NEUROPACE

Amendment 8
to the
INVESTIGATIONAL PLAN
for the

RNS® System
Long-term Treatment Clinical Investigation

Protocol #: NP10005

June 24, 2014

i. Protocol Synopsis

RNS® System Long-term Treatment Clinical Investigation June 24, 2014	
Test Device	RNS® System (NeuroPace RNS® System Premarket Approval Application (PMA) approved by the FDA on November 14, 2013)
Indication for Use	The RNS® System is an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that has localized no more than 2 epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and / or secondarily generalized seizures). The RNS® System has demonstrated safety and effectiveness in patients who average 3 or more disabling seizures per month over the three most recent months (with no month with fewer than two seizures), and has not been evaluated in patients with less frequent seizures.
Cohort	Subjects implanted with the RNS® System who have completed the RNS® System Feasibility or Pivotal Clinical Investigations.
Primary Objectives	To assess the ongoing safety and to evaluate the long-term efficacy of the RNS® System as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than 2 epileptogenic foci, that are refractory to two or more antiepileptic medications, and currently have frequently or disabling seizures.
Device Sizes	The RNS® Neurostimulator is an implantable, battery powered, microprocessor controlled device that is designed to detect electrographic patterns from intracranial electrodes and to deliver a short train of current pulses to the brain upon detection of those patterns. The Neurostimulator connects to up to two intracranial leads.

Study Design	An open-label multi-center prospective clinical investigation. Data regarding safety and efficacy are collected at 6-month intervals beginning at enrollment, and data regarding quality of life are collected at yearly intervals. Each subject participates for 7 years following completion of the RNS® System Feasibility or Pivotal Clinical investigations.
Number of Subjects to be Enrolled	Enrollment will be offered to all subjects completing the RNS® System Feasibility or Pivotal Clinical Investigations. Assuming that all subjects completing these investigations elect to enroll in the Long-term Treatment Clinical Investigation, the anticipated enrollment is 280.
Number of Sites	All sites participating in the RNS® System Feasibility and Pivotal Clinical Investigations
Key Inclusion Criteria	Subject has completed the RNS® System Feasibility or Pivotal Clinical Investigation. Subject has elected to continue to receive responsive neurostimulation therapy after completion of the RNS® System Feasibility or Pivotal Clinical Investigation.
Key Exclusion Criteria	Subject has active psychiatric or medical illness that, in the opinion of the investigator, makes it inadvisable for the subject to continue to receive responsive neurostimulation therapy with the RNS® System.

Primary Efficacy Objective, Analysis, and Methods	Primary objectives: The primary efficacy objective is to evaluate the long-term efficacy of the RNS® System. The primary efficacy outcome variable is the average percentage change in the mean frequency of total disabling seizures relative to pre-implant baseline. (Total disabling seizures are defined as simple partial motor, complex partial, and generalized tonic-clonic seizures.) The percent change will be calculated for each subject over 6-month intervals beginning 6 months after implant of the RNS® System (during the Feasibility or Pivotal Clinical Investigations open label period) and continuing through completion of the Long-term Treatment Investigation. Wilcoxon's signed-rank test will be used to assess the statistical significance of the percent change in mean seizure frequency from baseline at each 6-month interval. The sustainability of results will be assessed by fitting a GEE model to the 6-month periods.
Primary Safety Objective, Analysis and Methods	The primary safety objective is to describe the long-term RNS® System Serious Adverse Event (SAE) rate. The primary safety outcome variable is the SAE rate. Descriptive statistics (rate, standard deviation, 95% confidence interval) will be used to summarize results.
Other Safety Objective	To collect data on the frequency of sudden unexplained death in epilepsy (SUDEP) and upon completion of the clinical investigation estimate the SUDEP rate.
Secondary Efficacy Objectives, Analysis and Methods	<u>Responder Rate</u> The responder rate (defined as the proportion of subjects with a greater than or equal to 50% reduction in mean frequency of total disabling seizures compared to pre-implant baseline) will be calculated for each 6-month interval beginning 6 months post-implant. For every 6-month interval, the responder rate will be determined based upon the per-subject percentage change in seizure frequency. McNemar's test will be used to assess the statistical significance of the change in response rates from baseline at each 6-month interval. A linear logistic regression model will be used to assess the sustainability of the effect over time. The model will be linear in time. The outcome of interest is the slope over time.

	Quality of Life (QOL) QOLIE-89 scores (QOLIE-31-P for Spanish-speaking subjects) collected at each year of follow-up after implantation of the RNS® System will be compared to the QOLIE-89 (or QOLIE-31-P) at pre-implant baseline. The effect of treatment with the RNS® System on QOL will be assessed by fitting a GEE model to the yearly outcome assessments.
Secondary Safety Objectives, Analysis and Methods	The frequency and rate of occurrence of all adverse events (AEs) will be described.

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[redacted]

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1 Device Description

The NeuroPace® RNS® System includes an implantable programmable RNS® Neurostimulator that senses and records brain electrical activity and implantable NeuroPace® Leads. The Neurostimulator detects previously identified electrical patterns in the brain and then delivers electrical stimulation to the brain to interrupt those patterns before the patient experiences clinical seizures. The non-implantable RNS® System products include the NeuroPace® Programmer, Remote Monitor, Wand, PDMS (Patient Data Management System) and Magnet.

A depiction of the implanted system is provided in **Figure 1-1**.

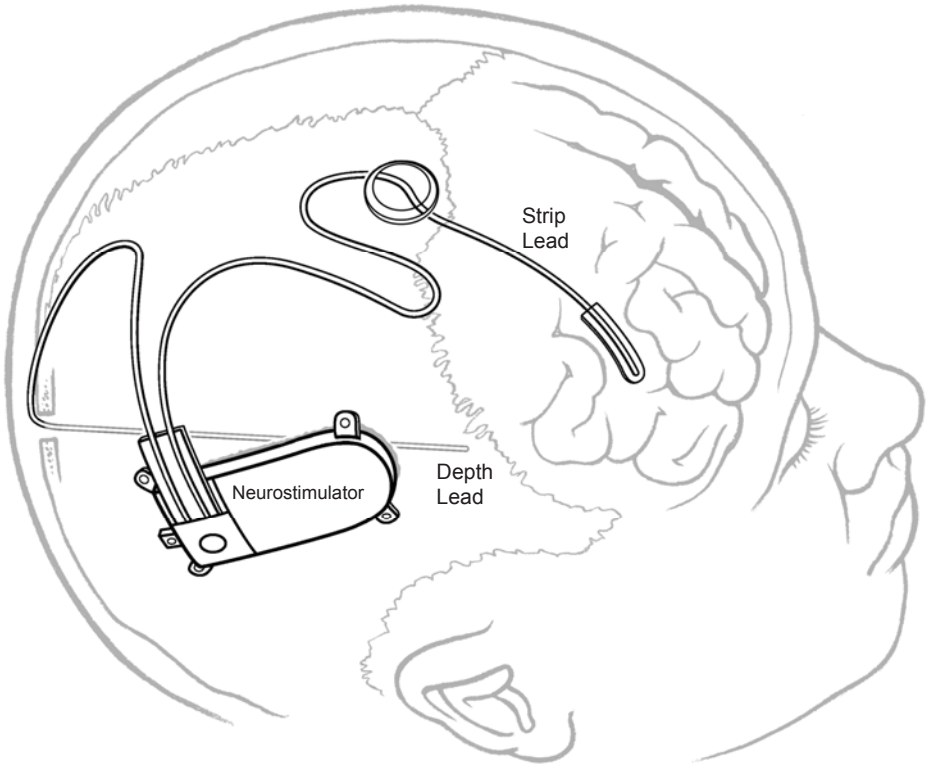


Figure 1-1: Neurostimulator mounted in a ferrule connected to depth and cortical strip lead

1.1. Implantable Devices

1.1.1. Responsive Neurostimulator

The RNS® Neurostimulator is a battery powered, microprocessor-controlled device that is surgically implanted in the cranium and is covered by the scalp. A Ferrule (a titanium tray, which is secured to the skull) mechanically supports and secures the Neurostimulator in the skull so that there is no direct contact of the Ferrule or Neurostimulator with the brain. The Neurostimulator is connected to one or two NeuroPace® Leads that are surgically implanted within (Depth Lead) or on the surface (Cortical Strip Lead) of the brain in the area of the epileptic seizure focus. The Neurostimulator monitors electrocorticographic (ECoG) activity and can be programmed to detect abnormal electrical activity (as defined by the physician). When detection criteria are met, the Neurostimulator delivers responsive stimulation to one or two epileptic foci. Detection and stimulation parameters can be non-invasively adjusted.

1.1.2. Leads

The NeuroPace® Leads provide an interface through which electrical activity of the brain can be sensed and recorded by the RNS® Neurostimulator and through which responsive electrical stimulation can be delivered. Depth Leads are stereotactically introduced into the epileptic seizure focus in the brain and Cortical Strip Leads are placed on the surface of the brain near the seizure focus. The Leads have a flexible, silicone Lead body that encloses four insulated wires, and have four platinum/iridium electrodes at their distal end. The proximal end has four contacts designed to connect to the RNS® Neurostimulator.

1.2. External Devices

1.2.1. Programmer

The NeuroPace® Programmer communicates with the Neurostimulator using a Wand with a short-range wireless radiofrequency link. The physician uses the Programmer to program the Neurostimulator and to view electrocorticograms. In addition, the Programmer tests the integrity of the Neurostimulator and Leads and uploads data from the Neurostimulator. The Programmer can also use a secure Internet connection to transmit these data to the Patient Data Management System (PDMS) for storage and later physician review.

1.2.2. Remote Monitor

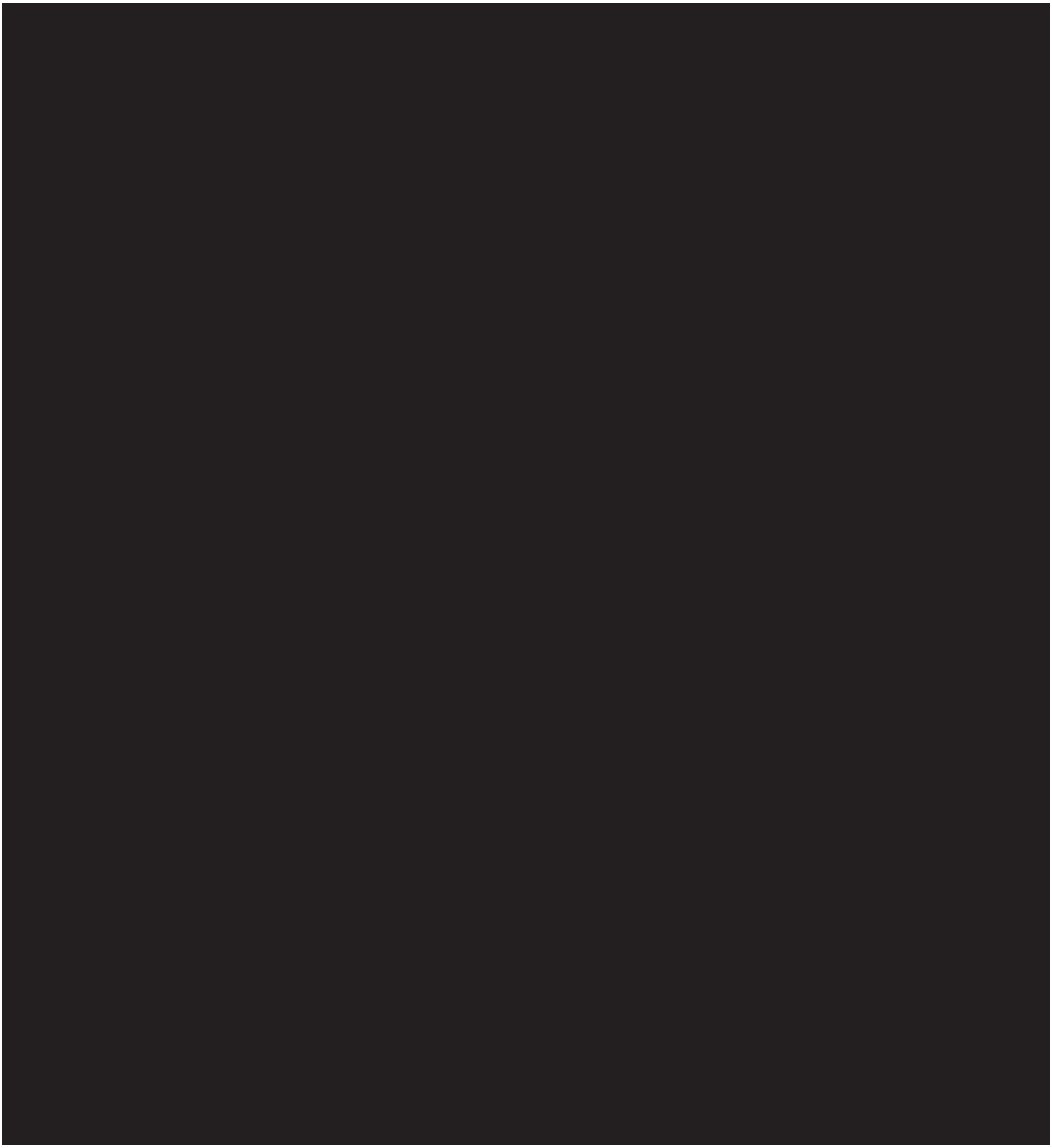
The NeuroPace® Remote Monitor is a home-use monitoring device that communicates with the Neurostimulator using a Wand with a short-range wireless radiofrequency link. A patient or caregiver uses the Remote Monitor to collect data from the Neurostimulator, and then transmits these data using a secure Internet connection to the PDMS. The Remote Monitor cannot be used by the patient to reprogram the Neurostimulator.

1.3. Patient Data Management System (PDMS)

The NeuroPace® Patient Data Management System (PDMS) is a central database used for storage and access to historical Neurostimulator and patient data. The uploaded data are accessible for review on the Internet by physicians through the PDMS web site using a secure web browser.

1.4. Magnet

The Magnet provided by NeuroPace to the patient can be swiped over the Neurostimulator to trigger the storage of a record of the date and time of the Magnet swipe.



2 Introduction and Rationale

2.1. Prevalence and Incidence of Epilepsy

Epilepsy is a common chronic neurological disorder for which available therapies are often not effective. Approximately 2.5 million in the United States have active epilepsy and 181,000 new cases of epilepsy are diagnosed each year. By 20 years of age, 1% of the population has developed epilepsy and by 75 years of age, the prevalence of epilepsy reaches 3% (Begley et.al. 2000).

2.2. Standard Treatments

AEDs offer hope for seizure control with minimal or no medication related adverse effects in about 70% of persons with epilepsy. However, approximately 30% of persons with partial onset seizures are refractory to pharmacotherapy, or have clinically significant AED related adverse effects (Kwan and Brodie, 2000). Some of the patients are candidates for epilepsy surgery. Others are not good candidates for epilepsy surgery because risk is unacceptably high and potential benefits are unacceptably low. These patients may choose the vagus nerve stimulator as a palliative therapy. Subjects participating in the RNS® System Feasibility or Pivotal Clinical Investigations have elected this option because existing options are not desirable. Patients concluding participation in the Feasibility or Pivotal Clinical Investigations should have the option to continue treatment with the RNS® System therapy within the context of an open-label long-term treatment investigation.

2.3. Rationale for Developing the RNS® System

Since many patients with partial onset seizures do not achieve the therapeutic goal of no seizures and no side effects with available therapies, a new treatment is needed. The RNS® System has been designed to provide patients with medically intractable epilepsy with an option for improved seizure control as well as excellent tolerability and safety.

2.3.1. Device Attributes

The RNS® System has been developed to meet the needs of patients with medically intractable partial onset seizures who are not candidates for epilepsy resective surgery or do not choose to pursue this type of surgical therapy. The RNS® System is intended to reduce the frequency of disabling seizures in this patient population and to have a safety profile that compares favorably to standard treatments. The RNS® System has advantages over AEDs in that it does not require daily patient compliance and operates independently of concomitant medications. Compared to the VNS, the RNS® System Neurostimulator is cranially implanted and therefore will not be visible. Also the RNS® System should not have effects on swallowing or vocal quality. Unlike

epilepsy surgery, the RNS® System therapy can be optimized non-invasively after the surgical intervention.

2.3.2. Rationale to Conduct a Long-term Treatment Investigation

The RNS® System Feasibility and Pivotal Clinical Investigations were designed to establish safety and efficacy of the RNS® System. When completed these investigations will provide safety data for 2 years post-implant and blinded efficacy data during an 84-day period followed by open-label efficacy data through 2 years post-implant.

The Long-term Treatment Investigation will provide additional data on the safety and efficacy of the RNS® System for 7 years following a subject's completion of the RNS® System Feasibility or Pivotal Clinical investigations. [redacted]

2.4. FDA Approval of the RNS® System

FDA approved the NeuroPace RNS® System Premarket Approval Application (PMA) on November 14, 2013. The RNS® System was approved for the following indication for use:

The NeuroPace RNS® System is approved as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than 2 epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and/ or secondarily generalized seizures). The RNS® System has demonstrated safety and effectiveness in patients who average 3 or more disabling seizures per month over the three most recent months (with no month with fewer than two seizures), and has not been evaluated in patients with less frequent seizures.

[redacted]

3 Study Objective

The intent of the Long-Term Treatment Clinical Investigation is to assess the ongoing safety and to evaluate long-term efficacy of the RNS® System as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than 2 epileptogenic foci, that are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures. Another objective of the Long-Term Treatment Clinical Investigation is to collect data on the frequency of sudden unexplained death in epilepsy (SUDEP).

[redacted]

[redacted]

[redacted]

Efficacy data will also be collected post-marketing as described below. Data for the following long-term efficacy and safety analyses will be submitted to FDA after completion of the study.

3.1. Primary Objectives

3.1.1. Primary Efficacy Objective and Outcome Variable

The primary efficacy objective is to evaluate the long-term efficacy of the RNS® System in reducing the frequency of disabling seizures in subjects who have participated in the RNS® System Feasibility or Pivotal Clinical Investigations.

[redacted]

[redacted]

[redacted]

3.1.2. Primary Safety Objective and Outcome Variable

The primary safety objective is to assess the ongoing safety of the RNS® System in subjects who have participated in the RNS® System Feasibility or Pivotal Clinical Investigations. The primary safety outcome variable is the Serious Adverse Event (SAE) rate. The SAE rate is defined as the proportion of subjects having a serious adverse event. Definitions for serious and mild adverse events are provided in **Table 10-1:** Adverse Event Classification.

3.1.3. SUDEP Objective and Outcome Variable

Another objective of the Long-Term Treatment Clinical Investigation is to collect data on the frequency of sudden unexplained death in epilepsy (SUDEP) and upon completion of the clinical investigation estimate the SUDEP rate. [redacted]

The reported incidence of SUDEP ranges from 3.5 deaths per 1000 person-years in a population based cohort with epilepsy (Lhatoo et.al., 1991), 6 per1000 patient years in patients with medically refractory epilepsy followed in an epilepsy clinic (Sperling et.al., 1999), to 6.3 deaths per 1000 person-years in a population based Swedish cohort with refractory epilepsy who were candidates but did not choose to undergo epilepsy surgery (Nilsson et.al., 2003), and 9.3/1000 person-years in patients followed in an epilepsy surgery program (Dasheiff, 1991).

Cases of SUDEP have occurred during clinical trials of epilepsy therapy. The rate of SUDEP in a well-defined cohort of 4,700 patients (5,747 patient-years of exposure) included in the worldwide clinical development database of the antiepileptic drug lamotrigine (Leetsma et.al., 1997) was 3.5 per 1,000 patient-years. This rate was comparable to the rate that would be expected in young adults with severe epilepsy.

SUDEP rates were also examined for 791 patients followed for 1,335 person-years from implantation of the Cyberonics Vagus Nerve Stimulator (VNS). Six of the 15 deaths that occurred during VNS stimulation were considered definite or probable SUDEP and two as possible SUDEP. The incidence of definite/probable SUDEP was 4.5 per 1,000 person-years and 6.0 per 1,000 person-years for definite/probable/possible SUDEP. A subsequent 2-year extension of the study followed 1819 patients for 3,176.3 person-years from implantation and found that the SUDEP rate dropped to 1.7/1000 after the first 2 years of use. The SUDEP rates during the first two years of VNS use were thus similar to those reported from clinical trials of new drugs and cohorts of severe epilepsy. The drop in SUDEP rates after 2 years has not been confirmed in other epilepsy therapy trials.

Patients participating in the NeuroPace RNS® System Clinical Investigations have medically refractory partial epilepsy and would fall into the category of persons with the highest risk for SUDEP. The risk would thus be comparable to the rates described in the Dasheiff study, as well as the rates for definite/probable/possible SUDEP in the initial experience in the VNS trials. Therefore, the upper limit for the expected SUDEP rate during the NeuroPace RNS® System clinical investigations is considered to be 9.3 per 1000 patient stimulation years.

3.2. Secondary Objectives

3.2.1. Secondary Efficacy Objectives and Outcome Variables

The following efficacy outcome variables will be monitored for each 6-month interval beginning 6 months after implantation of the RNS® System. These variables will be used to perform secondary analyses to evaluate the long-term efficacy of the RNS® System:

Responder Rate

- Proportion of subjects with greater than or equal to 50% reduction in total disabling seizures compared to pre-implant baseline

Quality of Life

- QOLIE-89 (for English-speaking subjects) or QOLIE-31-P (for Spanish-speaking subjects) scores collected at each year of follow-up after implantation of the RNS® System compared to the QOLIE-89 / QOLIE-31-P at pre-implant baseline.

3.2.2. Secondary Safety Objectives and Outcome Variables

The following safety outcome variable will be monitored as a secondary safety analysis:

- The rate of occurrence of any adverse event (AE) observed during the Long-term Treatment Investigation.

4 Study Design

4.1. Overview

4.1.1. General Characteristics

The RNS® System Long-term Treatment Investigation will enroll adult subjects with medically refractory partial epilepsy who have completed either the RNS® System Feasibility or Pivotal Clinical Investigation and elect to continue therapy with the RNS® System. A maximum of 280 subjects may be enrolled.

4.1.2. Design Features

The RNS® System Long-term Treatment Investigation is an open-label multi-center prospective clinical investigation conducted at sites that have participated in the RNS® System Feasibility or Pivotal Clinical Investigations.

4.1.3. Duration of Subject Participation

Each subject participates for 7 years following completion of the RNS® System Feasibility or Pivotal Clinical Investigations.

A time line of overall subject participation in the RNS® System Clinical Investigations is provided in **Figure 4-1**.

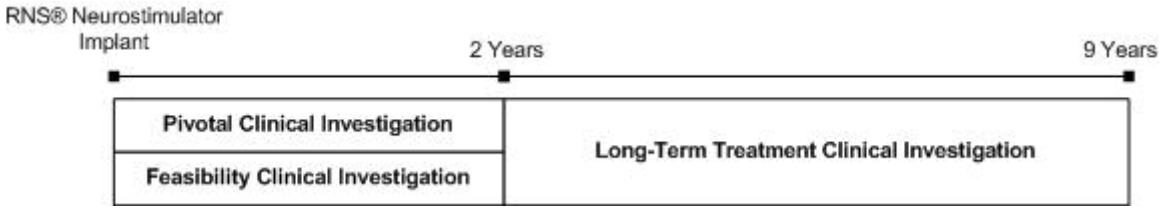


Figure 4-1: Timeline for subject participation in the RNS® System Clinical Investigations

4.2. Management of the RNS® System

Programming changes in detection and stimulation parameters may be made during the investigation to provide optimal detection and response to therapy.

Subjects participating in the investigation may elect to keep their Remote Monitors. The Remote Monitors will be used as directed by that subject's physician, however it is suggested that the subject interrogate the Neurostimulator and upload the data to the PDMS at least once a week.

4.3. Concomitant Antiepileptic Medications (AEDs)

AED adjustments (dose/type) may be made in order to provide optimal medical care.

5 Study Population

5.1. Eligibility Criteria

All subjects completing the RNS® System Feasibility or Pivotal Clinical Investigations are potential candidates for the RNS® System Long-term Treatment Investigation. Subjects who do not meet all inclusion/exclusion criteria will not be enrolled.

Enrollment into the investigation begins when the clinician determines that the subject has met the inclusion and exclusion criteria and the subject (or legal guardian) has signed the informed consent. Enrollment is confirmed once the relevant electronic case report forms (Inclusion and Exclusion Criteria and Consent Information) have been entered into the Patient Data Management System.

5.2. Inclusion/Exclusion Criteria

A subject must meet the inclusion/exclusion criteria in order to be enrolled and participate in the RNS® System Long-term Treatment Clinical Investigation.

5.2.1. Inclusion Criteria

- Subject has completed either the RNS® System Feasibility or Pivotal Clinical Investigation
- Subject has an implanted RNS® System
- Subject has elected to continue to receive responsive neurostimulation therapy after completion of the RNS® System Feasibility or Pivotal Clinical Investigations
- Subject is able to attend scheduled appointments for the RNS® System Long-term Treatment Clinical Investigation

5.2.2. Exclusion Criteria

- Subject has active psychiatric or medical illness that, in the opinion of the investigator, makes it inadvisable for the subject to continue to receive responsive neurostimulation therapy with the RNS® System
- Subject has been diagnosed with psychogenic or non-epileptic seizures, or primarily generalized seizures during the RNS® System Feasibility or Pivotal Clinical Investigations
- Subject has been noncompliant with scheduled appointments during the RNS® System Feasibility or Pivotal Clinical Investigations
- Subject has been noncompliant with maintaining seizure diaries during the RNS® System Feasibility or Pivotal Clinical Investigation
- Informed consent cannot be obtained from subject or caregiver

5.3. Withdrawal of Subjects

Withdrawal is strongly discouraged. A subject may withdraw consent at any time and exit the investigation. Withdrawal is defined as premature conclusion, which may occur at any time.

Subjects will be withdrawn from the Long-term Treatment Clinical Investigation if:

- Subject is enrolled in another therapeutic investigational drug or device trial
- Subject receives a device other than the RNS® System Neurostimulator that provides electrical energy to the brain
- Subject is noncompliant with scheduled appointments
- The investigator feels that it in the best interest of the subject to withdraw from the study
- The subject elects to discontinue responsive neurostimulation with the RNS® System or does not replace an RNS® System Neurostimulator that has reached end of service.

[redacted]

[redacted]

See **Section 6.3.9** for activities required when a subject withdraws. If the subject withdraws from the Clinical Investigation and has all NeuroPace devices explanted, there is no longer a need for a physician to monitor the RNS® System.

Subjects who withdraw from the investigation and have responsive stimulation enabled at the time of withdrawal should continue to be followed by a physician trained in the use of the RNS® System.

6 Protocols & Procedures

6.1. Protocol Guidelines

6.1.1. Standard of Care

All surgical and medical care should be provided according to best medical practice. This includes required protocol activities as well as any care provided in an emergent situation.

[redacted]

[redacted]

[redacted]

6.1.5. Recruitment Procedures

Subjects can only be recruited from the pool of subjects that have completed the RNS® System Feasibility or Pivotal Clinical Investigations. Recruitment of potential subjects for participation in the Clinical Investigation must comply with the requirements of the Institutional Review Board (IRB) for the site performing the Clinical Investigation and must comply with the appropriate Food and Drug Administration (FDA) regulations 21 CFR Part 50 for informed consents, 21 CFR Part 56 for the IRB.

[redacted]

6.2. Appointment Timelines

Office appointments occur every 6 months (26 weeks) during the clinical investigation. The appointments may be scheduled within a window of ± 14 days.

[redacted]

6.3. Protocol Appointments & Activities

6.3.1. Enrollment and Registration

- Screen subject and discuss investigation
  - Review Inclusion / Exclusion Criteria
  - Determine subject's dominant language for participation in the clinical investigation*
  - Provide the subject with the language appropriate consent for review [redacted]
  - Obtain signed Consent
- Register subject with NeuroPace [redacted]
- Confirm subject enrollment in investigation by completing selected eCRFs (Consent, Inclusion / Exclusion Criteria)
- If Spanish is determined to be the subject's dominant language, enter the Spanish Participation Confirmation eCRF

*Note: Through the remainder of the trial, ensure that the subject is provided with the language appropriate materials and that language appropriate testing and data collection is performed.

6.3.2. Initial Office Appointment

[redacted]

[redacted]

6.3.3. Office Appointments

[redacted] Appointments occur every 6 months

[redacted]

6.3.4. Unscheduled Telephone Appointments

- There are no required telephone appointments during the clinical investigation, however should an unscheduled telephone appointment occur, the following steps should be followed as appropriate:
  - Obtain telephone appointment packet
  - Review medications
  - Assess emergent or ongoing adverse event information

[redacted]

[redacted]

6.3.8. Explant and Revision Procedures

- If implant revisions (explanted devices, adjustments to implanted devices, device replacement) are required during this clinical investigation, complete the following activities:
  - Complete product registration information included in the device packaging.
  - Mail the product registration form using the provided envelope. A copy should be filed in the subject binder.
  - Return explanted devices to NeuroPace.
  - Complete and file required source documents regarding the explant/revision procedure (Clinical Notes, Medical Records)

[redacted]

6.3.9. Conclusion/Withdrawal

- Conclusion of participation occurs at the end of the Clinical Investigation.
- Withdrawal is premature conclusion, which may occur at any time (reasons for and timing requirements around withdrawal are identified in **Section 5.3**).

[redacted]

7 Statistical Methods

7.1. Primary Analyses

7.1.1. Efficacy

The average percentage change in the mean frequency of total disabling seizures for each 6-month interval beginning 6 months after implantation of the RNS® System relative to pre-implant baseline will be reported. ("Total disabling seizures" is defined as simple partial motor, complex partial, and generalized tonic-clonic seizures.) Data will thus be included from the Feasibility and Pivotal Clinical Investigations and gathered throughout the duration of the Long-term Treatment Investigation. Seizure frequency will be calculated as average frequency per day for each 6-month period.

1. The pre-implant baseline mean frequency of total disabling seizures will be calculated for each subject. This is defined as the average number of seizures per day during the 84-day Baseline Period immediately preceding the date of qualification for RNS® System implant in the RNS® System Feasibility or Pivotal Clinical Investigations.
2. All patients in the Feasibility and Pivotal Clinical Investigation have therapy enabled by 6 months post-implant (the Open Label Period). The mean frequency of total disabling seizures will be calculated for each subject at 6-month intervals between months 6 to 24 during the Feasibility or Pivotal Clinical Investigations, and for each 6-month interval during the Long-term Treatment Investigation (years 2 to 9 post-implant). The mean frequency is defined as the average number of seizures per day during the relevant 6-month period.

[redacted]

The Wilcoxon signed rank test, which does not assume normal distribution of data, will be used to assess the statistical significance of the percent change in mean seizure frequency from baseline at each of the 6-month intervals.

[redacted]

[redacted]

7.1.2. Safety

The Serious Adverse Event (SAE) rate will be calculated for the Long-term Treatment Investigation. The SAE rate is defined as the proportion of subjects having a serious adverse event.

[redacted]

7.3. Secondary Analyses

7.3.1. Efficacy

7.3.1.1. Responder Rates

The responder rate is defined as the proportion of subjects with a greater than or equal to 50% reduction in mean frequency of total disabling seizures for a given 6-month interval beginning 6 months post-implant compared to pre-implant baseline.

[redacted]

[redacted] A linear logistic regression model will be used to assess the sustainability of the effect over time. The model will be linear in time. The outcome of interest is the slope over time.

7.3.1.2. Quality of Life

Quality of life in individual subjects will be measured with the QOLIE-89 assessment inventory (or QOLIE-31-P for Spanish-speaking subjects) for each year of follow-up as well as for the pre-implant baseline. The effect of treatment with the RNS® System on QOL will be assessed by fitting a GEE model to the yearly outcome assessments. The model will be linear in time. The outcome of interest is the slope over time.

7.3.2. Safety

7.3.2.1. Adverse Event Rates

All adverse events (AEs) will be recorded on the case report forms. The frequency and rate of occurrence of each type of AE will be presented in Tabular form, on both a per-subject and a per-event basis.

[redacted]

[redacted]

7.4.1. Missing Data

Every effort will be made to collect all data points in the study. The sponsor plans to minimize the amount of missing data by appropriate management of the prospective clinical investigation, proper screening of study subjects, and training of participating investigators, monitors and study coordinators.

[redacted]

7.4.2. Treatment Failures

Data from subjects with protocol violations that seriously affect the integrity of the data collected or make it impossible to legally include the data will be excluded from the efficacy analyses, but *will* be included in the analyses of safety. The protocol violations that will result in subject data being excluded from the efficacy analyses are:

- Subjects whose data were excluded from the RNS® System Feasibility Clinical Investigation efficacy analyses for protocol violations
- Subjects whose data were excluded from the RNS® System Pivotal Clinical Investigation efficacy analyses for protocol violations
- Subjects who *did not* meet the following Long-term Treatment inclusion criteria
    - Subject or legal guardian is able to provide appropriate consent to participate.
- Subjects who *did not* meet the following Long-term Treatment exclusion criteria
    - In the opinion of the investigator, the subject has active psychiatric or medical illness that, in the opinion of the investigator, makes it inadvisable for the subject to continue to receive responsive neurostimulation therapy with the RNS® System
    - Subject has been diagnosed with psychogenic or non-epileptic seizures, or primarily generalized seizures during the RNS® System Feasibility or Pivotal Clinical Investigations

[redacted]

[redacted]

[redacted]

7.5. Poolability Analyses for Investigational Sites

For the primary and secondary objectives, baseline information for all subjects will be provided for each participating institution and for all institutions combined. This information will be used to assess whether or not the data can be pooled. The analysis investigating site differences will include combining small sites and including sites as indicator variables in the analysis. The analysis of variance (ANOVA) will be the statistical assessment method. This study will be conducted such that; 1) the same protocol will be used at each site; 2) site investigators and personnel will receive uniform training; and 3) central data management and monitoring will be applied with equal rigor at all sites. The diversity of hospital and clinical practice settings will add to the scientific validity and generalizability of the findings.

[redacted]

8 Data Management

8.1. Data Types and Sources

Data required during the Clinical Investigation comes from or can be traced to various sources. The primary means of collecting and verifying data are defined below. [redacted]

8.1.1. Source Documents

Source documents are reports or records of medical and health information that are required to be filed in the subject binder or must be made available during monitoring visits or audits. Examples include the signed consent form, clinical notes, completed surveys, seizure diaries and medical record documents.

[redacted]	[redacted]
QOLIE 89 / QOLIE-31-P	The Quality of Life Inventory - 89 (QOLIE-31-P for Spanish-speaking subjects) is provided to the subject to complete during investigational appointments. The inventory itself is the source document. [redacted]

8.1.2. Electronic Case Report Forms (eCRF)

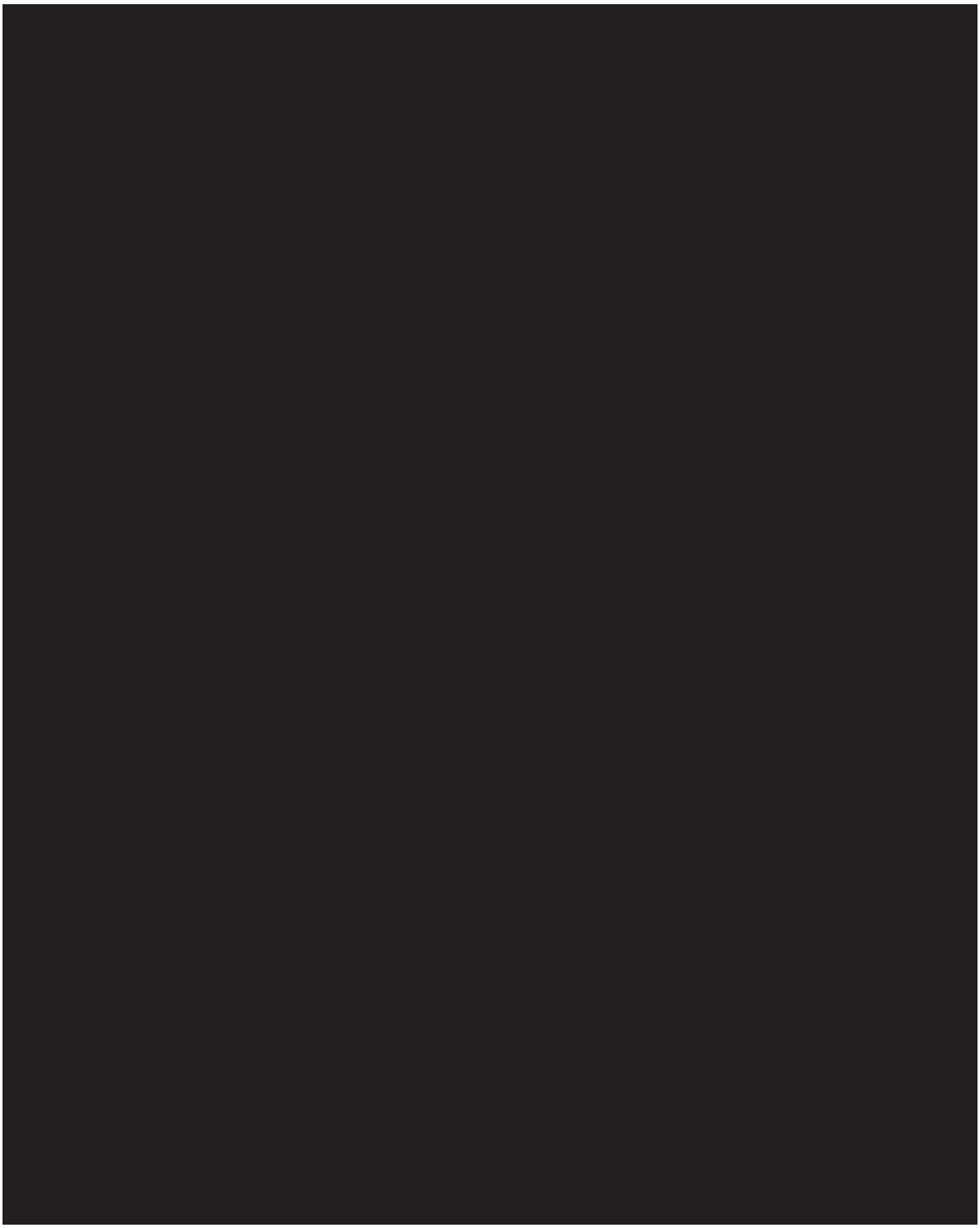
[redacted]

Data entered and captured on the electronic CRFs are the official record. Direct entry is defined as recording original observations directly into the electronic record (i.e. the electronic record is the original capture of the data). Original observations are those values that represent the first recording of study data (i.e. can be information obtained during interviews with the subject, through medical exams, and any other information (excluding seizure data) captured during subject appointments). [redacted]

[redacted]

8.2. Required Data

The investigation requires that a unique data set be collected for each subject. The data collected are categorized by type and source as described in **Table 8-2:** Data for Clinical Investigation below.



[redacted]

Survey	Description
Quality of Life in Epilepsy – 89	Data from the QOLIE-89 survey.
Quality of Life in Epilepsy – 31	Data from the QOLIE-31-P survey.

8.3. Collecting Data – Special Instructions

8.3.1. Informed Consents

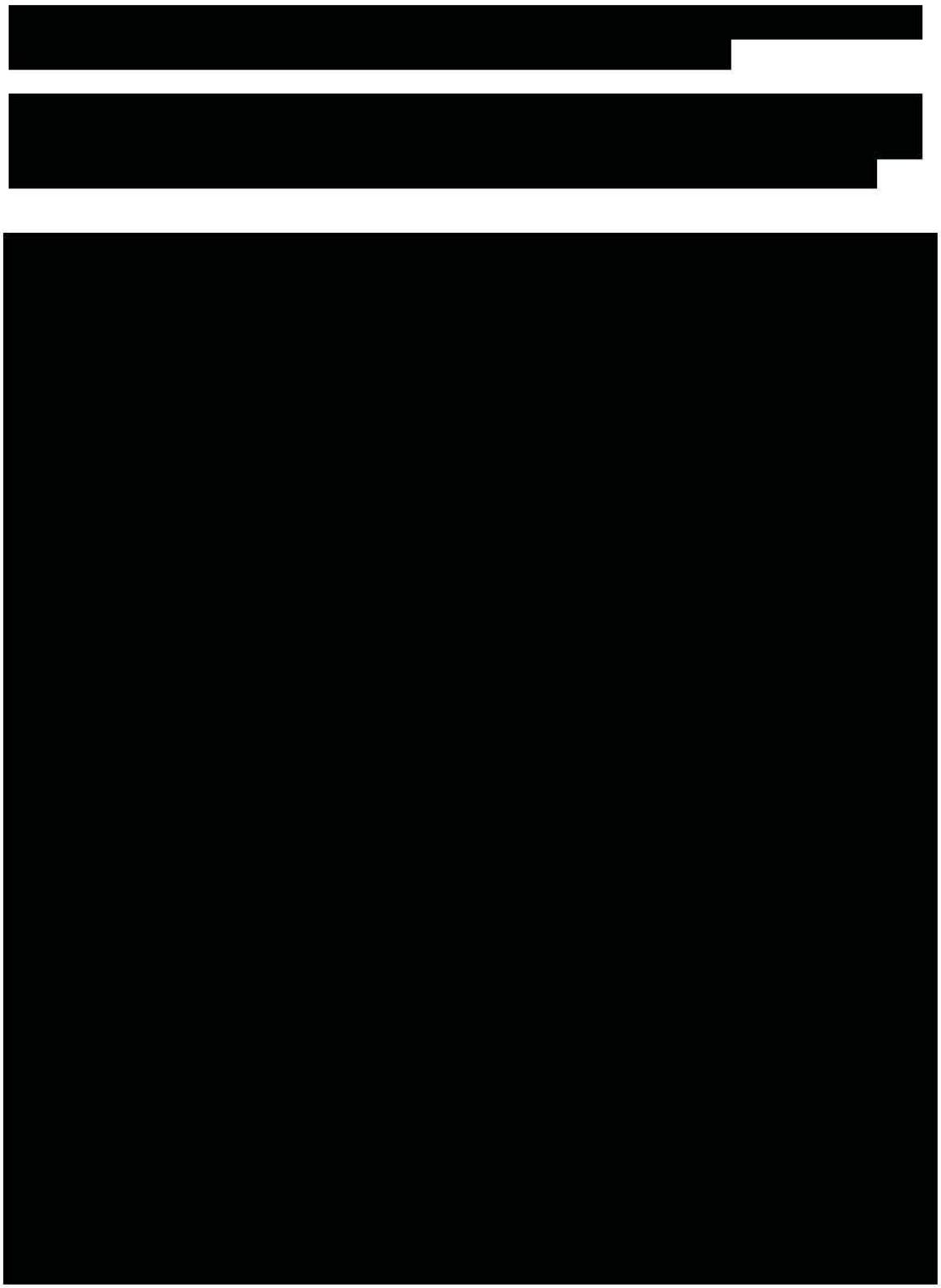
A Consent Information eCRF should be submitted [redacted] for each Informed Consent form that the subject is required to sign during the clinical investigation (e.g. the original consent plus any additional consenting requirements due to informed consent changes, updated expiration dates, etc).

8.3.2. Seizure Data

NeuroPace provides official copies of a Seizure Calendar used to record the subject's seizures each month. The seizure calendar is provided to the subject and is reviewed by the investigator at office appointments. [redacted]

[redacted]

[redacted]



8.3.3. Quality of Life Data

8.3.3.1. Quality of Life in Epilepsy in adults (QOLIE-89 / QOLIE-31-P)

The Quality of Life survey (QOLIE-89 for English-speaking subjects / QOLIE-31-P for Spanish-speaking subjects) survey measures overall quality of life, emotional well-being, role limitations due to emotional problems, social support, social isolation, energy/fatigue, worry about seizure, medication effects, health discouragement, work/driving/social function, attention/concentration, language, memory, physical function, pain, role limitations due to physical problems, and health perceptions. A reference copy of the QOLIE-89 and QOLIE-31-P surveys are provided in **Appendix 16.4** (Devinsky et al 1995, Wiebe et al. 2001 and Cramer et al. 2003).

8.4. Collection Tools for Subject Data

8.4.1. Subject Binders

Subject binders are provided by NeuroPace to maintain the originals (or copies) of all source documents and all materials. This includes all source documents and Appointment Packets.

8.4.2. Appointment Packets

NeuroPace provides official copies of the Clinical Notes as part of the Appointment Packets to use to record subject data during office appointments.

8.5. Data Maintenance

8.5.1. Required Data Fields

All fields indicated with an asterisk (*), either on an eCRF or a clinical note, are required and should not be left blank.

- eCRFs:
  - If a required field is not applicable (n/a) or not available (missing), indicate such by choosing the appropriate choice from the drop-down list on the eCRF (e.g. “n/a”, “missing”, etc).
  - A comment should be entered at the bottom of the eCRF explaining the reason for the missing data.
- Clinical Notes:
  - If a required field is not applicable (n/a) or the data point is not available (missing), indicate such data as “n/a” or “missing”, respectively.

- For data fields (required or not required) on a clinical note where direct entry into an eCRF on PDMS was used, cross-out, sign and date the question or data field.

Fields which are 'not required' may be left blank if the question is not applicable to the subject.

8.5.2. Data Queries

NeuroPace will initiate data queries via email or fax to clarify missing, inconsistent, or erroneous data entries. A documented and recorded response to the query is necessary for resolution. Data queries should be addressed within thirty (30) days from receipt of the query.

Providing missing data and/or outstanding information to NeuroPace will resolve the query. If the missing data or outstanding information is unknown or not available, that should be recorded as a response to resolve the query.

8.5.3. Edits

[redacted]

Edits to Clinical Notes or the seizure collection materials must have a single line through the values changed, be made legibly, initialed, and dated by the person making the change. Correction fluid or covering label must not be used. All entries made to Clinical Notes should be made with permanent ink. No pencils or erasable pens should be used.

8.5.4. Protocol Deviations

Two types of deviations can occur during the clinical investigation: Protocol deviations and Protocol Violations. Each type is defined below.

Protocol Deviations

Protocol deviations are defined as instances when the protocol is not adhered to, and the result likely has little impact upon the data collected. While not a comprehensive list (as all types of deviations cannot be foreseen prior to conductance of the investigation), issues that are considered deviations are identified below:

- Subject does not meet inclusion and exclusion criteria for the investigation with the exceptions of those inclusion and exclusion criteria listed below, for which failure to meet eligibility constitutes a protocol violation.
- Failure to adhere to appointment schedule
- Failure to report mild device related adverse events
- Failure to enter data into eCRFs in a timely manner

Protocol Violations

Protocol violations are defined as instances when the protocol is not adhered to and the impact is substantial. Protocol violations that are considered "treatment failures" are described in **Section 7.4.2.** While not a comprehensive list (as all types of deviations cannot be foreseen prior to conductance of the investigation), issues that are considered violations are identified below:

- Subject has *not* completed either the RNS® System Feasibility or Pivotal Clinical Investigations
- Investigator does not obtain informed consent prior to performing any study procedure
- Investigator does not record and/or inform NeuroPace of any serious adverse event
- Failure to schedule or conduct appointments
- Failure to provide data to sponsor

The principal investigator is responsible for documenting protocol deviations and protocol violations that occur during the Clinical Investigation. It is important to describe what happened and how the situation will be corrected to avoid future occurrences.

NeuroPace representatives will audit the data at clinical sites and may find protocol deviations/violations and regulatory compliance issues during the review of subject data and records. In the event of an identified deviation or violation, the investigator is required to notify the Institution's IRB per their standard procedures. Confirmation of receipt of the deviation or violation by the IRB is required to be forwarded to NeuroPace.

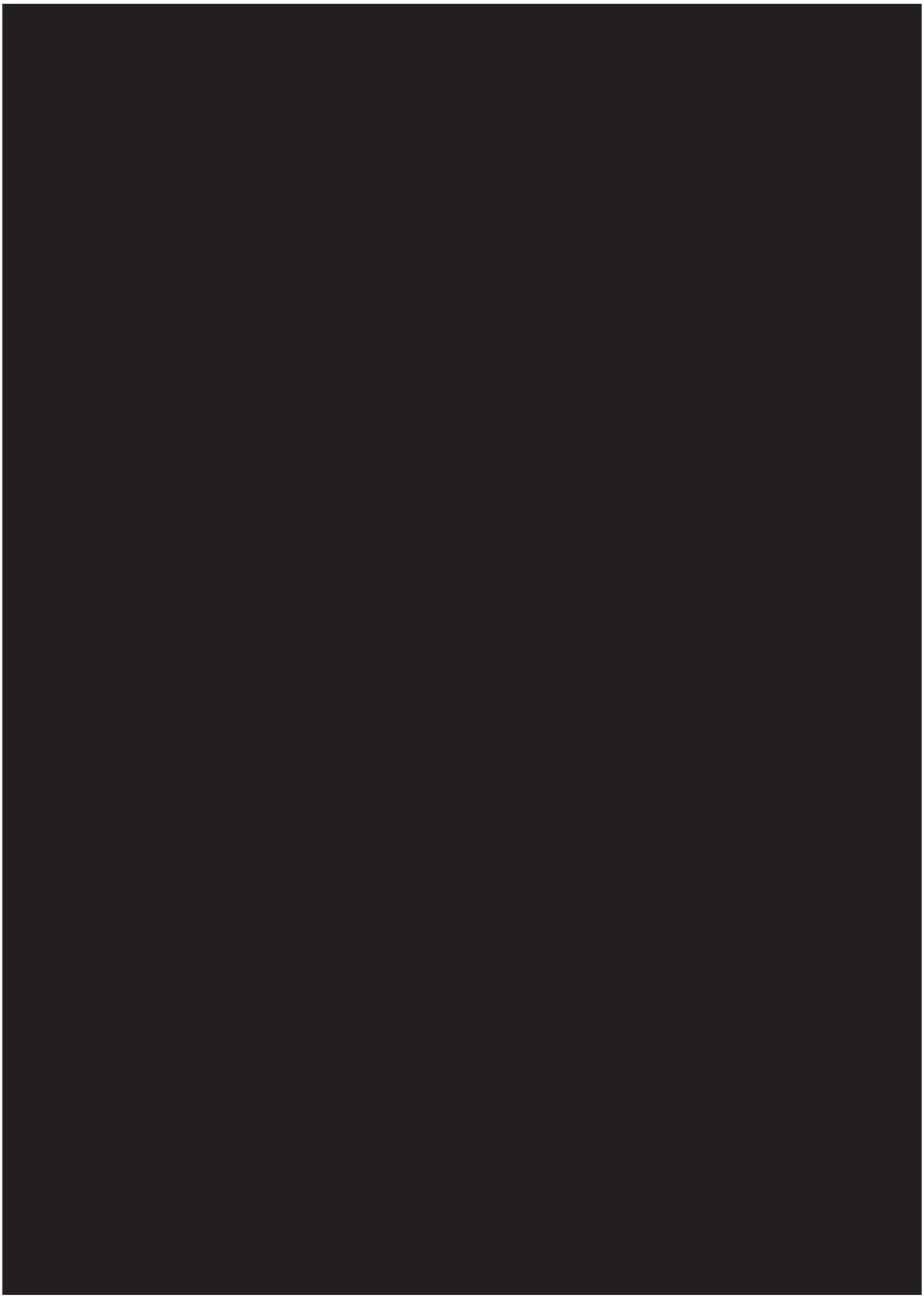
Issues that affect protocol or data integrity or patient safety

- Report to NeuroPace immediately upon discovery of the issue

8.6. Confidentiality, Use and Disclosure of Subject Data

A subject's participation in the study and the health information collected about that subject (study data) are considered confidential and will be managed by NeuroPace in accordance with NeuroPace's Privacy Policy [redacted].

[redacted]



[redacted]

8.7. Data Processing

The NeuroPace Clinical department members (including Field Clinical Representatives) and the NeuroPace Research department are responsible for study management, study monitoring and coordinating and/or performing statistical analysis.

[redacted]

9 Monitoring Procedures

NeuroPace is responsible for implementing the investigation in accordance with applicable FDA regulations, 21 CFR Part 11, 21 CFR Part 50, 21 CFR Part 56, and *Oversight of Clinical Investigations-A Risk-Based Approach to Monitoring* (August 2013).

9.1. NeuroPace Representatives

A NeuroPace representative is an individual trained in the procedures and responsibilities of the RNS® System Long-term Treatment Clinical Investigation. [redacted] The principal investigator and staff are welcome to contact a NeuroPace representative at any time.

9.2. Site Visits

The principal investigator, co-investigators and clinical research staff must agree to cooperate and allow NeuroPace representatives to conduct initial, periodic and final on-site audits.

9.2.1. Study Initiation/Training Visit

The initial visit occurs prior to the initiation of the clinical investigation (prior to the enrollment of the first subject). The visit entails a review of the clinical site facilities, a review of the regulatory obligations, protocol training, and a review of all required documents on file to date.

9.2.2. Interim Monitoring Visit

The interim visits to the investigational site are made to review the subject data and records, to resolve queries or discrepancies in data and documents, to account for devices and to review compliance to regulatory standards and guidelines. Sites will be monitored based on data available and will occur at a minimum of every three months unless no data are available. The principal investigator is responsible for clarification and resolution of any discrepancies.

9.2.3. Final/Close Out Visit

The close-out visit to the investigational site is to close outstanding queries and discrepancies, to review and complete subject data and records, to remove devices and confirm adherence to regulatory standards and guidelines. The principal investigator is responsible for clarification and resolution of any discrepancies before the Clinical Investigation is closed at the site.

9.3. Device Accountability

Device accountability records must be maintained at each clinical site for investigational product only. The number of investigational devices delivered to and returned by the Investigator and the used investigational devices should be documented. At a minimum, the investigational device information listed below must be recorded. Any accountability discrepancy at the end of the investigation will be explained in writing by the Investigator.

- Investigational Device Model #
- Investigational Device Serial #
- Date of Investigational Device Receipt
- Date of Investigational Device Use
- How Investigational Device Used
- Patient ID (If provided to or implanted in a subject)
- Investigational Device Disposition if Explanted

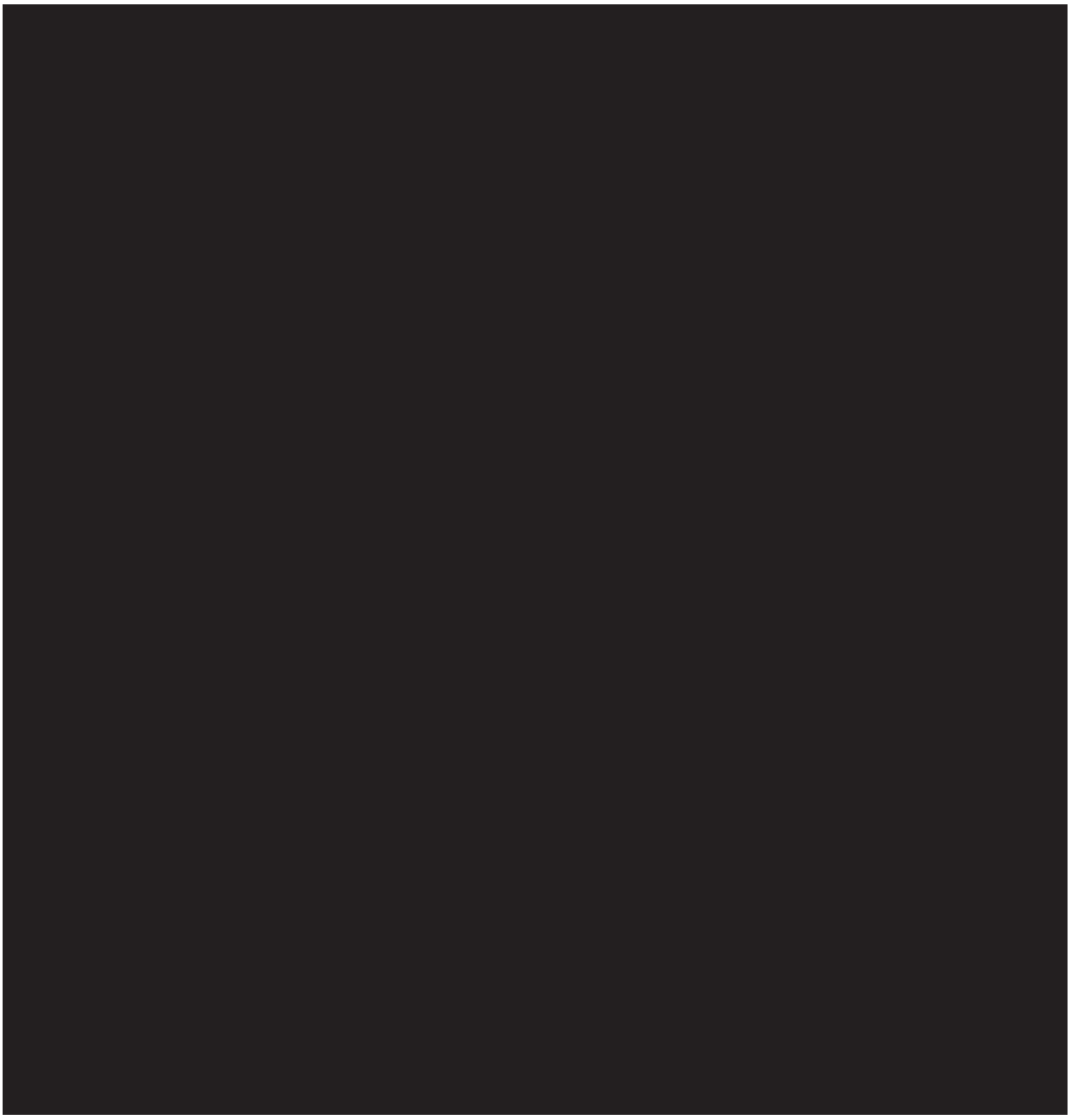
9.4. Monitoring Procedure

A standard monitoring procedure for Clinical Investigations is followed by NeuroPace monitors [redacted].

10 Adverse Events

10.1. Event Definitions

For the purposes of the clinical investigation the definitions listed below will be used for adverse event reporting.



10.1.2. Adverse events

An adverse event is defined as a negative change in the subject's physical or mental health as experienced by the subject or observed by the clinician during any part of the Clinical Investigation.

Adverse events are classified relative to two main variables (severity and investigational device relation) as defined in detail in **Table 10-1:** Adverse Event Classification.

Table 10-1: Adverse Event Classification

Severity	
Mild (Non-serious)	**Serious**
▪ Minor in nature or behavior ▪ Acute and self-limited, or transient ▪ No need for invasive medical or procedural intervention to alleviate the adverse event ▪ Any adverse event that is not serious	▪ Significant risks or consequences to the subject's acute or long-term health, serious injury or death ▪ Hospital admission or invasive medical intervention required to alleviate the adverse event
Device Relation	
Device Related	**Not Device Related**
▪ The event is definitively or potentially related to a NeuroPace device	▪ The event is not related to a NeuroPace device

For adverse events (device-related or of uncertain device relation) it is necessary to define whether the adverse event is anticipated or unanticipated. Anticipated (expected) adverse events are events previously identified in nature, severity or degree of incidence in the investigational plan.

[redacted] The clinical department reviews and responds promptly to [redacted] reported events and to adverse events otherwise reported by the site, by the field clinical engineers or by the site monitors. The NeuroPace clinical department ensures that proper recording and reporting occurs. All serious adverse events are brought to the attention of the Chief Medical Officer.

10.1.2.1. Event Resolution

It is necessary to identify the status (ongoing vs. resolved) for each adverse event reported during the clinical investigation. An ongoing event should be checked at each subsequent appointment to identify if the event has resolved or if additional interventions or diagnostic testing have been performed in response to the event. Any event which develops into a chronic health condition should be identified by a status of "Ongoing – Chronic".

10.2. Event Documentation

10.2.1. Deaths

For any death, copies of autopsy reports or other medical or diagnostic information pertinent to cause of death must be collected and provided to NeuroPace. NeuroPace will provide this information to the SUDEP Analysis Committee and the Data Monitoring Committee.

[redacted]

In addition, clinicians will be asked to complete a Death and Autopsy Information Form to collect information required as specified by the FDA as part of the conditions for approval for the RNS® System. [redacted]

10.2.2. Adverse events

The clinician who observes or learns of the adverse event is responsible for documenting the occurrence on required source documents [redacted]

10.2.2.1. Exception for Documenting an Adverse Event

Stimulation testing will be performed under an investigator's supervision to determine a subject's tolerance to proposed settings.

Transient phenomena that are mild, such as sensations, motor responses, or suspected brief afterdischarges (AD's) on an ECOG are expected. Generally these phenomena are resolved by a change in the settings for stimulation testing and do not need to be documented as an Adverse Event.

Documentation is required if the transient phenomena is:
- Serious and resolved by a change in the stimulation testing settings;
- Mild or serious and not resolved by a change in the settings for stimulation testing.

10.3. Event Reporting

Adverse events may required to be reported to the reviewing Institutional Review Board (IRB). The minimum reporting responsibilities are as follows:

Event Type	Severity	Device-Relation	Expectedness[1]	Reporting Obligation to IRB
Adverse event	Mild (non-serious)	No	Not applicable	Per reviewing IRB processes
Adverse device effect	Mild (non-serious)	Yes	Anticipated	Per reviewing IRB processes
Adverse device effect	Mild (non-serious)	Yes	Unanticipated	Per reviewing IRB processes
Adverse event	Serious	No	Not applicable	Per reviewing IRB processes
Adverse device effect	Serious	Yes	Anticipated	Per reviewing IRB processes
Adverse device effect	Serious	Yes	Unanticipated	Immediately[2]

[1] It is necessary to define whether the device related event is:

Anticipated (expected) that the device contributed to or caused the adverse event; or

Unanticipated (not expected) that the device would contribute to the adverse event

[2] Serious Unanticipated Adverse Device Effects are reported to the reviewing IRB and NeuroPace as soon as possible but no later than ten (10) working days after first learning of the event.

10.3.1. Deaths

All subject deaths occurring during the investigation should be reported to NeuroPace within 24 hours of first learning of the event.

11 Risk Benefit Analysis

Refer to the RNS® System Clinical Summary, located at www.neuropace.com, for discussion of the risk benefit analysis for the FDA approved RNS® System.

12 Study Committees

12.1. Data Monitoring Committee

NeuroPace has established an independent Data Monitoring Committee (DMC) for the RNS® System Clinical Investigations (Feasibility, Pivotal, and Long-term Treatment) in accordance with applicable FDA regulations and in general as informed by the FDA draft guideline, Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees (March, 2006). [redacted]

12.1.1. DMC Scope

The DMC is responsible for independently monitoring the safety of interventions during the investigation by reviewing data made available by NeuroPace acting in the capacity of the Coordinating Center. The DMC will make recommendations to NeuroPace (the Sponsor) about safeguarding the interests of trial participants and about stopping, modifying or continuing the investigation.

12.1.1.1. SUDEP

Information regarding all deaths that occur during the investigation, the SUDEP Analysis Committee's classification with respect to SUDEP, as well as the data supporting that classification, will be communicated to the Chair of the Data Monitoring Committee (DMC) by NeuroPace.

[redacted]

12.1.2. Member Composition

The DMC is headed by a chairperson and is composed of clinicians with expertise in relevant clinical specialties. [redacted]

12.1.3. Meetings

[redacted] In particular, the DMC has the responsibility of determining if the data quality is adequate and if the data suggests there are safety issues that warrant action up to and including suspension of the Clinical Investigation.

The DMC reports their recommendations to NeuroPace as the sponsor of the Clinical Investigations. NeuroPace compensates members of the DMC for their time and expenses incurred by serving on the DMC, and provides funds for administrative assistance if requested by the Chairperson of the DMC. No DMC members have a financial interest in the Sponsor. [redacted]

[redacted]

12.2. SUDEP Analysis Committee

NeuroPace has established an independent SUDEP Analysis Committee for the RNS® System Clinical Investigations (Feasibility, Pivotal, and Long-term Treatment).

12.2.1. SUDEP Analysis Committee Scope

The committee is responsible for reviewing data regarding any deaths that occur for subjects participating in the RNS® System Clinical Investigations. All data provided by the investigator will be made available to members of the committee. The investigator will be requested to provide autopsy information as well as medical records and other diagnostic information relevant to cause of death.

[redacted]

[redacted]

[redacted]

12.2.2. Member Composition

At a minimum, the SUDEP Analysis Committee will consist of 3 members [redacted] Committee members will not have a current relationship to NeuroPace as an investigator. No members of the Committee will have a financial relationship with NeuroPace, other than receiving appropriate compensation for participation on the committee.

[redacted]

[redacted]

13 Ethical Considerations

13.1. Declaration of Helsinki

The Clinical Investigation will be performed in accordance with the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki (Refer to **Appendix 16.12**), and applicable FDA regulations.

13.2. Institutional Review Board

The Institutional Review Board (IRB) at each investigational site must administrate the Clinical Investigation in compliance with the applicable FDA regulations 21 CFR Part 50 for the informed consent, 21 CFR Part 56 for the Institutional Review Board.

It is the Investigators' responsibility to obtain and maintain written approval of the investigational protocol, the Informed Consent form, other written subject information, and any proposed advertising material from the appropriate IRB. The Investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the Informed Consent form.

A copy of the written approval, the approved versions of the documents must be forwarded to the NeuroPace clinical department upon receipt from the local IRB. The approval should include study identification and the date of approval. A list of the IRB members, including titles and occupations, or the IRB assurance number must also be provided to the NeuroPace clinical department. NeuroPace will provide a standard form to capture this information.

At a minimum the Investigator should notify the IRB of deviations from the protocol, serious unanticipated adverse events, and data reports provided by the NeuroPace. The Investigator's IRB may impose additional requirements with which the Investigator must comply. All correspondence with the IRB should be maintained in the regulatory and subject files as appropriate and copies of such correspondence should be forwarded to NeuroPace.

13.3. Emergency Actions

NeuroPace accepts the right of the Investigator to initiate emergent medical intervention that may not be defined in the study protocol when necessary to safeguard the life or physical well-being of a study subject. The Investigator must give notice of any emergency deviations and justification for the deviation to the study personnel responsible at NeuroPace and the IRB as quickly as possible after the episode, and in any event no later than 24 hours after the emergency.

13.4. Informed Consent Materials

Consent must be provided in a manner consistent with the Institutional Review Board (IRB) requirements for the site performing the Clinical Investigation and in compliance with Food and Drug Administration (FDA) regulations, 21 CFR Part 50, prior to a subject's participation in the Clinical Investigation.

The clinical protocol procedures, the risks and potential benefits, and the rights of the subject must be discussed with each potential subject and/or legal guardian (if applicable).

It is required by FDA regulations and Good Clinical Practices to document the informed consent process (either initial or subsequent consents) for all subjects participating in an FDA approved clinical investigation. The record of the informed consent process for the initial consent should document that the informed consent was obtained prior to participation in the study and should be filed in the subject's binder.

The consent is an important legal document that explains the research study and expectations for a subject participating in a research study. The potential subject, or legal guardian having power of attorney over health decisions must provide a written consent to participate in the Clinical Investigation. [redacted]

Note: The principal investigator or co-investigators are responsible for obtaining the initial informed consent.

Note: Information collected on an individual subject is considered confidential and will be managed in accordance with the NeuroPace Privacy Policy [redacted].

13.5. Amending the Investigational Plan

This investigational plan and clinical protocol are to be followed exactly. An official amendment from NeuroPace must be received by the clinical site and approved by the local IRB in order to alter any investigational information or activity. Administrative changes that do not affect the subject benefit/risk ratio may be made by NeuroPace without further approvals from the local IRB; sites will be notified in the event of these circumstances.

14 Study Administration

14.1. Required Documents and Record Retention

The principal investigator is responsible for implementing the Clinical Investigation in accordance with the investigational plan, agreements, any conditions of approval imposed by the Institutional Review Board (IRB) and applicable FDA regulations, 21 CFR Part 50 and 21 CFR Part 56.

14.3. Initiating the Clinical Investigation

The following activities and materials are required to be completed prior to enrolling a subject in the Clinical Investigation. Note that the investigation will not be initiated before NeuroPace has received written approval from the FDA and a copy of the IRB approval letter and IRB approved Consent Form for the participating clinical site (as described below). An investigation Administrative Binder is provided to each site to organize and maintain required documents in order to meet regulatory compliance.

Note: Initiation of clinical sites for participation in the LTT study is complete. While this section is no longer relevant to the current stage of the study, it is being maintained for documentation purposes.

14.3.1. IRB Approval

- Submit prepared Protocol and Consent Form to NeuroPace for review
- Submit agreed upon Protocol application and Consent Form to the IRB and NeuroPace
- Receive full approval for the Protocol and Consent Form from your IRB
- Submit a copy to NeuroPace and file a copy in Administrative Binder:
    - IRB approval letter
        - This document is prepared by the IRB and provides authorization to conduct the protocol and approves the Consent Form
        - Final IRB approved version of the protocol
        - Final version of the IRB approved Informed Consent Form
        - The Informed Consent Form should have an IRB approval stamp and/or other means of designating the version or approval date of the specific Consent Form approved by the IRB.
- All IRB correspondence must be filed in the Administrative Binder
- If available, a copy of the IRB Regulations and Guidelines should be filed in the Administrative Binder.
- The original investigational plan sent on CD must be filed in the Administrative Binder

14.3.2. Signed Agreements

- Clinical Investigation Agreement (and Financial Terms)

[redacted]

- Financial Disclosure Form

[redacted]

- Electronic Signature Agreement

[redacted]

- Site Signature and Delegation Log

[redacted]

- Protocol Signature Page (**Appendix 0**)

[redacted]

14.3.3. Good Clinical Practices (GCP)/Human Subjects Protection (HSP)

- All site personnel participating must provide proof of GCP or HSP training

14.3.4. Curriculum Vitaes (CV)

- Each individual involved in the Clinical Investigation must provide a CV
- The CV should provide a statement of experience for that individual
- Submit each participant's CV to NeuroPace and file a copy in the Administrative Binder

14.3.5. Training Documentation

- Participating site personnel are required to be trained on applicable topics before participating in the Clinical Investigation
- NeuroPace personnel will contact the site prior to enrollment of the first subject to conduct required training
- Signed training documentation must be filed in the Administrative Binder and a copy provided to NeuroPace

[redacted]

14.4. Conducting and Maintaining the Investigation

The following activities and materials are required to maintain proper compliance during the course of the Clinical Investigation. All materials (including all correspondence with the IRB, NeuroPace, the monitor, another investigator, or the FDA) must be filed appropriately in the Administrative Binder.

14.4.1. Demonstrate Proper Conduct of the Investigation

- At a minimum, the investigator must continue to perform the following responsibilities in order to continue the investigation
  - Comply with protocol and applicable FDA regulations
  - Complete required documents and training for newly added investigators
  - Obtain signed Informed Consent Forms before conducting any study-specific tests or procedures
  - Complete all electronic CRFs and other source documents, data queries and monitoring reports promptly
  - Oversee the use and handling of the investigational device
  - Maintain the Monitoring Visit Log
  - Maintain investigational device accountability and tracking documentation as referenced in **Section 9.3**
  - Abide by the Publication Policy (see below)
  - Obtain updated CVs for site personnel every 2 years and file in Administrative Binder
  - Obtain annual IRB approval for the continuation of the Clinical Investigation

14.4.2. Obtain IRB Approval for Protocol/Consent Form Amendments

- Submit prepared Protocol and/or Consent Form Amendments to NeuroPace for review
- Submit agreed upon Protocol and/or Consent Form Amendments to the IRB and NeuroPace
- Receive full approval for the amended Protocol and/or Consent Form to the IRB
- Submit to NeuroPace and file in Administrative Binder:
    - IRB approval letter for the Amendment
    - Final version of newly approved protocol
    - Final version of newly approved Informed Consent Form
        - The amended informed consent should have an IRB approval stamp and/or other means of designating version or approval date of the specific Consent Form approved by the IRB.
- Investigation amendments (sent on CD) must be filed in the Administrative Binder

14.4.3. Provide Necessary Information to the Sponsor and/or IRB

- The principal investigator is responsible for providing written documentation to the IRB and Sponsor for the items below and for maintaining all such correspondence in the Administrative Binder:
    - Adverse events*
    - Withdrawal of IRB approval
    - Protocol deviations*
    - Annual progress reports and final report

* Refer to **Section 10.3** for event reporting obligations and **Section 8.5.4** for protocol deviation and violation reporting obligations

14.5. Concluding the Clinical Investigation

The principal investigator must provide any missing regulatory documents, all required documents for each subject enrolled and resolve any outstanding queries before the Clinical Investigation may be concluded at the institution.

14.6. Criteria for Terminating the Clinical Investigation

NeuroPace reserves the right to terminate the Clinical Investigation but intends only to exercise this right for valid scientific or administrative reasons or reasons

related to the protection of subjects. Investigators and associated IRBs will be notified in writing in the event of termination.

Possible reasons for termination of the Clinical Investigation include:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the clinical investigation.
- A decision on the part of NeuroPace to suspend or discontinue development of the device.

14.7. Criteria for Terminating a Clinical Investigation Center

NeuroPace reserves the right to terminate the participation of a Clinical Investigation center at any time for the following reasons:

- If the site is unable to obtain IRB and contract approval within four months of receiving investigational trial materials
- If the center has severe protocol deviations without sufficient justification
- If the Investigator fails to comply with the responsibilities of this investigational plan and applicable FDA regulations

14.8. Record Retention

The principal investigator is responsible for maintaining all required records and reports for a period of two years after the latter of the following two dates: the date on which the investigation is terminated or complete, or the date that the records and reports are no longer required for purposes of supporting the premarket approval application submitted by the sponsor to the FDA or other regulatory agency.

14.9. Publication Policy

Because this Clinical Investigation is part of a multi-center study, the Institution and the Investigators agree that the first publication of the results of the Clinical Investigation shall be made in conjunction with the presentation of a joint, multi-center publication of the Clinical Investigation results, with the investigators from all appropriate sites contributing data, analyses, and comments. If such a multi-center publication is not submitted within twelve (12) months after the conclusion of the Clinical Investigation at all sites, the Institution and/or Investigators may publish the results from the Institution's site individually, subject to the procedures described below.

The Principal Investigator or the Institution shall submit to NeuroPace a copy of any proposed publication at least thirty (30) days for manuscripts and seven (7) days for abstracts prior to submission for publication. NeuroPace shall review

the proposed publication and may provide comments. Any comments by NeuroPace shall be considered in good faith. NeuroPace may request deletion of portions of the publication containing confidential information or information reasonably considered trade secret-type information regarding specific commercial applications, constructions, processes, or formulations, and the submitter agrees to remove such information, or may require that the presentation or publication be withheld for up to ninety days to allow patent applications to be prepared and filed.

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16 Appendices

16.4. Quality of Life Survey

The following surveys are found in this section:

- QOLIE-89 (for English-speaking subjects)
- QOLIE-31-P (for Spanish-speaking subjects)

Investigation RNS™ System Long-term Treatment Clinical Investigation

Site | Subject ID | Subject Initials

QOLIE-89 (SURVEY)

INVESTIGATIONAL USE ONLY

NP-Q1. * Date survey administered (mm/dd/yyyy) ___/___/___

NP-Q2. * Indicate the appointment time point during which the survey was administered:

☐ 12 Month ☐ 24 Month ☐ 36 Month ☐ 48 Month
☐ 60 Month ☐ 72 Month ☐ 84 Month ☐ Unscheduled

INSTRUCTIONS

This survey asks about your health and daily activities. Answer every question by circling the appropriate number (1, 2, 3…).

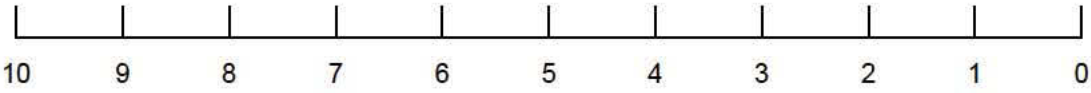
If you are unsure about how to answer a question, please give the best answer you can and write a comment or explanation in the margin.

Please feel free to ask someone to assist you if you need help reading or marking the form.

1. In general, would you say your health is:

Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. Overall, how would you rate your quality of life?



Best Possible Quality of Life

Worst Possible Quality of Life (as bad as or worse than being dead)

3. Compared to 1 year ago, how would you rate your health in general now?

Much better now than 1 year ago	1
Somewhat better now than 1 year ago	2
About the same as 1 year ago	3
M Somewhat worse now than 1 year ago	4
Much worse now than 1 year ago	5

4-13 The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
4.	*Vigorous activities*, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
5.	*Moderate activities*, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
6.	Lifting or carrying groceries	1	2	3
7.	Climbing several flights of stairs	1	2	3
8.	Climbing *one* flight of stairs	1	2	3
9.	Bending, kneeling, or stooping	1	2	3
10.	Walking *more than one mile*	1	2	3
11.	Walking several blocks	1	2	3
12.	Walking *one block*	1	2	3
13.	Bathing or dressing yourself	1	2	3

The following questions are about your regular daily activities, such as working at a job, keeping house, taking care of children, attending school, volunteer work, or taking part in a community services.

14-18: During the past 4 weeks, have you had any of the following difficulties with your regular daily activities or work as a result of any physical problems? (Please answer YES or NO for each question by circling 1 or 2 on each line)

		YES	NO
14.	Cut down on the amount of time you spent on work or other activities	1	2
15.	Accomplished less than you would like	1	2
16.	Were limited in the kind of work or other activities you do	1	2
17.	Had difficulty performing the work or other activities you do (for example, it took extra effort)	1	2
18.	Did your work or other activities less carefully than usual	1	2

19-23: During the past 4 weeks, have you had any of the following difficulties with your regular daily activities or work as a result of any emotional problems? (Please answer YES or NO for each question by circling 1 or 2 on each line)

		YES	NO
19.	Cut down on the amount of time you spent on work or other activities	1	2
20.	Accomplished less than you would like	1	2
21.	Were limited in the kind of work or other activities you do	1	2
22.	Had difficulty performing the work or other activities you do (for example, it took extra effort)	1	2

	YES	NO
23. Did your work or other activities less carefully than usual	1	2

24. How much bodily pain have you had during the past 4 weeks?

None	1
Very Mild	2
Mild	3
Moderate	4
Severe	5
Very Severe	6

25. During the past 4 weeks, how much did bodily pain interfere with your normal work (including both work outside the home and housework)?

Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

26. During the past 4 weeks, to what extent have your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

27-35: these questions are about how you FEEL and how things have been for you during the past four weeks. For each question, please indicate the one answer that comes closest to the way you have been feeing.

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
27.	Did you feel full of pep?	1	2	3	4	5	6
28.	Have you been a very nervous person?	1	2	3	4	5	6
29.	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
30.	Have you felt calm and peaceful?	1	2	3	4	5	6
31.	Did you have a lot of energy?	1	2	3	4	5	6
32.	Have you felt downhearted and blue?	1	2	3	4	5	6
33.	Did you feel worn out?	1	2	3	4	5	6
34.	Have you been a happy person?	1	2	3	4	5	6

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
35.	Did you feel tired?	1	2	3	4	5	6

36-43: How much of the time during the past 4 weeks….

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
36.	Has your epilepsy limited your social activities (such as visiting with friends or close relatives)?	1	2	3	4	5	6
37.	Have you had difficulty concentrating and thinking?	1	2	3	4	5	6
38.	Did you have trouble keeping your attention on an activity for long?	1	2	3	4	5	6
39.	Were you discouraged by problems related to you health?	1	2	3	4	5	6
40.	Have you worried about having another seizure?	1	2	3	4	5	6
41.	Did you have difficulty reasoning and solving problems (such as making plans, making decisions, learning new things)?	1	2	3	4	5	6
42.	Were you discouraged by your epilepsy-related problems?	1	2	3	4	5	6
43.	Have your physical health or emotional problems interfaced with your social activities (like visiting with friends, relatives, etc)?	1	2	3	4	5	6

44-48: Please choose the answer that best describes how TRUE or FALSE each of the following statements is for you.

		Definitely true	Mostly true	Not sure	Mostly false	Definitely false
44.	I seem to get sick (any kind of sickness) a little easier than other people	1	2	3	4	5
45.	I am as healthy as anybody I know	1	2	3	4	5
46.	I expect my health will get worse	1	2	3	4	5
47.	My health is excellent	1	2	3	4	5
48.	When there is an illness going around, I usually catch it	1	2	3	4	5

49. How has the QUALITY OF YOUR LIFE been during the past 4 weeks (that is, how have things been going for you)?

Very well: could hardly be better	1
Pretty good	2
Good & bad parts about equal	3
Pretty bad	4
Very bad: could hardly be worse	5

The following question is about MEMORY.

		Yes, a great deal	Yes, somewhat	Only a little	No, not at all
50.	In the past 4 weeks, have you had any trouble with your memory?	1	2	3	4

51-54: Circle one number for how often in the past 4 weeks you have had trouble *remembering* or how often these memory problems have interfered with your normal work or living.

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
51.	Names of people	1	2	3	4	5	6
52.	Where you put things	1	2	3	4	5	6
53.	Things people tell you	1	2	3	4	5	6
54.	Things you read hours or days before	1	2	3	4	5	6

55-59: The following questions are about LANGUAGE problems you may have. Circle one number for how often you have trouble speaking or how often these problems have interfered with your normal work or living.

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
55.	Finding the correct word	1	2	3	4	5	6
56.	Understanding what others are saying in conversation	1	2	3	4	5	6
57.	Understanding directions	1	2	3	4	5	6
58.	Understanding what you read	1	2	3	4	5	6
59.	Writing	1	2	3	4	5	6

60-64: The following questions are about CONCENTRATION problems you may have. Circle one number for how often in the past 4 weeks you had trouble concentrating or how often these problems have interfered with your normal work or living.

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
60.	Concentrating on conversations	1	2	3	4	5	6
61.	Concentrating on a task or job	1	2	3	4	5	6
62.	Concentrating on reading	1	2	3	4	5	6
63.	Concentrating on doing one thing at a time	1	2	3	4	5	6
64.	How often do you feel you react slowly to things that are said or done?	1	2	3	4	5	6

65-68: The following questions are about problems you may have with certain ACTIVITIES. Circle one number for how much during the past 4 weeks your epilepsy or antiepileptic medication has caused trouble with…

		A great deal	A lot	Somewhat	Only a little	Not at all
65.	Working	1	2	3	4	5
66.	Friendships and relationships (romantic)	1	2	3	4	5
67.	Leisure time (such as hobbies, going out)	1	2	3	4	5
68.	Driving	1	2	3	4	5

69-73: The following questions relate to the way you FEEL about your seizures.

		Very fearful	Somewhat fearful	Not very fearful	Not fearful at all
69.	How fearful are you of having a seizure during the next month?	1	2	3	4

		Worry a lot	Occasionally worry	Don't worry at all
70.	Do you worry about hurting yourself during a seizure?	1	2	3

		Very worried	Somewhat worried	Not very worried	Not worried at all
71.	How worried are you about embarrassment or other social problems resulting from having a seizure during the next month?	1	2	3	4
72.	How worried are you that medications you are taking well be bad for you if taken a long time?	1	2	3	4

		Very poorly	Not well	Fair	Well	Very Well
73.	How well do you do with complicated projects that require organization?	1	2	3	4	5

74-80: For each of these PROBLEMS, circle one number for how much they bother you on a scale of 1 to 5, where 1 = Not at all bothersome, and 5 = Extremely bothersome.

		Not at all bothersome				Extremely bothersome
74.	Seizures	1	2	3	4	5
75.	Memory difficulties	1	2	3	4	5
76.	Driving limitations	1	2	3	4	5
77.	Work limitations	1	2	3	4	5
78.	Social limitations	1	2	3	4	5
79.	Physical effects of antiepileptic medication	1	2	3	4	5
80.	Mental effects of antiepileptic medication	1	2	3	4	5

81-83: In terms of your satisfaction with your family and social life, circle one number to indicate the following:

		Poor	Fair	Good	Very good	Excellent
81.	The amount of togetherness you have with your family and/or friends	1	2	3	4	5
82.	The support and understanding your family and/or friends give each other	1	2	3	4	5
83.	The amount you talk things over with your family and/or friends	1	2	3	4	5

84-88: In terms of your satisfaction with your family and social life, circle one number to indicate the following:

		Very satisfied	Somewhat satisfied	Neither satisfied nor dissatisfied	Somewhat dissatisfied	Very dissatisfied
84.	Overall, how satisfied were you with your sexual relations during the past 4 weeks?	1	2	3	4	5

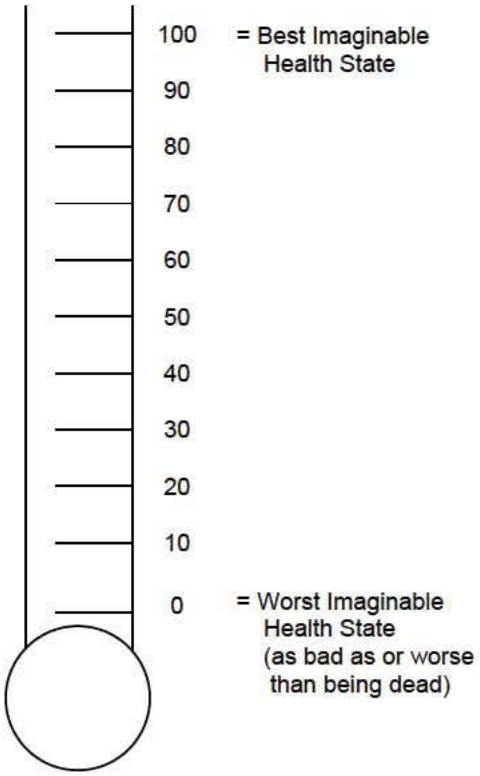
		Much more limited	Somewhat more limited	About the same	Somewhat less limited	Much less limited
85.	How limited are your social activities compared with others your age because of your epilepsy or epilepsy-related problems?	1	2	3	4	5

		Yes, as much as I wanted	Yes, quite a bit	Yes, some	Yes, a little	No, not at all
86.	During the past 4 weeks, was someone available to help you if you needed and wanted help?	1	2	3	4	5

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
87.	How much of the time during the past 4 weeks did you feel left out?	1	2	3	4	5	6

		Always	Very often	Fairly often	Sometimes	Almost never	Never
88.	During the past 4 weeks, how often did you feel isolated from others?	1	2	3	4	5	6

89. How good or bad do you think your health is? On the thermometer scale below, the best imaginable state of health is 100 and the worst imaginable state is 0. Please indicate how you feel about your health by circling one number on the scale. Please consider your epilepsy as part of your health when you answer this question.



Investigation RNS™ System Long-term Treatment Clinical Investigation

Site | Subject ID | Subject Initials

QOLIE-31-P (SURVEY)

INVESTIGATIONAL USE ONLY

NP-Q1. * Date survey administered (mm/dd/yyyy) ___/___/___

NP-Q2. * Indicate the appointment time point during which the survey was administered:

☐ 12 Month ☐ 24 Month ☐ 36 Month ☐ 48 Month
☐ 60 Month ☐ 72 Month ☐ 84 Month ☐ Unscheduled

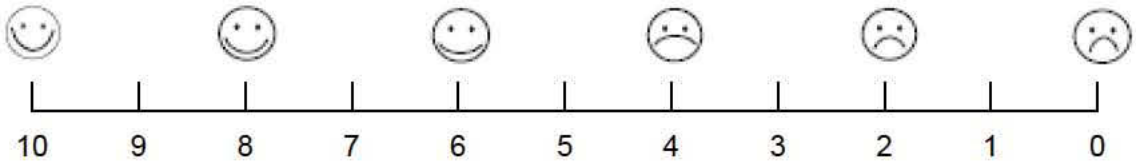
INSTRUCCIONES

Este cuestionario le pregunta por su salud y sus actividades diarias. **Conteste a todas las preguntas** rodeando con un círculo el número de respuesta adecuado (1,2,3...).

Si no está seguro de qué respuesta contestar, elija la respuesta que crea más apropiada y escriba un comentario o explicación al margen izquierdo.

Si lo necesita, no dude en pedir que alguien le ayude a leer o rellenar el formulario.

1. En términos generales, ¿cómo calificaría su calidad de vida?
(Rodee con un círculo un solo número de la siguiente escala)



La Mejor Calidad de Vida Posible

La Peor Calidad de Vida Posible

Cramer et al., Epilepsy Behav 2003

Parte A.

Estas preguntas hacen referencia a cómo se ha SENTIDO durante las últimas 4 semanas. En cada pregunta responda lo que se parezca más a cómo se ha sentido usted.

Durante las últimas 4 semanas ¿cuánto tiempo...
(Rodee con un círculo un solo número)

		Siempre	Casi siempre	Muchas veces	Algunas veces	Sólo alguna vez	Nunca
2.	Se sintió lleno de vitalidad?	1	2	3	4	5	6
3.	Tuvo mucha energía?	1	2	3	4	5	6
4.	Se sintió agotado?	1	2	3	4	5	6
5.	Se sintió cansado?	1	2	3	4	5	6

*Revisando solamente las preguntas en la **Parte A**, considere el impacto global de estos problemas en su vida **en las últimas 4 semanas**.*

(Haga un círculo en un número)

		Nada/ En absoluto	Algo	Moderadamente	Mucho	Muchísimo
6.	¿En qué medida los problemas y las preocupaciones anteriores sobre <u>energía</u> le **afligen** en general?	1	2	3	4	5

Cramer et al., Epilepsy Behav 2003

Parte B.

Estas preguntas hacen referencia a cómo se ha SENTIDO durante las últimas 4 semanas. En cada pregunta responda lo que se parezca más a cómo se ha sentido usted.

Durante las últimas 4 semanas, ¿cuánto tiempo...
(Rodee con un círculo un solo número)

		Siempre	Casi Siempre	Muchas veces	Algunas veces	Sólo alguna vez	Nunca
7.	Estuvo muy nervioso?	1	2	3	4	5	6
8.	Se sintió tan bajo de moral que nada podía animarle?	1	2	3	4	5	6
9.	Se sintió calmado y tranquilo?	1	2	3	4	5	6
10.	Se sintió desanimado y triste?	1	2	3	4	5	6
11.	Se sintió feliz?	1	2	3	4	5	6

*Revisando solamente las preguntas en la **Parte B**, considere el impacto global de estos problemas en su vida **en las últimas 4 semanas.***

(Haga un círculo en un número)

		Nada/ En absoluto	Algo	Moderadamente	Mucho	Muchísimo
12.	¿En qué medida los problemas y las preocupaciones anteriores sobre emociones le **afligen** en general?	1	2	3	4	5

Cramer et al., Epilepsy Behav 2003

Parte C.

Las siguientes preguntas hacen referencia a cómo se SIENTE y a los problemas que puede tener con sus ACTIVIDADES diarias durante las últimas 4 semanas. En cada pregunta responda lo que se parezca más a cómo se ha sentido usted.

La siguiente pregunta hace referencia a cómo se SIENTE y a cómo le han ido las cosas.

Durante las últimas 4 semanas, ¿cuánto tiempo..
(Haga un círculo en un número)

		Siempre	Casi Siempre	Muchas veces	Algunas veces	Sólo alguna vez	Nunca
13.	Su salud ha limitado sus actividades sociales (como visitar a amigos o parientes cercanos)?	1	2	3	4	5	6

Las siguientes preguntas hacen referencia a los problemas que pueda tener con ciertas ACTIVIDADES.

Durante las últimas 4 semanas, ¿cuánto tiempo su epilepsia o su medicación antiepiléptica le ha causado problema con ...

(Rodee con un círculo un solo número)

		Muchísimo	Mucho	Algo	Solo un poco	Nada / En Absoluto
14.	Su tiempo libre (como aficiones, salir)?	1	2	3	4	5
15.	Conducir (o viajar en transporte público)?	1	2	3	4	5

		Nada molestas				Extremada-mente molestas
16.	¿En qué grado le molestan sus limitaciones en el trabajo?	1	2	3	4	5
17.	¿En qué grado le molestan sus limitaciones en su vida social?	1	2	3	4	5

Cramer et al., Epilepsy Behav 2003

*Revisando solamente las preguntas en la **Parte C,** considere el impacto global de estos problemas en su vida **en las últimas 4 semanas**.*

(Haga un círculo en un número)

		Nada/ En absoluto	Algo	Moderadamente	Mucho	Muchísimo
18.	¿En qué grado los problemas y las preocupaciones anteriores sobre las actividades diarias **le afligen** en general?	1	2	3	4	5

Parte D.

Estas preguntas hacen referencia a los problemas que puede haber tenido con el pensamiento, la lectura, la concentración y la memoria durante las últimas 4 semanas. En cada pregunta responda lo que se parezca más a cómo se ha sentido usted.

Durante las últimas 4 semanas, ¿cuánto tiempo..

(Haga un círculo en un número)

		Siempre	Casi Siempre	Muchas veces	Algunas veces	Sólo alguna vez	Nunca
19.	Ha tenido dificultades para razonar y resolver problemas (como hacer planes, tomar decisiones, aprender cosas nuevas)?	1	2	3	4	5	6

		Sí, muchos	Sí, algunos	Sólo un poco	No, ninguno
20.	En las últimas cuatro semanas, ¿ha tenido algún problema con su memoria ?	1	2	3	4

Durante las últimas 4 semanas, ¿cuántas veces ha tenido...
(Rodee con un círculo un solo número)

		Siempre	Casi Siempre	Muchas veces	Algunas veces	Sólo alguna vez	Nunca
21.	Problemas para recordar cosas que la gente le dice ?	1	2	3	4	5	6
22.	Problemas de concentración al leer?	1	2	3	4	5	6

Cramer et al., Epilepsy Behav 2003

		Siempre	Casi Siempre	Muchas veces	Algunas veces	Sólo alguna vez	Nunca
23.	Problemas para concentrarse en una sola cosa a la vez ?	1	2	3	4	5	6

		Nada molestas				Extremada-mente molestas
24.	¿En qué grado le molestan las dificultades de su memoria?	1	2	3	4	5

*Revisando solamente las preguntas en la **Parte D**, considere el impacto global de estos problemas en su vida **en las últimas 4 semanas**.*

(Haga un círculo en un número)

		Nada/ En absoluto	Algo	Moderada mente	Mucho	Muchísimo
25.	¿En qué medida los problemas y las preocupaciones anteriores sobre función mental le **afligen** en general?	1	2	3	4	5

Parte E.

Estas preguntas hacen referencia a los problemas que usted pueda tener relacionados con su epilepsia o medicación antiepiléptica.

Durante las últimas 4 semanas…

(Rodee con un círculo un solo número)

		Nada molestas				Extremada-mente molestas
26.	¿En qué grado le molestan los efectos físicos de la medicación antiepiléptica?	1	2	3	4	5
27.	¿En qué grado le molestan los efectos mentales de su medicación antiepiléptica?	1	2	3	4	5

Cramer et al., Epilepsy Behav 2003

		Me preocupa mucho	Me preocupa bastante	No me preocupa mucho	No me preocupa en absoluto
28.	¿Le preocupa que los medicamentos que está tomando puedan hacerle daño si los toma durante mucho tiempo ?	1	2	3	4

*Revisando solamente las preguntas en la **Parte E**, considere el impacto global de estos problemas en su vida **en las últimas 4 semanas**.*

(Haga un círculo en un número)

		Nada/ En absoluto	Algo	Moderada mente	Mucho	Muchísimo
29.	¿En qué medida los problemas y preocupaciones anteriores sobre los efectos de la medicación le afligen en general?	1	2	3	4	5

Parte F.

Estas preguntas hacen referencia a cómo se SIENTE sobre sus crisis durante las cuatro últimas semanas. En cada pregunta responda lo que se parezca más a cómo se ha sentido usted.

		Siempre	Casi Siempre	Muchas veces	Algunas veces	Sólo alguna vez	Nunca
30.	Le ha preocupado la posibilidad de sufrir otro ataque?	1	2	3	4	5	6

		Mucho Miedo	Bastante meido	No mucho meido	Nada de miedo
31.	¿Le da miedo sufrir un ataque durante las cuatro próximas semanas?	1	2	3	4

Cramer et al., Epilepsy Behav 2003

		Me preocupa mucho	Me preocupa un poco	No me preocupa en absoluto
32.	¿Le preocupa hacerse daño durante un ataque?	1	2	3

		Me preocupa mucho	Me preocupa bastante	Me preocupa un poco	No me preocupa en absoluto
33.	Le preocupa la vergüenza u otros problemas en su vida social que le pudiera causar sufrir un ataque durante las cuatro próximas semanas?	1	2	3	4

		Nada Molestas				Extremada-mente molestas
34.	¿En qué grado le molestan sus ataques?	1	2	3	4	5

*Revisando solamente las preguntas en la **Parte F,** considere el impacto global de estos problemas en su vida **en las últimas 4 semanas**.*

(Haga un círculo en un número)

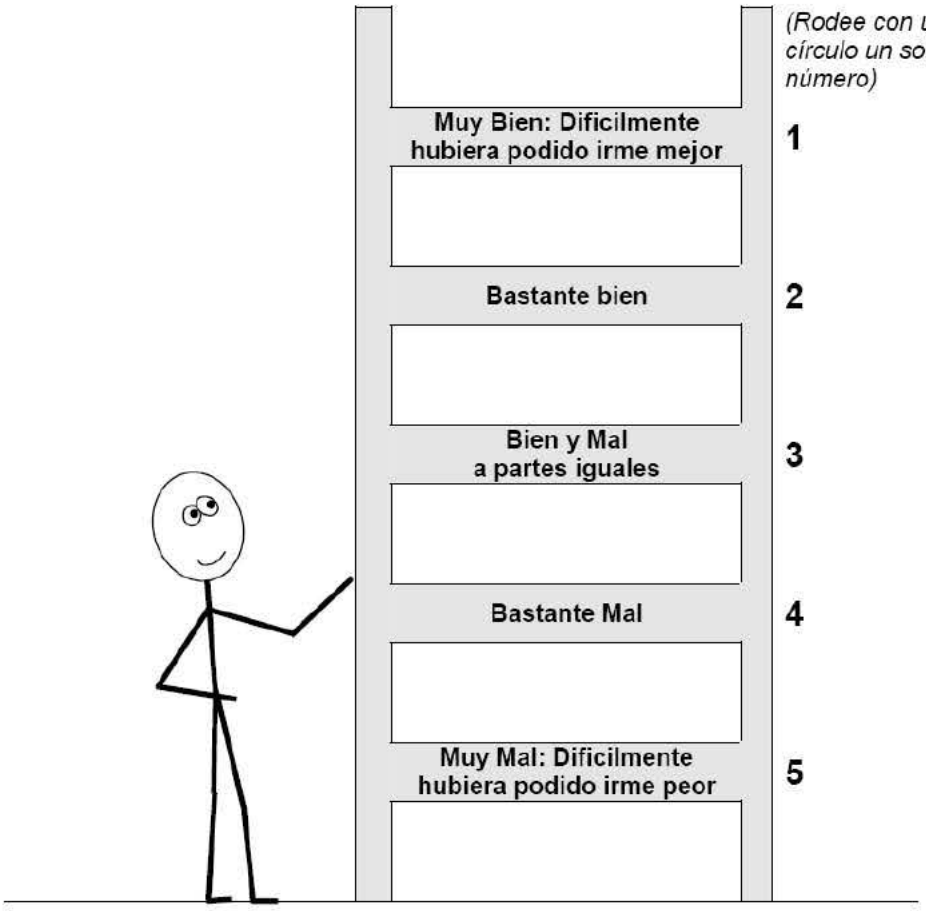
		Nada/ En absoluto	Algo	Moderada mente	Mucho	Muchísimo
35.	¿En qué medida los problemas y las preocupaciones anteriores sobre las crisis le afligen en general?	1	2	3	4	5

Cramer et al., Epilepsy Behav 2003

Parte G.

Las siguientes preguntas hacen referencia a cómo se SIENTE sobre su calidad de vida general. Por favor, indique la respuesta que más se aproxime a cómo se ha estado sintiendo.

36. ¿Qué tal ha sido su **CALIDAD DE VIDA** durante **las últimas 4 semanas** (es decir, cómo le han ido las cosas)?



Cramer et al., Epilepsy Behav 2003

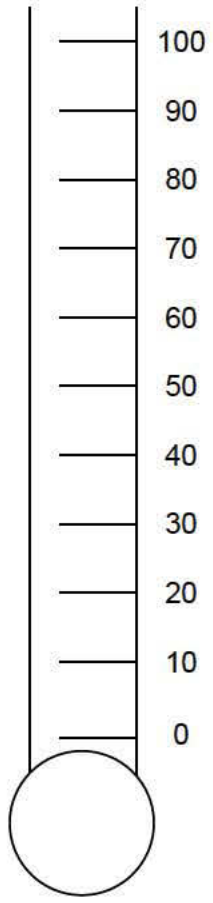
*Revisando solamente las preguntas 1 y 36 en la **Parte G** (en la página 1 y en esta página), considere el impacto global de su calidad de vida en **las últimas 4 semanas**.*

(Haga un círculo en un número)

		Nada/ En absoluto	Algo	Moderadamente	Mucho	Muchísimo
37.	¿En qué grado el estado de su calidad de vida le **aflige** en general?	1	2	3	4	5

Parte H.

38. ¿Cree usted que su SALUD es buena o mala?
En el siguiente termómetro el mejor estado de salud imaginable es 100 y el peor estado imaginable es 0. Indique cómo cree que es su estado de salud rodeando con un círculo un solo número de la escala. **Al responder a esta pregunta, tenga en cuenta que la epilepsia forma parte de su estado general de salud.**



= Mejor estado de salud imaginable

= Peor estado de salud imaginable

Cramer et al., Epilepsy Behav 2003

Parte I.

Considerando TODAS las preguntas que ha contestado, por favor, indique las áreas relacionadas con su epilepsia que son IMPORTANTES para usted AHORA.

39. *Numere los siguientes tópicos de "1" al "7", correspondiendo el "1" al tópico más importante y el "7" al menos importante. Por favor, utilize cada número solamente una vez.*

___ **A.** Energía (cansancio)

___ **B.** Emociones (humor)

___ **C.** Actividades diarias (trabajo, conducción, memoria)

___ **D.** Actividad mental (pensamiento, concentración, memoria)

___ **E.** Efectos de la medicación (fisicos, mentales)

___ **F.** Preocupación por las crisis (impacto de las crisis)

___ **G.** Calidad de vida global.

Por favor, asegúrese de que ha contestado a cada pregunta en cada página.

Cramer et al., Epilepsy Behav 2003

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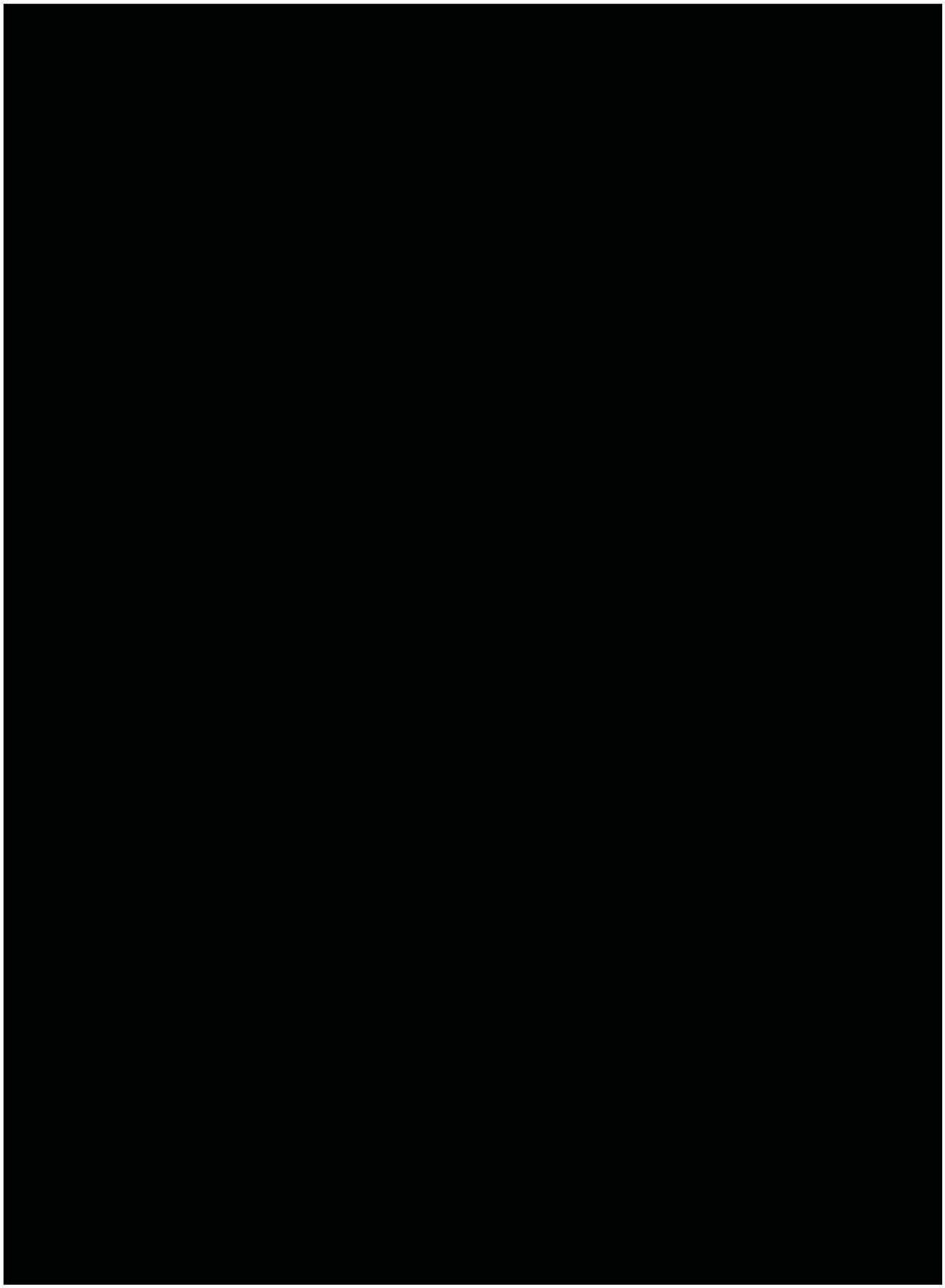
[redacted]



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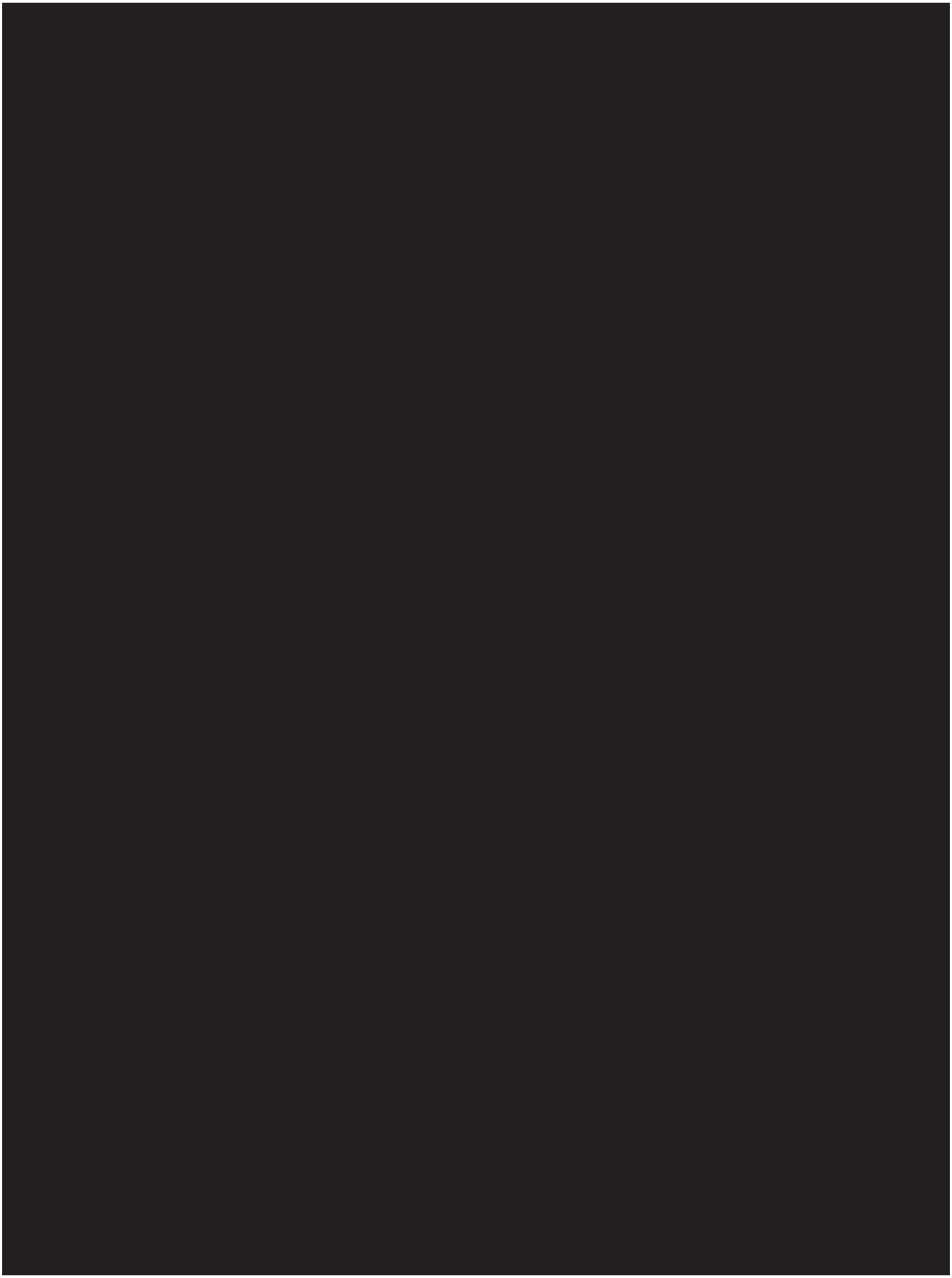


16.12. WMA Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized

representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or

new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Note: Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

– Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

– Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

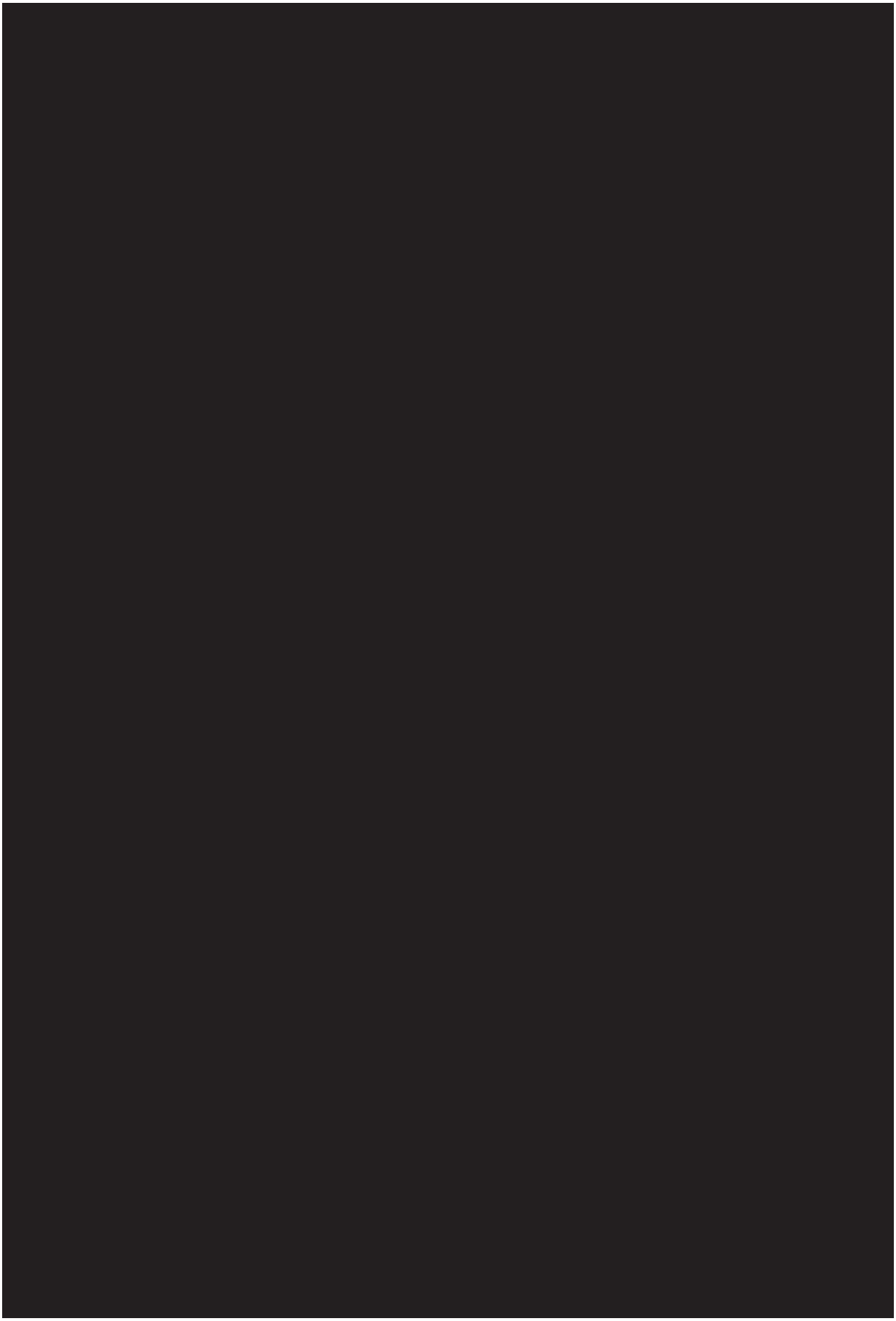
All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Note: Note of clarification on paragraph 30 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

9.10.2004



16.14. Table – Abbreviations

Abbreviation	Full Word or Phrase
AD	After discharge
AE	Adverse Event
AED	Antiepileptic Drug (or antiseizure medication)
ANOVA	Analysis of variance
CFR	Code of Federal Regulations
CRF	Case Report Form
CT	Computerized Tomography
DMC	Data Monitoring Committee
ECoGs	Electrocorticograms
eCRF	Electronic Case Report Form
EOS	End of Service
FDA	Food and Drug Administration
GTC	Generalized tonic clonic (seizure)
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
PMA	Pre-market Approval Application
PDMS	Patient Data Management System
QOLIE	Quality of Life in Epilepsy
SAE	Serious Adverse Event
SUDEP	Sudden Unexplained Death in Epilepsy
VNS	Vagus Nerve Stimulator

16.15. Table – Definitions

Term or Phrase	Definition
Adverse Event	A negative change in the subject's physical or mental health as experienced by the subject or observed by the clinician during any part of the Clinical Investigation.
AED Toxicity	Side effects caused by intolerance to an antiepileptic drug. In most instances these side effects are referable to the central nervous system and may include difficulty with memory or concentration, negative change in mood, visual blurring or diplopia, or problems with fine motor movements, balance or coordination. AED toxicity generally arises when serum concentrations are inappropriately high, although some individuals may be susceptible even at low serum concentrations.
Anticipated Adverse Event	A device-related adverse event noted in the Investigation Plan as potentially caused or contributed to by the study device.
Asthenia	Weakness, lack of energy or strength
Ataxia	The inability to coordinate muscle movements
Clustering	Refers to a series of seizures in a short period of time, such as hours or a day. If seizures arise frequently in succession, the patient may have difficulty differentiating each individual seizure for purposes of seizure counting.
Complex Partial Seizures	A clinically evident seizure that arises in a focus or region of the brain. The seizure, by definition, is associated with loss of awareness but does not include generalized tonic, clonic, myoclonic or tonic-clonic movements. The patient may display 'automatic' behaviors (automatisms) such as lip smacking, chewing, vocalization, picking or aimless wandering. The patient will not recall any events occurring during the seizure.
Device Related Adverse Event	The event is definitively or potentially related to a NeuroPace investigational device.
Diathermy	Diathermy is the use of electrical currents to heat tissue for medical or surgical purposes
Diplopia	A visual disorder characterized by double vision.
Disabling Seizures	Motor simple partial seizures or complex partial seizures with or without secondarily generalized seizures.
Dysarthria	A speech disorder due to weakness or incoordination of speech muscles. Speech is slow, weak or imprecise.
Dysesthesia	Altered sensations such as a feeling of burning, electric shock or pins and needles.
Dyskinesia	Difficulty or distortion in performing voluntary movements
Dysphasia	Characterized by a complete or partial loss of the ability to understand, speak, read or write.
Edema	Soft tissue swelling

Term or Phrase	Definition
Electroconvulsive therapy	Electroconvulsive therapy is a treatment for mental disorders that works by producing unconsciousness and convulsions through the use of an electric current
Emotional Lability	Severe mood swings, characterized by uncontrollable laughing or crying.
Epidural Hematoma	Mass of clotted blood in the space between the skull and the brain.
Epilepsy	Epilepsy is a common neurological disorder that produces seizures.
Extra-Temporal Lobe Epilepsy	Epilepsy beginning in a focal or regional area of the brain that does not include the temporal lobe. Such epilepsies are categorized as localization-related epilepsies of the frontal, parietal or occipital lobes.
Gait Difficulties	Disturbance in walking that could arise as a consequence of motor, sensory or coordination deficits
Generalized Tonic-Clonic Seizure	A seizure involving the entire body, usually characterized by muscle rigidity, rhythmic muscle contractions and loss of consciousness.
Hematoma	An abnormal collection of blood in which the blood is usually clotted or partially clotted.
Hemorrhagic Stroke	A disturbance in the function of the brain caused by bleeding from cranial vessels. The stroke may cause transient or permanent neurological symptoms.
Intracranial Hemorrhage	Bleeding from cranial vessels into the skull. Bleeding may be intraparenchymal (within the brain substance, subdural (beneath the dura mater) or extradural (above the dura mater).
Intractable Epilepsy	Difficult to treat epilepsy in which the subject continues to have seizures despite treatment.
Ischemic Stroke	Injury to the brain caused by a reduction in blood flow in intracranial or extracranial blood vessels supplying the brain. Neurological symptoms may be transient or permanent and are referable to the area of brain deprived of blood flow.
Lithotripsy	Lithotripsy is a treatment used to treat kidney and gall stones. This procedure involves the use of shock waves to crush stones in the urinary system into small enough pieces to wash out.
Mild (non-serious) Adverse Event	Minor in nature or behavior; acute and self-limited or transient; no need for invasive medical or procedural intervention to alleviate the adverse event or any adverse event that is not serious
Non-Epileptic Seizure	A period of seizure-like activity that is characterized by a loss of or change in physical function without a problem in the central nervous system but usually related to a mental health problem.
Not Device Related Adverse Event	The event is not related to a NeuroPace device.

Term or Phrase	Definition
Paresthesia	Numbness and tingling sensations that can occur anywhere in a person's body, but are often felt in the hands, feet, arms or legs.
Primary Generalized Seizure	A seizure that begins with a widespread electrical discharge that involves both sides of the brain at the same time.
Secondarily Generalized Seizures	Partial seizures that evolve into generalized seizures most often with tonic-clonic convulsions.
Seizure	Seizures are a disturbance in the normal electrical activity of the brain.
Seizure Onset Zone	The area of the brain (cerebral cortex) that contains the abnormal, epileptogenic tissue that causes seizures
Serious Adverse Event	Significant risks or consequences to the subject's acute or long-term health; serious injury or death; hospital admission or invasive medical intervention required to alleviate the adverse event.
Sham	A surgical intervention designed to prevent a subject from determining the treatment group to which he/she has been assigned during a blinded trial. Both blinded groups receive the same surgical intervention; however the device in one blinded group is inactive (sham) and the device in the other blinded group is active.
Simple Partial Motor Seizure	A seizure beginning in a focal or regional area of the brain that causes transient neurological motor symptoms. By definition, the patient retains full awareness during this type of seizure.
Simple Partial Sensory Seizure	A seizure beginning in a focal or regional area of the brain that causes transient neurological sensory symptoms. By definition, the patient retains full awareness during this type of seizure.
Status Epilepticus	Continuous seizure lasting longer than 30 minutes or a cluster of seizures in which subject does not regain baseline awareness.
Sub-dural Hematoma	A collection of blood between the dura and the surface of the brain.
Sub-galeal	A space between the scalp and the skull.
Temporal Lobe Epilepsy	A recurrent, unprovoked seizure disorder arising because of epileptogenic tissue within the temporal lobe of the brain.
Thrombophlebitis	Inflammation of a vein that occurs when a blood clot forms.
Tonic-Clonic Seizures	Seizures that involve bilateral involuntary movements of the arms and legs that begin with stiffening (extension, tonic) and are followed by a series of bending movements (flexion, clonic). Consciousness is lost during generalized tonic clonic seizures although some patients with frontal lobe onset tonic-clonic seizures will retain awareness.
Tremor	Involuntary movements, usually fine in amplitude and often principally involving the arms and hands. Tremor is typically persistent, although it may wax and wane.
Unanticipated Adverse Event	A device-related adverse event not noted in the Investigation Plan as potentially caused or contributed to by the study device.