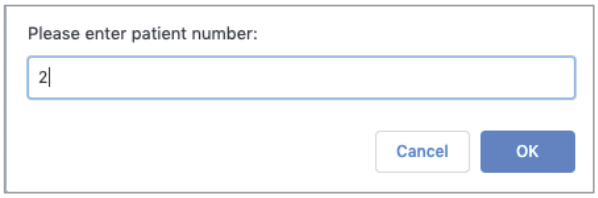


Figure 28: Creating new participant

Figure 29: New participant added

8) Select the Visit Type from the predefined list and press “Select” (see Figure 31). In case the visit type does not appear in the list, a new visit type can be created by pressing “Create Visit Type” (see Figure 31), typing a new visit type in the opened message, and clicking OK.

Figure 30: Choose visit type

9) Enter the visit date and time (see Figure 32) as well as the visit type (see Figure 31) and press "Select".

Note: By clicking on the calendar icon on the right, a calendar will appear and enable the selection of the applicable date and time (see Figure 32).

Figure 31: Choose visit date and time

Figure 32: Choose visit type

Note: During the session setup, the user can:

- *Go back to the previous tab by pressing "<" (see Figure 34, item 1),*

- *Skip setup by pressing the "Skip Setup" button (see Figure 34, item 2).*

Figure 33: Options of the setup tabs navigation

10) The main screen will open (see Figure 35) and allow the operator to pair and connect an AC to initiate the session.

Figure 34: Application main screen

11) To pair and connect the App with an AC, scan the ACs available near the repeater by clicking on the "scan" button (see Figure 36, left).

Note: If you click on the Bluetooth (BLE) icon before scanning for available ACs, a message will be displayed to instruct you to look for ACs first (see Figure 36, right).

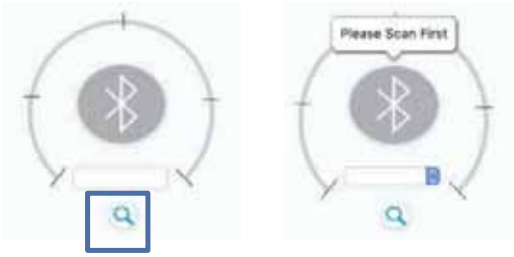


Figure 35: (Left) AC Scan button and (Right) Error message when BLE button pressed before scanning for ACs

12) The Genio® App will scan the repeater's surroundings to look for available ACs. At the end of the scanning process, the Application will display the serial number of one of the detected ACs above the scan button (see Figure 37).

Figure 36: (Left) AC Scanning in process (Right) AC Scanning completed

Note: In case the designated AC is not found, try scanning for available ACs again. If the AC does not appear in the list of the found ACs, make sure it is charged and properly connected to the DP. If the AC is charged and connected to the DP, reset the AC and restart scanning. If no AC is found after restarting the scan, reset the repeater by disconnecting it and reconnecting it to the power, repeat login process and scan for available ACs.

13) To choose the desired AC and connect it to the App, click on the AC serial number to display the list of all identified ACs in proximity to the repeater (see Figure 38).

Figure 37: List of available ACs in proximity to the repeater

Note: Every charged AC which is connected to a DP and positioned near the repeater can be detected by the App. In order to connect to the appropriate AC, make sure to choose the correct AC by verifying that its serial number displayed on the device label corresponds to the AC number displayed in the App.

14) Select the relevant AC serial number in the list, and click on the BLE icon to pair the AC and connect it with the application. The BLE icon will turn blue and the quality of the BLE communication will be represented by the green bar arround the BLE level (green = good connection, yellow = low quality connection, red = high risk of disconnection).

Note: Connection to an AC may take up to 30 seconds. In case connection has not been established after waiting the appropriate time, retry by clicking on the BLE icon.

15) Upon connection, AC stimulation parameters will be automatically read, and the AC battery level will be displayed (see Figure 39).

Note: For an activation visit or when a new AC is given to a patient, the AC real-time-clock (RTC) should be verified, and if needed, calibrated before being handed over to the patient. To calibrate the AC RTC, see Appendix D, step e.

Figure 38: AC Connected to application

16) Remove the DP protective liner in order to place the AC/DP under the participant's chin. The incision scar and the middle of the chin can be used as a reference point for optimal placement. Please refer also to the Participant Manual (Doc ID.: LAB-0001673) for full instructions related to DP placement.

Figure 39: AC/DP placement under the participant's chin

⚠ For male participants, before placing the DP, make sure the area under the participant's chin is carefully shaved. The DP works better on skin that has been shaved within the last 17 hours.

⚠ Before applying the DP, carefully wash off all facial creams on the participant's chin. Residual cream on this area may lead to system malfunction.

The setup is now completed, and the titration session can start!

4.1.5 Content of the Genio® Sleep Lab App main window

This main tab of the Application gives access to the following:

- **About:** Information about the Genio® Sleep Lab Application, including software version and legal statements.
- **Session summary:** The session summary information symbol "🛈" enables access to the current session's site number, participant number, visit date and visit type (see Figure 40). Visit date and type can be modified by pressing their respective "Edit" buttons (see Figure 40).

Figure 40: Session summary available via information symbol

Note: : In case of editing the visit date, the Genio® App will prompt messages for editing the year, month, day and session time. Use the same format as the session date as appears in the Session Summary window.

- **Usage Information**:
  The total time (see Figure 41), defined as the duration since session start (in HH:MM:SS format).
  The activation time (see Figure 41), defined as the total stimulation duration since stimulation start (in HH:MM:SS format).

Figure 41: Session Timers

Note: Timers will freeze in case the laptop's screensaver is active for a few minutes and the laptop enters sleep mode. When resuming the session, the timers will continue running from the same point.

Note: The activation timer will start when the AC is programmed to LAB mode, or when the AC is programmed to HOME mode after the delay ends. In case the AC is connected to the App and not reprogrammed, a deviation between the activation timer and actual stimulation duration may occur.

- **AC information:** The AC information symbol "ⓘ" enables access to the AC serial number (SN) and AC SW version (see Figure 42).

Figure 42: AC information

Note: In case the AC information does not appear in the AC information window, disconnect the AC by clicking on the BLE icon and reconnect it by clicking the BLE icon

again. This may happen when the AC is automatically reconnected to the App after being unintentionally disconnected.

- **Bluetooth information and status:** The Bluetooth level is displayed. The Bluetooth level gives an indication of the communication quality between the AC and the repeater. If the AC is connected, the Bluetooth button turns blue and the AC battery level is displayed. If not connected, the Bluetooth button appears in grey. Bluetooth communication can be disabled/enabled by pressing the Bluetooth button. To look for other ACs, 1) press the Bluetooth symbol to disconnect the currently connected AC, 2) press the Scan button "🔍", 3) click on the displayed AC SN, 4) select an AC from the found ACs list and 5) click on the Bluetooth button to connect the new AC.

4.2 Wakeful and PSG Sessions

The current section presents the AC parameters and describes the different steps to follow for titration visits, including reading and analyzing the AC Log, reading and configuring AC parameters and finally, closing a visit/session.

4.2.1 Activation Chip Parameters

Figure 45 shows the basic stimulation pattern delivered to the hypoglossal nerve by the Genio® System 2.1. It is comprised of a confirmatory train, characterized by its amplitude (c) followed by a delay period (d) during which the nerve is not stimulated in order to allow the participant to fall asleep.

After this delay time, the stimulation turns ON. The stimulation pattern is comprised of alternating ON and OFF phases. The lengths of these ON and OFF phases are respectively called Train Length (L) and Train Interval (i).

The ON phase of the stimulation train is made of successive stimulation pulses characterized by their amplitude (a), duration (p) and interval (r). To help the participant build up tolerance to the stimulation, the participant also has the ability to modify their pulse amplitude, using their Genio® Smartphone App, within a ranged defined by the sleep technician or sleep physician i.e., the highest and lowest amplitude limits. At the end of the visit, the treatment amplitude will be set at the lowest amplitude limit and the participant will be instructed to gradually increase the amplitude, the goal being to reach the highest amplitude limit by the next titration visit.

Two other important parameters are the pulse frequency and the duty cycle. The pulse frequency is the number of pulse repetitions in 1 second and depends on the pulse duration (p) and pulse interval (r). The duty cycle is the percentage of the time during which the stimulation is ON and depends on the train length (L) and train interval (i) $\left(DC\ [\%] = \frac{L}{L+i}.100\right)$.

All these parameters and their units are summarized in Table 1.

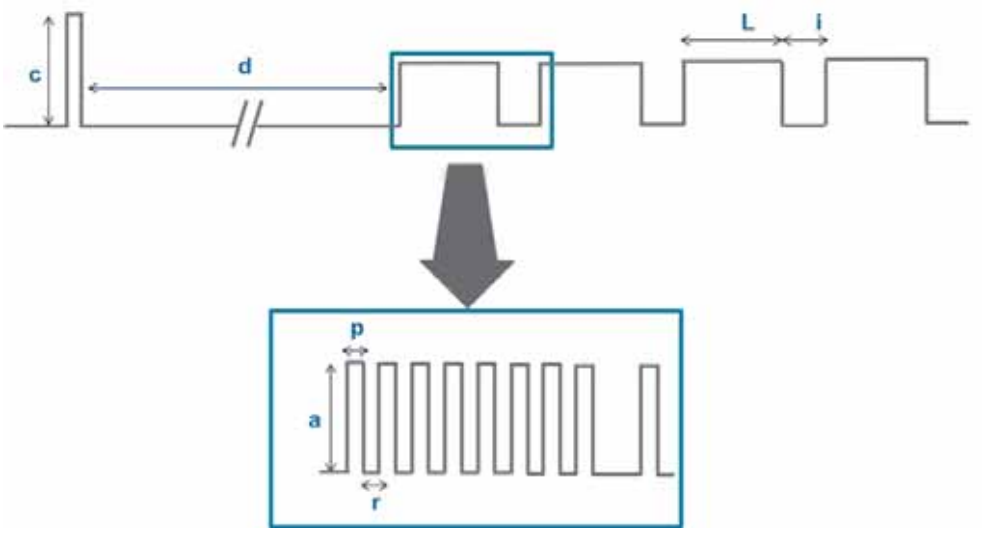


Figure 43: AC stimulation pattern and parameters

Table 1: AC stimulation parameters and their respective units

Stimulation Parameters	Meaning
Confirmatory Train (c)	Amplitude of the test train triggered upon AC/DP connection [%]
Delay Time (d)	Time before the beginning of the stimulation [min]
Train Length (L)	Duration of the stimulation train [sec], also known as "ON time"
Train Interval (i)	Duration between two stimulation trains [sec], also known as "OFF time"
Pulse Duration (p)	Duration of single stimulation pulse [µsec]
Treatment Amplitude (a)	Amplitude of the pulse, given as a percentage of total system output [%]
Highest Amplitude Limit	Upper amplitude limit that the user can set using the Smartphone App [%] *Note: Value ≥ Treatment Amplitude*
Lowest Amplitude Limit	Lower amplitude limit that the user can set using the Smartphone App [%] *Note: Treatment Amplitude ≥ Value*
Pulse Interval (r)	Duration between two stimulation pulses [µsec] *Note: this value is not configurable in the Genio® Sleep Lab App, and is defined by the Pulse Frequency and Pulse Duration*
Pulse Frequency (f)	Number of stimulation pulses per second [Hz]
Duty Cycle (DC)	Percentage of the stimulation during which the stimulation is ON [%]

In order to facilitate therapy acceptance, two additional features can also be activated, namely the "Ramp-up at stimulation onset" and the "Ramp within stimulation train".

The ramp-up at stimulation onset (see Figure 44.a) consists of a gradual increase in the stimulation amplitude from one stimulation train to another until reaching the target amplitude (see Figure 45, stimulation amplitude, "a") in order to avoid waking up the participant once the stimulation starts. This feature includes one configurable parameter, namely "Duration", i.e., a period of time (in minutes) just after the delay time during which the amplitude will increase gradually until the target amplitude is reached.

The ramp within stimulation train (see Figure 44.b) will start after the delay time or after the ramp-up at stimulation onset, if applicable. This feature is composed of three configurable parameters:

- The ramp-up duration
- The hold duration
- The step-down amplitude

The Ramp-Up Duration is defined as the time (in msec) it will take for the stimulation amplitude to ramp up to the target amplitude. This target amplitude will be maintained for a certain duration called Hold Duration (in msec) after which it will be decreased down to the defined Step-Down amplitude (in %). This feature's purpose is to increase therapy acceptance by gradually increasing the amplitude up to the target amplitude (in order to open the upper airway without waking up the participant), to hold this target amplitude for a shorter period of time and then decrease the amplitude without compromising airway opening as the force needed to maintain the upper airway open should be lower than the one needed to open a closed upper airway.

The operator can decide to activate none, one or both ramp features. All the parameters related to the ramp features are summarized in Table 2.

Table 2: AC ramp parameters definition and respective units

Ramp Parameters	Meaning
Ramp-up at stimulation onset – Duration	Duration of the gradual increase of the amplitude at stimulation onset [min]
Ramp within stimulation train – Ramp-Up Duration	Duration of the gradual increase of the amplitude within each stimulation train [msec]
Ramp within stimulation train – Hold Duration	Duration of the period during which the target amplitude is maintained within one stimulation train [msec]
Ramp within stimulation train – Step-Down Amplitude	Decreased stimulation amplitude within one stimulation train [%] *Note: Lowest Amplitude Limit ≥ Value*

(a)

(b)

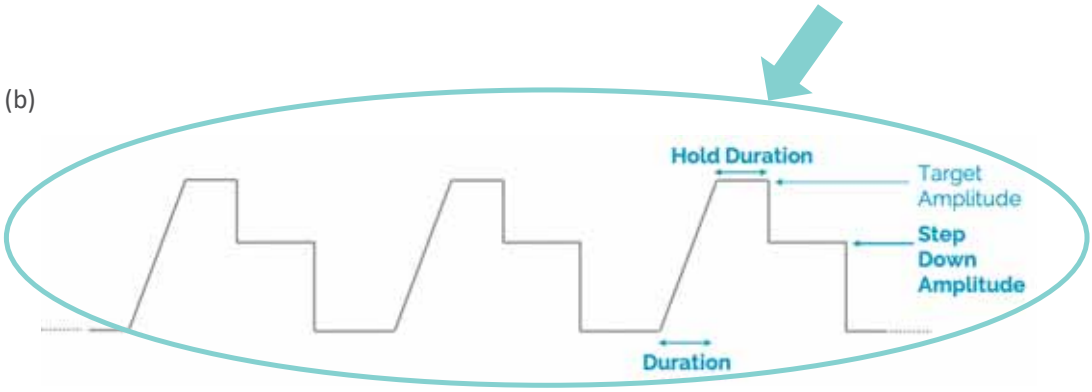


Figure 44: (a) Ramp-up at stimulation onset and (b) Ramp within stimulation train

4.2.2 Activation Chip Configurable Parameters

The AC parameters that can be configured using the Genio® Sleep Lab Application are the following (see Figure 45): Stimulation Mode, Pulse Frequency, Pulse Duration, Treatment Amplitude, Lowest Amplitude (i.e., Baseline amplitude), Highest Amplitude Limit (i.e., Target amplitude) Train Length, Train Interval, Delay Time, Confirmatory Train and the 4 ramp parameters.

The Total Cycle Length and Duty Cycle are automatically calculated by the Genio® Sleep Lab Application and displayed once the other parameters are set (see Figure 46).

Table 3 summarizes the AC parameters that can be modified using the Genio® Sleep Lab App, their meaning, their range and value increments.

Figure 45: AC parameters configurable through the Genio® Sleep Lab Application

Figure 46: AC Parameters automatically calculated by the Genio® Patient Application, Total train length and Duty Cycle

Table 3: Description and values of AC parameters configurable through the Genio® App

Configurable Parameters	Meaning	Ranges	Available Values
Stimulation Mode	Mode of the stimulation	HOME –Stimulation begins after a defined delay time LAB – Stimulation begins immediately	N/A
Pulse Duration [µsec]	Duration of single stimulation pulse	50-250 µsec	10 µsec
Pulse Frequency [Hz]	Number of stimulation pulses per second	30-50 Hz	5 Hz
Train Length [sec]	Duration of a stimulation train or of a series of stimulation pulses	0.2-5 sec	0.1 sec
Train Interval [sec]	Duration between two stimulation trains	0.2-5 sec	0.1 sec
Treatment Amplitude [%]	Amplitude of the pulse, given as a percentage of total system output	1-100%	1%
Lowest Amplitude Limit [%]	Lowest pulse amplitude that the user can set using the Genio® Smartphone App, given as a percentage of total system output	1-100%	1%
Highest Amplitude Limit [%]	Highest pulse amplitude that the user can set using the Genio® Smartphone App, given as a percentage of total system output	1-100%	1%
Delay Time [min]	Duration between AC/DP connection and the beginning of the stimulation	0-60 min	5 min
Confirmatory Train [%]	Amplitude of the test train emitted immediately after AC/DP connection as a percentage of total system output	1-100%	1%
Ramp-up at stimulation onset – Duration [min]	Duration of the gradual increase of the amplitude at stimulation onset	0-30 min	5 min
Ramp within stimulation train – Ramp-up Duration [msec]	Duration of the gradual increase of amplitude within each stimulation train	0-1000 msec	50 msec
Ramp within stimulation train – Hold Duration [msec]	Duration of the period during which the target amplitude is maintained within one stimulation train	0-500 msec	50 msec

Configurable Parameters	Meaning	Ranges	Available Values
Ramp within stimulation train – Step-Down [%]	Decreased stimulation amplitude within stimulation train	0*-99%	1%

*A step-down amplitude of 0 means that the step-down feature is deactivated.

4.2.3 Reading and Analyzing the Activation Chip Log

When a participant comes in for a titration session, the technician should first read the AC Log to check the functionality of the device by retrieving usage information stored in the AC, such as daily usage, errors and performance data. The main purpose of the Log is to look for potential device malfunctions, verify proper system usage and assess the user's compliance. In order to read the Log, follow these steps:

1) Start by pressing the "Stop Stimulation" button (see Figure 47) as the AC must be in OFF Mode in order to read the AC Log.
   Note: As the AC Log cannot be read when in LAB or HOME mode the "Read Genio® AC Log" button is disabled if the AC is not in OFF mode.

Figure 47: Stop stimulation button and disabled Read Genio™ AC Log button

2) Once the stimulation is properly stopped, the Stop Stimulation button will turn red, and the Read Genio® AC Log button will be enabled (see Figure 48).

Figure 48: Stimulation stopped

3) Press “Read Genio™ AC Log” (see Figure 49).

Figure 49: Read Genio® AC Log button

4) A pop-up message will be displayed asking the operator to enter the number of DPs. (i.e. Enter the number of nights the Genio® system was used since the LAST AC log read; or, enter the number of nights Genio® system was used since user’s AC was dispensed) (Figure 50). Enter that value and press “OK”.

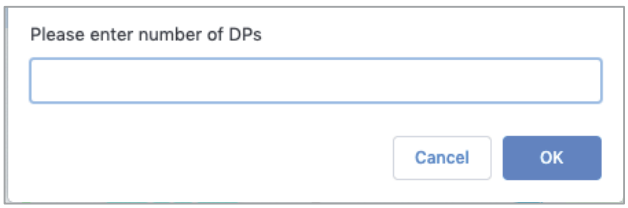


Figure 50: Number of used DPs since last visit

5) The download of the Genio® AC Log will start and the log records will appear on the screen during the download process. If the AC Log reading does not start within a few seconds, click on the “Read” button (see Figure 51).

⚠ Do NOT close the AC log reading window until log is fully read.

Note: Once Log reading is aborted, Log information needs to be entered again before reading the Log.

Figure 51: Reading Genio® AC Log

6) Once download is complete, a message will appear indicating that the AC Log reading is complete.

Figure 52: Genio® AC Log reading completed

Note: In case the message does not appear, close the Log reading window by clicking the X in the top right corner and retry reading the log again.

7) The complete log (see Figure 53) can be saved on the laptop connected to the repeater (in the Downloads folder) by clicking on the "Export" button. Normally, each log line corresponds to one night of use.

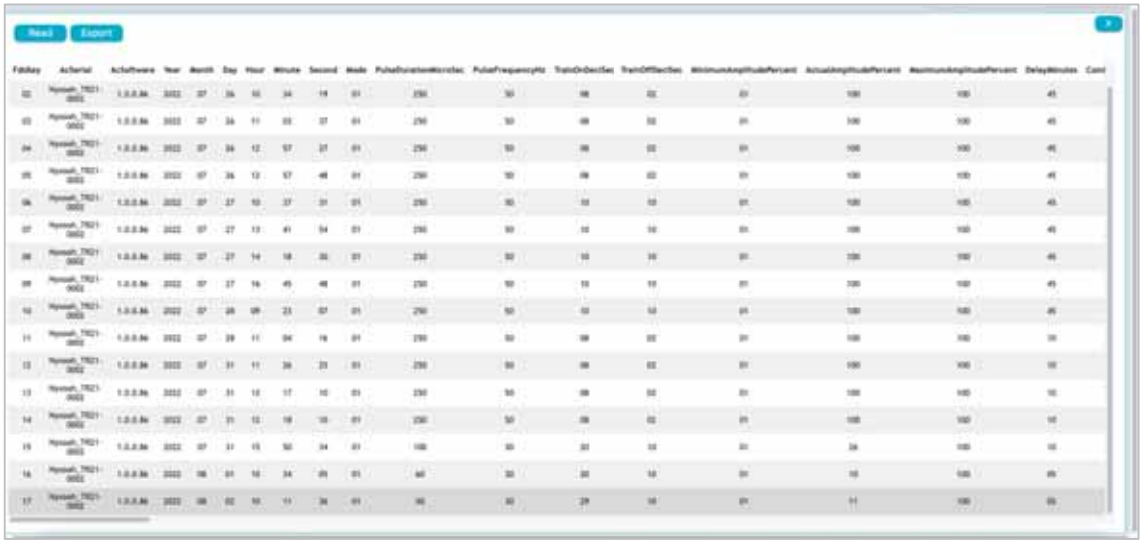


Figure 53: Genio® AC Log tab

Note: Verify that the log was fully read by reviewing the log record number on the left column and verifying that there are no gaps in the log numbering. In case a log shows missing records, click on the "Read" button to read the log again.

8) In order to analyze the log, begin with comparing the number of used DPs entered manually to the number of nights since last visit. These numbers should match. If not, ask the participant how many nights the Genio® System 2.1 was used since last visit and if more than one DP per night was used.

9) Check if there were any AC errors and/or any nights with battery depletion. If AC or battery errors are observed, it is recommended to assign a new AC to the participant.
10) Examine the treatment time reported by the AC (low values indicate partial use of the system over night and will be marked red) and check consistency with patient reports.
Note: Values marked red will not be colored red in the exported .csv file and appear red only when viewing the log within the Genio® Sleep Lab Application.

4.2.4 Reading Activation Chip Parameters

Once the participant usage data analyzed, go back to the stimulation tab by clicking the X in the top right corner of the log window, in order to read the AC parameters. The current AC parameters should be automatically displayed (see Figure 54).

Figure 54: Current AC parameters

If the current AC parameters are not displayed:

1) Press “Read Genio® AC”.
2) Once the reading is successful, a success message will be displayed above the Read Genio® AC button (Figure 55) and the AC parameters will be displayed.
Note: If a problem occurs while trying to read AC parameters, see Appendix C.

Figure 55: Read AC parameters success indication

4.2.5 Configuring Activation Chip Parameters

During wakeful and PSG titration sessions, the AC parameters will be customized according to the Therapy Optimization Guidelines. Modification of AC parameters must be performed using the Genio® Sleep Lab Application. To change the current AC parameters:

1) In the Parameters Configuration box, select the AC parameter to modify and choose the desired value in the dropdown list (see Figure 56.a). In the dropdown list, the selected one is highlighted in blue (see Figure 56.a). Once the change has been made, the modified field is marked by a blue arrow (see Figure 56.b).

Figure 56: Modification of AC parameters

Note: When using a laptop with MacOS, the current value in the dropdown list is preceded by "✓". Check does not appear when using a Windows based laptop.

⚠ The Duty Cycle value can NOT be set above 80%. If such a DC is reached, the Program Genio® AC button will be deactivated (see Figure 57), and the Duty Cycle will be highlighted in red. The DC can be modified by changing the Train Length and Train Interval values (see section 4.2.1).

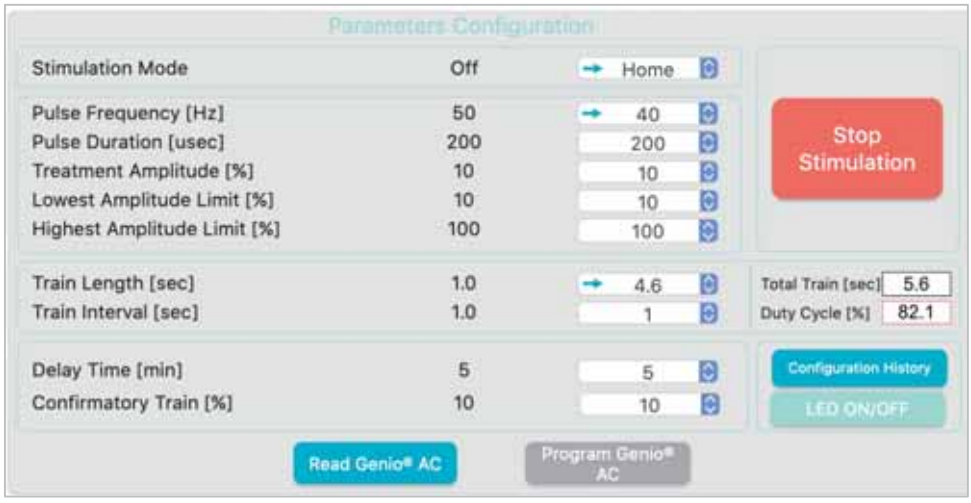


Figure 57: Maximum duty cycle value exceeded

2) Once all of the relevant parameters have been modified, press "Program Genio® AC" (see Figure 58).

Note: Ensure the treatment amplitude value is lower than highest amplitude limit and higher than the lowest amplitude value, otherwise an error message will be displayed.

Note: When programming new AC parameters, verify that the estimated stimulation time is sufficient for a full restful night (see Figure 59). This estimated stimulation time is calculated considering that the AC is fully charged, disregarding its current battery status.

Figure 58: Program Genio® AC

Figure 59: Stimulation time estimation (Example)

3) Once the programming is complete, a "Success" indication will be displayed above the Program Genio® AC button (see Figure 60) and the AC current parameters will be updated (see Figure 61).

Figure 60: Programming success indication

Note: In case of failure to program the AC, the Genio® Sleep Lab app will automatically retry programming the AC. Therefore, in case of a Timeout Error, wait a few seconds before clicking the Program Genio™ AC button again.

Figure 61: Stimulation parameters updated

Note: The stimulation will start according to the programmed parameters, i.e. (1) immediately if programmed in LAB mode or (2) after the defined delay time if programmed in HOME mode.

Note: If LAB mode is selected, the delay time field is disabled.

4) The stimulation can be turned off at any time by pressing the “Stop Stimulation” button. Once the stimulation is off, the Stop Stimulation button turns red (see Figure 62).

Figure 62: Stop Stimulation success message

To activate one or both ramp features:

1) Select the desired value in the drop-down lists of each parameter. As for the other AC parameters, the selected value will be marked by a blue arrow (see Figure 63).

Figure 63: Configuration of the ramp parameters

2) Once all the parameters are set, press “Program Genio® AC”.

Note: Ensure the Step-Down Amplitude does not exceed the lowest amplitude limit (see Figure 64).

Note: Ensure the Ramp-Up Duration and the Hold Duration all together do not exceed the Train Length. In case of such an inconsistency, the application will alert the operator that there is a conflict between the configured parameters (see Figure 64).

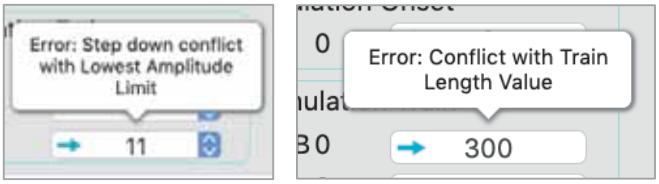


Figure 64: Example of conflict between parameters’ values

4.2.6 Closing Session/Visit

At the end of every session/visit:

1) At the end of a titration session, before sending the participant home, verify that the stimulation mode has been set to HOME and that the final parameters are correctly

programmed.

Note: If AC is reset, it will automatically go to HOME mode.

2) Disconnect the AC from the DP.
3) Remove the DP from the participant's chin.

⚠ The removal of the DP shall be done in a direction and manner as close as possible to the skin to minimize irritation/discomfort.

4) Reset the AC by using the CU (see section 4.1.3). This step allows the user to add the information collected during the titration session to the AC Log.

   Note: when connecting the AC to the CU for resetting it, wait for the AC charging indication to initiate before removing the AC from the CU.

5) Reconnect the AC to a DP.
6) Press the Bluetooth button to disconnect the AC from the App and press it again to reconnect. Make sure the AC battery level is available (see section 4.1.4).
7) Read Genio® AC Log and save it by clicking on "Export".

   Note: A new log record will be added in case stimulation duration during the session lasted more than 30 minutes.

8) Exit AC Log and press "End Session".
9) A pop-up message will appear to confirm to close the session and will offer to save the data from the session. Press "OK" (see Figure 65). Session will be closed, and the session history will be exported and saved on the connected laptop.

Figure 65: Session closing approval

Note: If a problem occurs when trying to close a session/visit, see Appendix C.

10) Carefully disconnect the AC from the DP and place the AC in its protective cover.

⚠ In case the AC was dropped, check if any damage is observed. If damaged, contact Nyxoah.

11) Ensure the AC is returned to the participant.

4.2.7 Genio® App Additional Features

The Genio® Sleep Lab Application contains other useful functionalities described in this section.

- ***LED ON/OFF***

In order to visualize when the AC is stimulating, the LED ON/OFF button may be pressed. When the LED ON/OFF button is pressed, the button turns red (see Figure 66) and the AC LED will turn green when stimulating. To deactivate this feature, press the LED ON/OFF button which will turn blue.

Figure 66: AC LED ON/OFF feature

- ***Configuration History Table***

Clicking on the "Configuration History" button will open a window listing all of the parameter changes made per patient, or for all of the patients whose AC was programmed using this specific repeater (see Figure 67).

The configuration history table can be exported in two ways:

1) By clicking "CSV" to create a .csv file of the entire configuration history according to the selected filter
2) by clicking the "PDF" button to create a specific session report in a PDF format

Figure 67: Configuration History table

Note: In order to filter the configuration history table to the current patient, first click on "All Patients" and then click on "This Patient".

This table can also be used to select previously configured AC parameters:

1) Select a specific row in the Configuration History table containing the desired set of parameters.
2) Double click on this specific row.
3) The changes will be displayed in the Parameters Configuration tab and the modified parameters will be marked by a blue arrow.
4) Exit the Configuration History Table by clicking the X in the top right corner of the configuration history window.
5) Press “Program Genio® AC”.

Note: The Configuration History is saved on each specific Repeater.

- ***Monitoring Tab***

The Genio® AC/DP Monitoring option (see Figure 68) allows the operator to monitor the AC during stimulation. Pressing “Monitor” will give an indication on AC stimulations for 30 seconds. When stimulation is detected, a blue dot next to the Monitor button will blink.

Figure 68: Genio® AC/DP Monitoring box

Note: For short train length and train interval settings (i.e., less than 1sec), synchronization between stimulation and the blue dot indication may be suboptimal.

To enable monitoring of the AC/DP for an unlimited duration, the “Endlessly” checkbox can be checked, and monitoring indication will be active as long as the Endlessly checkbox is checked. Uncheck the checkbox to deactivate the monitoring function.

5 Symbols on Product and Package Labelling

Symbol/Title	Explanatory Text	Standard/Reference Number
 Manufacturer	Indicates the manufacturer of the medical device	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.1.1] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [3082]
 Catalogue number	Indicates the manufacturer's catalogue number so that the medical device can be identified	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.1.6] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2493]
 Serial number	Indicates the serial number of the medical device to allow for identification	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.1.7] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2498]
 Batch code	Indicates the batch code so that the batch or the lot of the medical device can be identified. Other synonyms for "batch code" are "lot number", "lot code" and "batch number"	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.1.5] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2492]
 Date of manufacture	Indicates the date when the medical device was manufactured	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.1.3] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2497]
 Use-by date	Indicates the date after which the medical device is not to be used. Other synonyms for "use-by date" are "use by", "expiry date" and "expiration date"	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.1.4] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2607]

Symbol/Title	Explanatory Text	Standard/Reference Number
 Follow instructions for use	Indicates that reading the instruction manual prior to operating the device is mandatory	IEC 60601-1:2005/A1:2012 – Medical electrical equipment – Part 1: General requirements for basic safety and essential performance [Table D.2, Symbol 10] ISO 7010:2019 – Graphical symbols – Safety colours and safety signs – Registered safety signs [M002]
 Caution	Indicates that caution is necessary when operating the device or control close to where the symbol is placed, or that the current situation needs operator awareness or operator action in order to avoid undesirable consequences	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.4.4] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [0434A]
 Sterilized using ethylene oxide	Indicates that the medical device has been sterilized using ethylene oxide	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.2.3] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2501]
 Do not use if package is damaged and consult instructions for use	Indicates that the medical device should not be used if the package has been damaged or opened and that the user should consult the instructions for use for additional information	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.2.8] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2606]
 Do not resterilize	Indicates that the medical device is not to be resterilized	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.2.6] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2608]
 Do not re-use	Indicates that the medical device is intended for one single use only	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.4.2] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [1051]

Symbol/Title	Explanatory Text	Standard/Reference Number
 Keep away from sunlight	Indicates that the medical device needs protection from light sources	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.3.2] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [0621]
 Keep dry	Indicates that the medical device needs to be protected from moisture	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.3.4] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [0626]
 Temperature limit	Indicates the temperature limits to which the medical device can be safely exposed	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.3.7] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [0632]
 Humidity limitation	Indicates the range of humidity to which the medical device can be safely exposed	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.3.8] ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2620]
 Magnetic Resonance (MR) Conditional	Indicates an item with demonstrated safety in the MR environment within defined conditions including conditions for the static magnetic field, the time-varying gradient magnetic fields and the radiofrequency fields	ASTM F2503-20 – Standard Practice For Marking Medical Devices And Other Items for Safety In The Magnetic Resonance Environment [3.1.11]
 Prescription Use Only	Indicates that Federal (USA) law restricts the device to sale by or on the order of a licensed physician	United States Code of Federal Regulations; 21 CFR 801.109(b)(1)
 Class II Equipment	Identifies equipment which meets the safety requirements specified for Class II equipment (double insulated equipment)	IEC 60417:2002 – Graphical symbols for use on equipment [5172] IEC 60601-1:2005/A1:2012 – Medical electrical equipment – Part 1: General requirements for basic safety and essential performance [Table D.1, Symbol 9]

Symbol/Title	Explanatory Text	Standard/Reference Number
 Non-ionizing electromagnetic radiation	Indicates medical electrical equipment that includes RF transmitters or that intentionally apply RF electromagnetic energy for diagnosis or treatment	IEC 60417:2002 – Graphical symbols for use on equipment [5140]
 Type BF applied part	Identifies a type BF applied part (a part which is generally not conductive and can be immediately released from the patient)	IEC 60417:2002 – Graphical symbols for use on equipment [5333] IEC 60601-1:2005/A1:2012 – Medical electrical equipment – Part 1: General requirements for basic safety and essential performance [Table D.1, 20]
 FCC Mark	Indicates that the electromagnetic radiation of the device is below the limits specified by the Federal Communications Commission	United States Code of Federal Regulations; Title 47
IP21 Degrees of protection provided by enclosures	Indicates that the device is protected against the ingress of solid objects over 12.5mm and protected against ingress of vertically dripping water	IEC 60601-1:2005/A1:2012 – Medical electrical equipment – Part 1: General requirements for basic safety and essential performance [Table D.3, Symbol 2]
IP22 Degrees of protection provided by enclosures	Indicates that the device is protected against the ingress of solid objects over 12.5mm and protected against ingress of dripping water at any angle up to 15 degrees from vertical	IEC 60601-1:2005/A1:2012 – Medical electrical equipment – Part 1: General requirements for basic safety and essential performance [Table D.3, Symbol 2]
 Quantity in box	Indicates the amount of devices contained within the box	ISO 7000:2019 – Graphical symbols for use on equipment – Registered symbols [2794]
 Unique device identifier	Indicates a carrier that contains unique device identifier information	ISO 15223-1:2021 – Medical devices – Symbols to be used with information to be supplied by the manufacturer – Part 1: General requirements [5.7.10]

Symbol/Title	Explanatory Text	Standard/Reference Number
 Waste electrical and electronic equipment	Indicates that the disposal of the device requires separate collection in the European Union	Directive 2012/19/EU on waste electrical and electronic equipment (WEEE)

6 EMC Requirements

6.1 Use environment

The Genio® System 2.1 (AC, DP, IS, CU, Power Adapter, ES parts) is intended for use in professional healthcare facility environment (such as Operating Room, Sleep Lab, Physician offices and clinics and hospitals, except medical treatment areas with high-powered RF equipment).

The Genio® System 2.1 (AC, DP, IS, Power Adapter and CU parts) is intended for use in home healthcare environment.

6.2 Essential Performance

The following table lists the Genio® System 2.1's essential performance functions per system component:

Device	Essential performance functions
IS	Delivering stimulation pulses according to 8 MHz electromagnetic field transmitted from an external device (AC or ES)
AC and DP	Transmission of modulated 8 MHz EM field to power the IS
AC	Activation and handling of BLE interface Charging AC battery
ES	Transmission of modulated 8 MHz EM field to power the IS
CU and PS	Charging AC battery

6.3 Medical device Wireless functions

System component	Intended use environment	Specific RF wireless type	Type	Wireless functions
IS	Sleep lab, Surgery Operation Room	Wireless modulated energy transfer 8 MHz	Receiver	Receiving stimulation energy and pattern from ES or AC-DP

	and Home use			
AC-DP	Sleep lab	Wireless modulated energy transfer 8 MHz	Transmitter	Energy transfer to IS
		BLE (Bluetooth Low Energy) 2.4 GHz	Transceiver	Communication
Patient smartphone Genio® application	Home	BLE (Bluetooth Low Energy) 2.4 GHz	Transceiver	Communication and data transfer between Genio® AC and Smartphone application software
Genio® Repeater with Sleep Lab Application	Sleep lab	BLE (Bluetooth Low Energy) 2.4 GHz	Transceiver	Communication and data transfer between Genio® AC and Genio ® Sleep Lab application software

6.4 EMC Warnings

WARNING: Use of this equipment adjacent to or stacked with other equipment should be avoided because it could result in improper operation. If such use is necessary, this equipment and the other equipment should be observed to verify that they are operating normally.

WARNING: Use of accessories, transducers and cables other than those specified or provided by Nyxoah could result in increased electromagnetic emissions or decreased electromagnetic immunity of this equipment and result in improper operation.

WARNING: Portable RF communications equipment (including peripherals such as antenna cables and external antennas) should be used no closer than 30 cm (12 inches) to any part of the Genio® System 2.1, including cables specified by Nyxoah. Otherwise, degradation of the performance of this equipment could result.

WARNING: The Genio® System 2.1 needs special precautions regarding EMC and needs to be installed and put into service according to the specific instructions for maintaining basic safety and essential performance with regard to electromagnetic disturbances for the expected service life provided in sections 2.3, 2.4 and 4.1.

6.5 Power Inputs and Frequencies

The following table lists The Genio® System 2.1 devices power inputs and Radio frequencies (if applicable):

Device	Power Inputs	Radio Frequencies
AC+DP	4.2 V, 160 mAh (Battery Powered)	8 MHz BLE: 2.4 GHz
ES	3.7 V, 120 mAh (Battery Powered)	8 MHz

CU	110-240 V, AC 50-60 Hz	N/A

6.6 EMC Guidance Tables

6.6.1 Guidance and MANUFACTURER'S declaration – ELECTROMAGNETIC EMISSIONS IEC 60601-1-2 Ed.4

Emissions test	Compliance	Electromagnetic environment - guidance
RF emissions CISPR 11	Group 1	The Genio® System 2.1 uses RF energy only for its internal function. Therefore, its RF emissions are very low and are not likely to cause any interference in nearby electronic equipment
RF emissions CISPR 11	Class B	The Genio® System 2.1 is suitable for use in all establishments, including domestic establishments and those directly connected to the public low-voltage power supply network that supplies buildings used for domestic purposes.
Harmonic emissions IEC 61000-3-2	Class A	
Voltage fluctuations/flicker emissions IEC 61000-3-3	Complies	

6.6.2 Guidance and manufacturer's declaration – electromagnetic IMMUNITY IEC 60601-1-2 Ed.4

Immunity test	IEC 60601 level	Compliance level	Electromagnetic environment - guidance
Electrostatic discharge (ESD), IEC 61000-4-2	8 kV contact 15 kV air	8 kV contact 15 kV air	The relative humidity should be at least 5%.
Electrical fast transient/burst, IEC 61000-4-4	2 kV for power supply lines 1 kV for SIP/SOP lines	2 kV for power supply lines 1 kV for SIP/SOP lines	Mains power quality should be that of a typical commercial or hospital environment
Surge, IEC 61000-4-5	1 kV line to line 2 kV line to earth	1 kV line to line (class II ME equipment and ME systems according to Table 5, Note "k" of EN/IEC 60601-1-2)	Mains power quality should be that of a typical commercial or hospital environment.
Voltage dips and interruptions on power supply input lines IEC 61000-4-11	0 % U_T for 0.5 cycle 0 % U_T for 1 cycle 70 % U_T for 25/30 cycles 0 % U_T for 250/300 cycles	0 % U_T for 0.5 cycle 0 % U_T for 1 cycle 70 % U_T for 25/30 cycles 0 % U_T for 250/300 cycles	Mains power quality should be that of a typical commercial or hospital environment. If the user of the equipment requires continued operation during power mains interruptions, it is recommended that the equipment be powered from an uninterruptible power supply or a battery.
Power frequency magnetic field, IEC 61000-4-8	30 A/m	30 A/m	Power frequency magnetic fields should be at levels characteristic of a typical location in a typical commercial or hospital environment.
NOTE: U_T is the AC mains voltage prior to application of the test level.			

6.6.3 Guidance and manufacturer's declaration – electromagnetic IMMUNITY IEC 60601-1-2 Ed.4

Immunity test	IEC 60601 level	Compliance level
IEC 61000-4-6 Conducted RF	3 Vrms 150 kHz to 80 MHz 6 Vrms in ISM bands (6.765 MHz to 6.795 MHz; 13.553 MHz to 13.567 MHz; 26.957 MHz to 27.283 MHz; and 40.66 MHz to 40.70 MHz) and amateur radio bands (1.8 MHz to 2.0 MHz, 3.5 MHz to 4.0 MHz, 5.3 MHz to 5.4 MHz, 7 MHz to 7.3 MHz, 10.1 MHz to 10.15 MHz, 14 MHz to 14.2 MHz, 18.07 MHz to 18.17 MHz, 21.0 MHz to 21.4 MHz, 24.89 MHz to 24.99 MHz, 28.0 MHz to 29.7 MHz and 50.0 MHz to 54.0 MHz)	[*V*] = 3 Vrms [*V*] = 6 Vrms
IEC 61000-4-3 Radiated RF	10 V/m 80 MHz to 2.7 GHz	[*E*] = 10 V/m
Proximity fields from RF wireless communications equipment	385 MHz	27 V/m
	450 MHz	28 V/m
	710 MHz	9 V/m
	745 MHz	
	780 MHz	
	810 MHz	28 V/m
	870 MHz	
	930 MHz	
	1720 MHz	28 V/m
	1845 MHz	
	1970 MHz	
	2450 MHz	28 V/m
	5240 MHz	9 V/m
	5500 MHz	
	5785 MHz	

6.6.4 RF Receivers and Transmitters Specifications

RF	Tx/Rx	Frequency, MHz	Assigned Frequency Range, MHz	Modulation	EIRP / Transmitter Power
Bluetooth	Tx/Rx	2400 [2402-2480]	2400-2483.5	GFSK	EIRP: -14.20 dBm (38 µW)
Power Transfer (ES)	Tx	8 [7.985-8.01125]	7.4-8.8	Per Treatment Protocol	H-Field strength: -2.88 dB (µA/m) (0.72 µA/m)
Power Transfer (AC-DP)	Tx	8 [7.985-8.01125]	7.4-8.8	Per Treatment Protocol	H-Field strength: 34.7 dB (µA/m) (54.3 µA/m)

7 Cybersecurity

- The Genio® 2.1 System is designed to reduce cyber-security threats and minimize the system's vulnerability to cyber security attacks.
- The Genio® Repeater mini-computer runs on a Linux based OS (Raspbian GNU/Linux 10, "Buster").
- The Genio® Repeater mini-computer includes an Anti-virus SW (ClamAV) which runs automatically when the Genio® Repeater is powered.
- Using the Genio® Repeater remotely in the Sleep Lab is enabled by connection of the Repeater to a Laptop using a P2P LAN connection, and running the Genio® application in a web browser using a dedicated IP Address.
- Connection to the repeater and login to the Genio® Application are password protected. Password is unique for each Genio® Repeater.
- Communication between the Repeater and AC is based on Bluetooth Low Energy (BLE) communication which requires pairing and bonding of the devices prior to use, and is protected by data encryption (AES 128).
- No sensitive data is stored on any component of the Genio® 2.1 System
- In order to reduce cyber-security threats during use of the system in the Sleep Lab, it is recommended to follow the guidelines listed below:
    - Laptop used for connection with the Genio® Repeater shall have an updated Antivirus and anti-malware SW installed, and its firewall should be active as applicable
    - Laptop used for connection with the Genio® Repeater shall be password protected to prevent login and use by unauthorized personnel and shall be configured to be locked automatically in case the laptop was not used for a defined period of time.
    - Do not connect any external drives or USB sticks to the Genio® Repeater's USB ports.
    - Do not leave your laptop unattended while it is connected to the Genio® Repeater.
    - Do not connect the Genio® Repeater to unknown or public networks without authorization from Nyxoah.
    - Do not remove the SD card from the Repeater SD card slot or replace it with SD cards which were not provided solely by Nyxoah.
    - Installation, setup and updates of the Genio® Repeater shall be done only by certified and trained Nyxoah personnel.
- The Genio® Application includes and Advanced Mode with monitoring and troubleshooting functionalities for the Genio® AC. Advanced mode is password protected.
- All AC programming events performed during a Sleep Lab session are logged on the Repeater and can be used for tracing of programming activities as needed.
- At end of a session, the Genio® Application enables saving the session data for backup and monitoring of session activities. Upon approval of ending the session and saving the data, the data file is saved locally on your laptop.

Appendix A – LED Indications

Table 4: AC LED indications

AC Action	AC LED Indication
AC Reset	Red then yellow then green LED
The Activation Chip is ready to be connected to a Disposable Patch and is fully charged	Green LED blinking
The Activation Chip is ready to be connected to a Disposable Patch and is not fully charged	Yellow LED blinking
The Activation Chip is properly connected to the Disposable Patch and is fully charged	Green LED constantly ON for a few seconds
The Activation Chip is properly connected to the Disposable Patch and is not fully charged	Yellow LED constantly ON for a few seconds
AC non-functional	Red LED blinking (following reset)
AC is charging	Green LED blinking (when connected to the CU)
AC Charging Complete	Green LED constantly ON (when connected to the CU)

Table 5: CU LED indications

CU Action	CU LED Indication
CU connected to power	LED ON
CU disconnected from power	LED OFF

Table 6: Power adaptor LED indications

CU Power Adapter Action	LED Indication
Power adaptor connected to power outlet	LED ON
Power adaptor not connected to power outlet	LED OFF

Appendix B – Ethernet Switch Set Up

If there is more than one participant during the same titration night, use an Ethernet switch (see Figure 69) in order to connect several Repeaters to one Laptop.

Figure 69: Ethernet Switch with 8 Ethernet ports

As an example, a complete set up with two Repeaters is described below. To realize this setup, follow these steps:

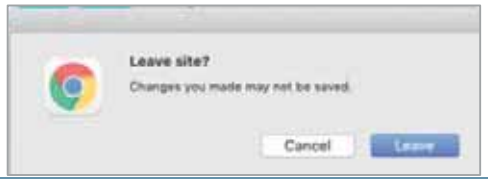
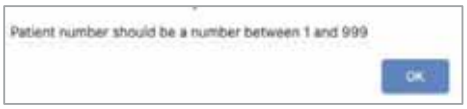
1) Connect the laptop, Repeaters and Ethernet switch to the power outlet using their respective charger.
2) Connect the Repeaters to the Ethernet switch using Ethernet cables.
3) Connect the Laptop to the Ethernet switch using an Ethernet cable.
4) Turn on the Laptop.
5) Log into one Repeater by opening a browser, typing in the Repeater's IP address and inserting the provided Repeater password in the application login screen.

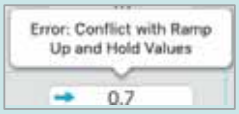
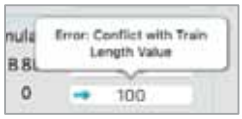
   Note: Preferably connect the AC to the Repeater before setting up the second Repeater.

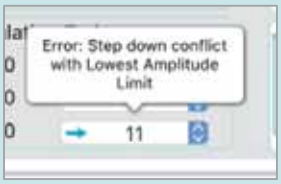
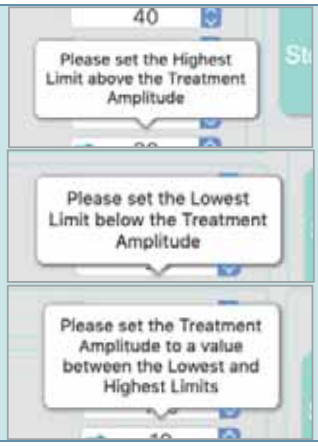
6) Open a new browser web page and type in the second Repeater's IP address in order and use the second Repeater's password to login the application.

Appendix C – App Notifications and Troubleshooting

Table 7: Genio® Sleep Lab Application notifications and troubleshooting table

Name	Message Text	Meaning	Troubleshooting
Quit App		Displayed when quitting the app mid-session.	Select Cancel, and Click on "End Session" in order to securely close the Application
Add New Participant Invalid		Displayed after user entered a new participant ID and input value was rejected.	Re-enter participant number, the input shall be a number between 1-999
Add New Patient Invalid		Displayed after user entered a new patient ID which is not a numeric value	Re-enter patient number, the input shall be a number between 1-999
Read AC Stimulation Parameters		Displayed when "Read Genio AC" was pressed and the reading was successful	N/A
Read AC Stimulation Parameters Error		Displayed after pressing the "Read Genio AC" button and reading was unsuccessful	**1.** Re-try reading/programming the AC parameters **2.** Make sure that AC is correctly connected to the DP and in proximity to the repeater **3.** Check the last reported AC battery level and verify it was not critically low **4.** Disconnect the AC from the Genio® Application, reset it and reconnect it. Re-try reading/programming the AC parameters **5.** If the problem persists, contact Nyxoah
Program AC Stimulation Parameters Error		Displayed after pressing the "Program Genio AC" button and programming was unsuccessful	
Program AC Stimulation Parameters		Displayed when "Program Genio® AC" was pressed and the programming was successful	N/A

Name	Message Text	Meaning	Troubleshooting
Enable Advanced Mode		Displayed when user selects the “Advanced” tab	Enter the Advanced Mode password or press Cancel to go back to the stimulation tab
Advanced Mode Password Invalid		Displayed after user entered a password and confirmed but the input value was rejected	Try again using the correct password
Close Session		Displayed when user pressed the “End Session” button.	Press OK to close the session, or Cancel to go back to the App screen The session information will be saved upon session closure
Toggle stimulation LED ON/OFF		Displayed when LED on/off button is pressed and LED indication is successfully activated	N/A
Stop Stimulation		Displayed when the AC is set to OFF mode and stimulation is stopped	N/A
Train Length and Ramp conflict		Displayed in case the selected Train Length does not comply with Ramp within train duration and Hold Duration values	Set the parameters values according to the following rule: Train Length ≥ Ramp within train duration + Hold Duration
Hold Duration and Train Length conflict		Displayed in case the selected Hold Duration parameter does not comply with Ramp Up duration and Train Length values	Set the parameters values according to the following rule: Train Length ≥ Ramp within train duration + Hold Duration

Name	Message Text	Meaning	Troubleshooting
Step Down and Stimulation amplitude conflict		Displayed in case the selected Step-Down value is larger than the lowest amplitude limit	Set the Step-Down parameter to a value lower than lowest amplitude limit
Step Down and Ramp Parameters conflict		Displayed in case the user selects a Step-Down value other than 0, while the Ramp Up + Hold Duration are equal to the Train Length	In case setting a Step-Down value other than 0, set the parameters values according to the following rule: Train Length > Ramp within train duration + Hold Duration
Treatment amplitude, Highest and Lowest Amplitude Limits		Conflict between treatment amplitude, highest and lowest amplitude limits	Set the parameters values according to the following rule: Lowest Amplitude Limit ≤ Treatment Amplitude ≤ Highest Amplitude Limit
Sensors activation confirmation		Displayed when activating the Genio® AC Sensors in the Advanced Mode	N/A
Real Time Clock Calibration		Displayed when setting the RTC is attempted when the AC is in “Home” or “Lab” Stimulation Modes.	Return to the main application window and change the Stimulation Mode to “Off” before setting the RTC.

Appendix D– Advanced Mode

The Advanced Mode is a password protected tab. To enable the Advanced Mode, follow these steps:

1) Press “Advanced” on the right side of the Genio® Sleep Lab application main screen and enter the supplied password in the pop-up window (see Figure 70).

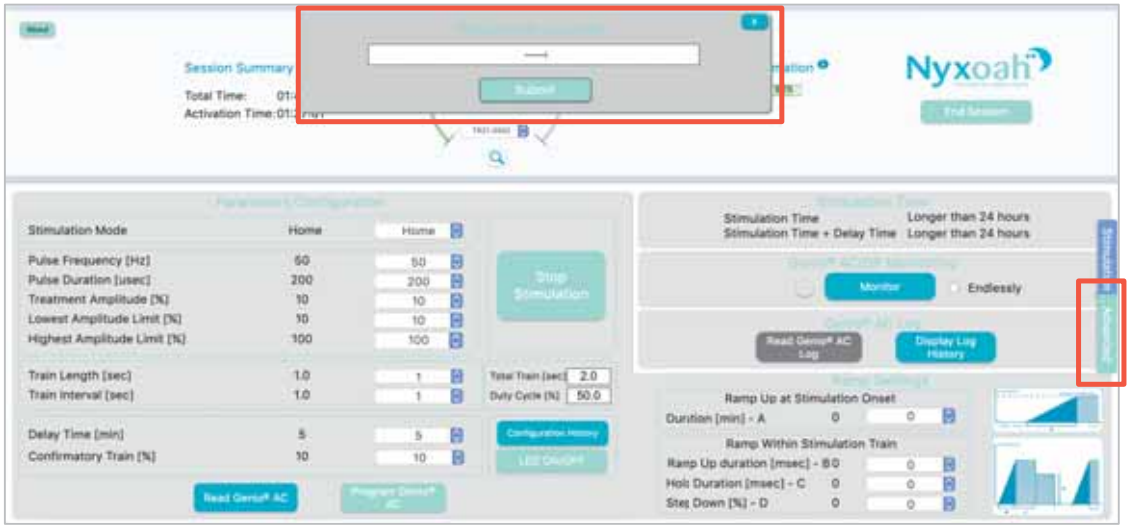


Figure 70: Access Advanced Mode

2) The advance tab will open (see Figure 71) and is comprised of different features detailed in the following:

Figure 71: Advanced Tab

a. **Smartphone Application Simulation:** The AC can be controlled by the Smartphone Application which allows the user to pause and resume stimulation and to increase/decrease the treatment amplitude within the configured range. The advanced

mode allows the technician to simulate the AC Smartphone application commands (see Figure 72):

- **Intensity Up:** Increases stimulation amplitude by 1% (can be increased until the highest amplitude limit is reached).
- **Intensity Down:** Decreases stimulation amplitude by 1% (can be decreased until the lowest amplitude limit is reached).
- **Pause:** Pauses stimulation for a defined duration, configurable in the "Pause" field. Treatment will resume, starting with a new delay period followed by the stimulation activation, either at the end of the pause duration or if "resume" is pressed. Following the pause duration completion and initiation of the Delay period a 1-min resolution timer indicates the remaining time before the end of the Delay duration.

  Note: Following the pause, a delay period will be initiated even if the AC was configured to LAB mode.

  Note: a deviation of a few seconds may be observed between the expected total pause and delay duration and the actual stimulation resume.

  Note: a deviation of a few seconds may be observed between the "remain" value and the actual stimulation resume.
- **Resume:** Resumes stimulation in case paused. Treatment will resume by initiating the delay period followed by stimulation.

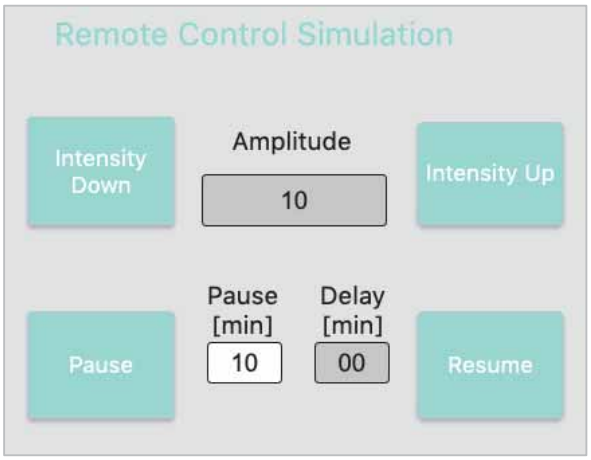


Figure 72: Smartphone Application simulator

b. **Genio® AC/DP Monitoring:** The Genio® Sleep Lab Application allows the technician to check for AC stimulation activity on demand (see Figure 73). Pressing "Monitor" will give indication on AC stimulation. When stimulation is generated by the AC, a dot will blink upon stimulation detection. The AC-DP monitoring duration can be defined manually by modifying the monitoring "Time" value. Default setting is 30 sec. Ticking "Endlessly" will keep the monitoring indication ON until the checkbox is pressed again.

   Clicking on the Blink LED will activate the AC LED during stimulation (similarly to the LED ON/OFF button in the main screen).

Figure 73: Genio® AC/DP Monitoring

c. **AC Sensors:** The AC includes integrated Sensors – IMU (Gyro and Accelerometer) and Microphone. Real time readings of the sensors can be done by clicking the relevant "Read" button (see Figure 74). The Repeater will read the Sensors data and save it to a local file. . In order to export the file to the user's connected laptop, connect to the Repeater using a VNC viewer (use the same IP address used for connecting to the Genio® App), and copy the file from the root folder to a connected removable storage device using a dedicated tool approved by Nyxoah. The sensor data file includes a timestamp for the raw data readings.

Figure 74: Sensors reading

Recording of personal audio data is prohibited and may lead to violation of Nyxoah's GDPR and data privacy policy.

When activating the sensors a pop-up alert will be displayed on screen requiring an active confirmation that the recording is done under approved conditions only. Do not use the AC for recording unless approved by Nyxoah.

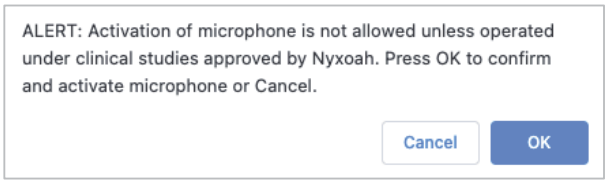


Figure 75: Sensors reading alert message

Once approved, the microphone will start recording and send the data along with the IMU sensor data to the Repeater. The sensors activation button will become red. To stop recording – press the button again

Figure 76: Sensors button while sensors are active

In order to ensure that the user is aware of the microphone activation, a visual indication will be displayed on the Genio® App main screen (in the top left corner) while the microphone is active

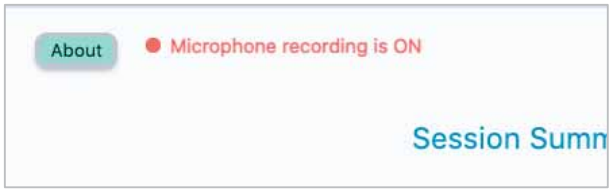


Figure 77: Microphone active indication

Figure 78: Microphone active indication – full screen view

<u>Important:</u> recording of personal audio data is prohibited. Activate sensors only when patient is asleep. In case patient is awake and personal conversations are being held in the patient's room – make sure to deactivate the sensors.

<u>Note:</u> when reading the sensors data, other wireless commands between the AC and Repeater may be disturbed resulting in Timeout Errors. In case the AC parameters needs to be read or programmed while the sensors are active and communication errors persist,, stop the sensors reading temporarily.

d. **Communication:** By default, the "Auto Reconnect" feature is enabled, meaning that the Genio® Sleep Lab Application will automatically attempt to re-establish connection with the AC in case the connection fails (see Figure 75).

Figure 79: Communication

The RSSI number quantifies the quality of the AC/Repeater communication. In order to have a good Bluetooth communication and to avoid disconnection problems, the average RSSI number should be above -85 dBm in order to reduce the risk to encounter a disconnection. To display the RSSI number in real time, p1ress "Test RSSI".

e. **RTC Calibration:** The AC includes an integrated Real-Time-Clock (RTC) which is used for Log analysis. The **AC clock should be verified, and if needed - calibrated, at the Activation Visit or when a new AC is given to a patient** and can be calibrated afterwards upon need. Read the AC RTC value by clicking the Read button (Figure 76), in case of a discrepancy with the actual date and time, set the RTC by typing in the correct settings and clicking "Set". Setting the RTC requires stimulation to be stopped.
Note: Time should be entered in 24-hour format and Weekday is presented in a numeric value (01=Sunday, 02=Monday, etc.).

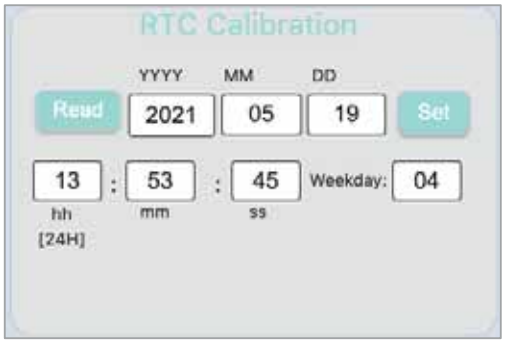


Figure 80: RTC calibration