An Early Feasibility Study to Evaluate the User Interfaces and Sensitivity of the SENSE Device in Patients with Intracranial Hemorrhage

PROTOCOL:	SENSE-001
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DEVICE:	*Sensor Evaluation of Neurologic Status in Emergencies* (SENSE Device)
SPONSOR:	SENSE Diagnostics LLC 1776 Mentor Ave., Suite 411 Cincinnati, Ohio 45212 Telephone: 844-373-6730 Fax: 513-828-6982
MEDICAL MONITOR:	Opeolu Adeoye, MD, MS Associate Professor, Emergency Medicine & Neurosurgery University of Cincinnati Medical Center Medical Sciences Building 0769 231 Albert Sabin Way Cincinnati, Ohio 45229 Telephone: (513)-558-5281 E-Mail: adeoyeo@ucmail.uc.edu
CLINICAL MONITOR:	Clinical Research Consultants, Inc. 3308 Jefferson Avenue, Upper Level Cincinnati, Ohio 45220 Telephone: (513)-961-8200 FAX: (513)-961-2858 E-Mail: bsfant@crc-regulatory.com

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INVESTIGATOR SIGNATURE PAGE

My signature below affirms that I have read this protocol and agree to conduct the study according to the procedures specified in the protocol.

SIGNATURE:_____ DATE: _____

NAME PRINTED: _____

INSTITUTION: _____

1.0 Background

The *Sensor Evaluation of Neurologic Status in Emergencies* (SENSE) device (Sense Diagnostics LLC; Cincinnati, OH) is a non-invasive radiofrequency (RF) sensor that detects and monitors intracranial hemorrhage (ICH). Both *in vitro* and *in vivo* animal laboratory studies have been completed with the device to establish the proof of concept for detecting acute hemorrhage in the brain.

Each year roughly 795,000 people suffer strokes in the United States. About 610,000 of these are initial events, with the remaining 185,000 being repeat strokes. Approximately 85% of strokes are ischemic (i.e. caused by a blockage in the blood vessels of the brain), ~10% result from intracerebral hemorrhage (ICH) (i.e., internal bleeding in the brain), and another ~5% result from subarachnoid hemorrhages.[2] In addition, about 1.7 million Americans suffer traumatic brain injury (TBI) each year resulting in 1.3 million visits to the emergency department (ED), 275,000 hospital admissions and 52,000 deaths. Intracranial hemorrhage often accompanies TBI.

The annual healthcare cost of TBI is over $60 billion when both direct medical costs (e.g., diagnosis, treatment, rehabilitation) and indirect costs (such as lost productivity, long term disability) are considered. TBIs are a contributing factor in over 30% of all injury related deaths.[3]

Ongoing or repeat bleeding in the brain following a hemorrhagic stroke or TBI contributes to decreased brain function. At the present time, the standard of care is for a nurse or physician to assess the patient at a frequency of every one to eight hours (depending on the hospital setting) by having the patient respond to a series of questions and commands such as:

- Knowing his/her name and what month it is;
- Tracking a moving object with his/her gaze;
- Being able to tell how many fingers the examiner is holding up;
- Being able to move facial muscles;
- Lifting his/her hands and legs and holding them steady;
- Touching a finger to his/her nose;
- Sensing pinpricks correctly on various parts of the body; and,
- Having the ability to speak clearly and understand verbal information to aid such assessments.

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[2]Roger VL, Go AS, Lloyd-Jones DM. Heart disease and stroke statistics – 2012 update: a report from the American Heart Association. Circulation. 2012 Jan;125(1):188-97.
[3] CDC, "Get the Stats on Traumatic Brain Injury in the United States," https://www.cdc.gov/traumaticbraininjury/pdf/bluebook_factsheet-a.pdf

Patients who are unresponsive or comatose are given higher severity scores by default.

1.1 Rationale for Study and Use of the SENSE Device

Bleeding after experiencing a stroke or TBI may be difficult to detect. Bleeding in the brain may not be severe enough early after experiencing a stroke or TBI to affect brain function. Among severely affected patients who are in poor neurological condition or require mechanical ventilation, ongoing bleeding may not be detected by physical examination since these patients are often sedated and already comatose. As a result, there is a window during which changes that may be occurring in the brain are not detected by bedside exams.

The intent of the SENSE device is to provide clinicians a better way to monitor patients with intracranial bleeding due to stroke or TBI, thus, enabling clinicians to identify patients with asymptomatic or undetected bleeding earlier and to perform further evaluation and treatment sooner. This rapid intervention will help reduce the long-term brain damage resulting from strokes and brain injuries.

If proven to be safe and effective, the SENSE device has the potential to offer more consistent and continuous monitoring of patients suffering from stroke or TBI. Doctors can use it in the field, intensive care unit (ICU), operating room (OR), emergency department (ED) or anywhere where patients risk unrecognized neurological worsening. Rather than rely on subjective measures to determine a patient's neurological status, the SENSE device may offer better and earlier information to trigger intervention.

2.0 Prior Experience

2.1 Preclinical Testing

Researchers at the University of Cincinnati have conducted *in vitro* and *in vivo* proof of concept testing using various prototype SENSE devices. *In vitro* testing used a gelatin model developed by Zhou et. al.[4] that mimics the electrical properties of the human brain.[5] *In vivo* testing used a porcine intracranial hemorrhage (ICH) model developed by Wagner et al.[6,7] which has a longstanding history of use.

An *in vitro* proof of concept study was completed using a prototype two antenna SENSE device to demonstrate the capability of a 400 MHz EM based device to detect an experimental ICH in a brain tissue simulating gel model. This frequency lies within the FCC authorized ISM (Industrial, Scientific and Medical) bands.[3] Specifically, the researchers tested the impact of citrated human blood, cadaver temporal bone and simulated cerebral spinal fluid (CSF) on the received power (P_R) of an antenna using a 400 MHz radio wave. The transmitting and receiving antennae were also set at varying distances to test the effect of distance on the received power. Changes in the received signal were found to be induced by the presence of blood. The received power (P_R) was found to be a linear function of the cross sectional area of blood, as measured normal to the incident wave. In addition, the sensor was able to detect as little as 1 mL of blood in this 1000 mL *in vitro* model.

Subsequently, an *in vivo* proof of concept study was performed in a porcine frontal lobe ICH model,[4,5] and the ability of the two antenna prototype SENSE device to detect intracranial hemorrhage using two linearly aligned transmitting and receiving antennae was confirmed.[8]

After appropriate placement of the SENSE device antenna, the pigs were subjected to either a 400 MHz scan or to a range of frequencies. Forty measurements were made over a 2-min period for three different experiments: after catheter insertion but before blood

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[4] Zhou Z-z, Pockett S, Brennat B, Xu C-h, Bold G. Physical characteristics of simulated human brain. J Chin Clin Med. (2)2007:231-235.
[5] Korfhagen JJ, Madhuvanthi AK, Clark JF, Adeoye O, Shaw GJ. A prototype device for non-invasive continuous monitoring of intracerebral hemorrhage. J Neurosci Methods; 213(1): 132-137. Feb 2013.
[6] Wagner KR, Xi G, Hua Y, Kleinholz M, de Courten-Myers GM, Myers RE, Broderick JP, Brott TG. Lobar intracerebral hemorrhage model in pigs: rapid edema development in perihematomal white matter.Stroke. 1996 Mar;27(3):490-7.
[7] Wagner KR, Xi G, Hua Y, Zuccarello M, de Courten-Myers GM, Broderick JP, Brott TG. Ultra-early clot aspiration after lysis with tissue plasminogen activator in a porcine model of intracerebral hemorrhage: edema reduction and blood-brain barrier protection.J Neurosurg. 1999 Mar;90(3):491-8.
[8] Kandadai MA, Korfhagen JJ, Beiler S, Beiler C, Wagner K, Adeoye OM, Shaw GJ. In vivo testing of a non-invasive prototype device for the continuous monitoring of intracerebral hemorrhage. J Neurosci Methods. 235:117-122. Sep 2014.

infusion (Control), immediately after blood infusion, and 30 minutes after the initial ICH measurements to give the blood time to clot. These measurements were averaged, and a standard deviation was calculated for each experiment. At 3 hours after blood infusion and completion of RF measurements, the pig brains were frozen in situ with liquid nitrogen; and the frozen heads were sectioned for anatomic imaging and measurement of the ICH.

Overall, for the 400 MHz experiment, the percent change measurements immediately after blood infusion (P_R (0)) and at thirty minutes (P_R (30)) showed an increase in P_R after blood infusion, corresponding to an average P_R (0) value of 14 ± 6% ($p < 0.05$). In 4 out of the 5 pigs studied, the increase in the P_R (0) values were sustained even after 30 min (P_R (30) measurements) ($p < 0.05$). However, no significant increase in the average P_R (30) value (13 ± 11%) compared to P_R (0) values was observed. The average volume of the retracted clots for these experiments determined from the frozen slices was 1.1 ± 0.3 cc.

For the Frequency Sweep experiment, a statistically significant increase in P_R (0) and P_R (30) was observed for the 750–1000 MHz frequency range. A significant increase in P_R (30) was also observed for 500, 550, and 700 MHz frequencies. There was not a significant increase between any of the P_R (0) and P_R (30) measurements, but a trend toward significance was observed for 750–1000 MHz. As visualized by the large standard deviations, pig-to-pig variability was observed in the frequency sweep experiments, similar to the 400 MHz experiments.[6]

In summary, these *in vivo* porcine frontal lobe ICH model experiments demonstrated that the prototype device detected the increase in the received power after ICH was induced in the pig brain. The results were consistent with the *in vitro* data at 400 MHz. However, a greater increase in received power (and a smaller pig-to-pig variation in P_R) was observed at higher frequencies in the 750–1000 MHz range. One of the limitations of the *in vivo* work was the fact that when the antennas were not aligned collinearly to the ICH, P_R increases were much smaller. While this was not unexpected, it pointed out the need for a multi-dimensional array.[9]

Further experiments were conducted using a two-dimension and three-dimension array design. By adding antenna in a third axis, it was theorized that ICH location could be more precisely pinpointed. Subsequently, a 9-antenna array was developed to enhance the ability of the device to detect intracranial hemorrhage anywhere in the brain. Using

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[9] Unpublished data on file, 2014. Research funded by University of Cincinnati Technology Commercialization Accelerator award.

the porcine intracranial hemorrhage model, blood was detected in different areas of the brain, at varying volumes; and, the impact of multiple hemorrhages within the same brain was studied.

In Vivo Testing of the 9-antenna array: For the *in vivo* experimentation, different types of experiments were performed (see Table 1). Each experiment was conducted on a separate pig (i.e. a total of 8 pigs). In the first four experiments (#1-4), the right frontal white matter was infused with 3 mL of blood. In the next two experiments (#5-6), there were two sequential infusions into the right frontal white matter to mimic hemorrhage expansion. In the final two experiments (#7-8), blood was infused sequentially in the left parietal and right frontal white matter to determine if two separate hemorrhages could be detected. For all of these experiments, the SENSE device ran continuously for 6-8 hours.

Table 1 – In vivo porcine ICH infusion study designs

Experiment #	**Infusion #1 Location**	**Infusion #1 Volume (mL)**	**Infusion #2 Location**	**Infusion #2 Volume (mL)**
1,2,3,4	Right Frontal	3	N/A	N/A
5	Right Frontal	2	Right Frontal	1
6	Right Frontal	1	Right Frontal	2
7	Left Parietal	1	Right Frontal	2
8	Left Parietal	2	Right Frontal	1

Main Results: In these experiments, the SENSE 9-antenna array device was able to detect blood in different areas of the brain, at varying volumes.

Adverse Events in the Preclinical Study of the 9-antenna SENSE Device
No adverse events were observed in any of the preclinical SENSE studies. In the 9-antenna *in vivo* study, an MRI was performed on each pig to assess whether continuous scanning with the SENSE device caused issues such as increased bleeding, tissue damage indicative of heating or otherwise. No evidence of tissue damage was apparent on MRI, nor were there signs of injury in the slices of pig brain after sacrifice. Additionally, 2,3,5-Triphenyltetrazolium chloride (TTC) staining was performed in one pig and there were no adverse effects on tissues other than staining at the location of the ICH, including those in which an MRI were performed on the pigs with no negative findings.

Preliminary Functionality of the 9-antenna SENSE Device
Using data from the *in vivo* SENSE experiments on 8 pigs, we developed a preliminary SENSE algorithm for determining ICH volume and to estimate the sensitivity of the device. The algorithm gathers the received power from all of the antennae and characterizes the changes observed in the signal over time to determine a location and

size of the hemorrhage. Furthermore, it incorporates antenna distance, angle, and beam profile to create a weighted response with changes in the signal observed by certain antennae being more important than other antennae depending on the location within the head being monitored. The algorithm also accounts for different changes in the signal over time such as absolute difference, percent difference, standard deviation, positive versus negative change, and coefficient of variance.

Using the current setup in the pig *in vivo* experiments described above, the algorithm was able to determine the location of all hemorrhages and was able to detect changes in signal due to as little as 1 mL of blood infused into the brain. Furthermore, system drift, which is defined as change of signal over time due to variance in the system or natural physiological changes, was studied during control measurements, and by setting a limit above the maximum drift observed, the algorithm could still detect and localize all hemorrhages studied.

This first-in-man study protocol investigates the 9-antenna SENSE device using the algorithm described above with the objectives of refining the device design and algorithm, and providing preliminary clinical data in humans to design further clinical investigations.

2.2 Clinical Experience

This study is the first use of the SENSE device in human clinical investigations, thus there is no prior human clinical experience.

3.0 Device Description

3.1 Intended Use

The SENSE Device is a non-invasive device that detects differences in the absorption of transmitted RF energy across the skull and brain and is intended to be used to evaluate intracranial hemorrhage.

3.2 Indications for Use

Based on the intended use and the preclinical testing performed in an animal model, the SENSE Device has the following indications for use:

> *The SENSE Device is indicated for the evaluation of intracranial hemorrhage within the cranial vault as an adjunctive device to the clinical evaluation in the acute hospital setting of patients 22 years of age or older with suspected or known intracranial hemorrhage. The device is indicated for use to monitor patients between CT scans but should not serve as a substitute for these scans. The SENSE Device is indicated for use by a physician, or under the direction of a physician, who has been trained in the use of the device.*

3.3 Device Description

The SENSE device transmits a low power tailored electro-magnetic (EM) pulse in the radio-frequency range across the patient's brain and detects changes in the signal that may indicate intracranial hemorrhage. The device consists of two parts:

(1) A molded plastic headpiece containing the antenna array, and
(2) A processing control unit that contains:
    a. The driving electronics for the array;
    b. A spectrum analyzer coupled with a computer; and,
    c. The operating software that controls the device function and data acquisition, processing and archiving.

The SENSE device is not an imaging modality. For this study the graphical display of the SENSE measurement data output is disabled.

For this study, the research personnel will place the headset over the subject's head. The headset will be sized to fit snuggly. As shown in Figure 1 below, the headset is a molded plastic form containing the antenna array. Each headset is marked with a unique headset identification number. The patient-contacting components of the molded plastic form are made from a medical grade (USP Class VI), biocompatible plastic and foam.

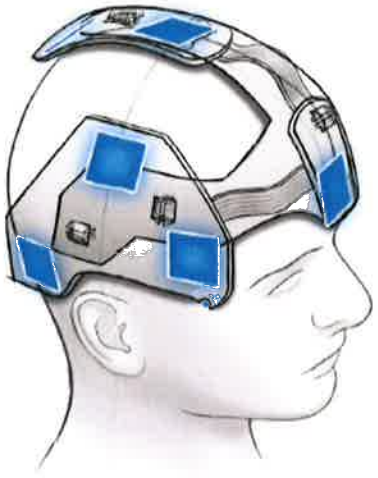

Figure 1: Depiction of SENSE Headset Showing Antenna Location and Orientation

Data from the scan will be entered into the processing control unit. The processing control unit is a separate device (control box – currently a laptop device) that contains the signal analyzer, operating software and user interface. The user interface requires the researcher to input the subject ID and headset ID so that the results can be entered into a database via upload or manually. Once these steps are completed, the research personnel can activate the device by selecting "Start Monitoring." The software will provide error messages if any required fields are blank.

Once activated, the device scans the patient according to the predetermined scanning cycle. Before each scan, the device software completes a self-diagnostic to ensure that all antenna signals can be detected. The processing control unit will store the results from each SENSE scan in a unique file for each subject ID on the device. If the subject ID is changed, the device will start a new file.

SENSE data will be transferred from the control unit to an external computer for analysis and correlation with clinical and CT imaging data, using the SENSE proprietary algorithm for detecting blood. All data will be encrypted when it is removed from the control unit to ensure patient confidentiality and data integrity.

4.0 Risk Analysis

The SENSE device settings for this clinical study use a pulsed RF signal, which minimizes the power exposed to the patient. Over the 72 hours the device will be on the patient, it will transmit a signal 7% of the time. Therefore, the total energy transmitted by the device to the patient will be 18 J, which is the equivalent amount of energy as a 36-second cell phone call. This level of transmitted RF energy exposure has been shown to be safe in previous *in vivo* porcine experiments and the transmitted power is exponentially lower than a typical cell phone operating at 900 MHz, as summarized below.

	Animals Tested	**Frequency Range**	**Exposure Time**	**Transmit Power**	**Total Energy Transmitted**
SENSE 9-antennae array in vivo[10]	N = 8 pigs	912 MHz	360 minutes	1 mW	22 J
Kandadai et al: 400-1000 MHz[11]	N = 5 pigs	400-1000 MHz	60 minutes	0.2 mW	1 J
Kandadai et al: 400 MHz[11]	N = 5 pigs	400 MHz	60 minutes	45 mW	162 J
Proposed SENSE settings using 9-antennae array	N/A	912 MHz	~302 minutes pulsed over 72 hours	1 mW	18 J
Cell Phone at 900 MHz	Not Applicable (Compliant with FCC Standard for Maximum Permissible Exposure)	900 MHz	~302 minutes	500 mW (average)	9000 J

Three different sets of pig experiments have been conducted, and the total energy transmitted from the antennae is shown in the table above. The most recent set of experiments described in section 2.1 using a 9-antennae array to monitor for changes due

[10] Unpublished data on file, 2015. Research funded by National Science Foundation SBIR phase I award.
[11] Kandadai MA, Korfhagen JJ, Beiler S, Beiler C, Wagner K, Adeoye OM, Shaw GJ. In vivo testing of a non-invasive prototype device for the continuous monitoring of intracerebral hemorrhage. J Neurosci Methods. 235:117-122. Sep 2014.

to hemorrhage most accurately mimics the proposed first-in-man study and showed no tissue damage related to the RF energy. All of these pig experiments have tried to minimize exposure to RF radiation to ensure safety. A cellular telephone with an average transmitting power of 500 mW would emit 9000 J of energy over the same time period as the proposed SENSE settings, which will only emit 18 J spread out over 72 hours.

Potential risks of RF energy exposure are summarized below. The SENSE device was designed to use an RF energy frequency and exposure that is well within Maximum Permissible Exposure (MPE) limits imposed by the Federal Communications Commission (FCC) for cellular telephone use, which mitigates any safety concerns of risk to biological tissues from exposure to RF radiation.

Thus, because the FCC MPE limits are based on the risk to biological tissues from exposure to RF radiation and the patient's exposure from the SENSE device is far less than the typical exposure from cell phones, the SENSE device is not anticipated to pose safety concerns.

Identified Potential Risk	**Mitigation**
Excessive RF energy	Electrical safety and electromagnetic compatibility (EMC) testing complies with international standards and FCC MPE limits
Interference with other devices	Electrical safety and EMC labeling Electrical safety and electromagnetic compatibility (EMC) testing complies with international standards and FCC MPE limits
Unit (hardware) malfunction	Performance testing Software verification, validation, and hazard analysis
Software malfunction	Software verification, validation, and hazard analysis
Operator errors	Labeling Training
Incorrect result (false positive; false negative)	Software verification, validation, and hazard analysis Labeling
Adverse tissue reaction	Biocompatibility testing complies with FDA and international standards
Power failure (Failure of device to operate	Performance testing Labeling

The low transmit power at which the SENSE device operates mitigates the risks of excess RF energy into the body from use of the SENSE device. These risks are no greater than those associated with the use of cell phone technology (see Table above), in fact are less than that with cell phone technology, and are well below FCC MPE limits. This will be confirmed by the electrical safety testing that will be performed on the device prior to its clinical use. Electromagnetic compatibility testing will also be performed to mitigate the

risk of interference with other medical devices that could be encountered in the patient care setting in which the SENSE-001 clinical study will be conducted.

The SENSE device headset is the only patient-contacting component of the device and the headset is constructed of materials that are known to be biocompatible and/or have been tested by the raw materials manufacturer for biocompatibility. This mitigates the risk of sensitization or irritation from patient-contacting materials used to construct the SENSE headset.

Enrollment of subjects with ICH presents a risk that these subjects may experience adverse changes in their clinical course that arise from the ICH itself, such as re-bleeding, seizures, headaches, depression and cognitive impairment. The risks of occurrence of these ICH-related events are the same for study subjects as non-study subjects. Standard of care treatment for ICH will mitigate the occurrence of these risks to the extent possible; however, there is a high probability that subjects enrolled in this study may exhibit one or more of these ICH-related adverse events.

In summary, the design specifications and non-clinical testing of the SENSE device have reduced the potential risks of patient exposure to the SENSE device as far as possible. Furthermore, the display of the SENSE device output will be disabled to mitigate the risk that clinical care personnel could inadvertently use the SENSE data to make clinical decisions. Study subjects will receive the usual standard of care for ICH, which mitigates the risk of further ICH-related sequelae to the extent that is practicable. Based upon these considerations, the potential benefit of information gained from this study that can be used to advance the development of the SENSE device outweighs any risks to the study subjects participating in the study.

5.0 Objectives

The primary objectives of this first-in-man early feasibility study are to obtain preliminary estimates of:

- Whether the SENSE Device can detect differences in the absorption of transmitted RF energy across the skull and brain to evaluate intracranial hemorrhage in patients with a CT-confirmed intracranial hemorrhage; and,
- Safety of the SENSE Device when it is used for its intended use in ICH patients.

Secondary study objectives include obtaining clinical experience with the SENSE Device to identify or obtain:

- Patient characteristics that may impact device performance;
- Operator technique challenges;
- Human factors information to optimize device design;

- Performance information to optimize device design, data processing, and algorithm development; and,
- Preliminary estimates of safety and effectiveness that can be used to design subsequent clinical investigation(s) of the SENSE Device, including the planned pivotal clinical study.

The data obtained from this study will be used to evaluate and optimize the design of the SENSE device. The data will also be used to optimize the clinical investigational plans for the SENSE device and provide preliminary estimates of outcome measures that can be used to plan subsequent clinical investigation(s) of the SENSE device. The data from SENSE monitoring in this first-in-man study will be shielded from clinical staff and will in no way inform clinical management.

6.0 Endpoints

The primary endpoint for this early feasibility study is the correlation of the SENSE signal with CT changes over time.

Secondary endpoints will include the ability to process collected data in a manner that allows application and use of the SENSE device in a clinical environment and a preliminary estimate of the safety of the device when used in a clinical setting. Serious, unexpected adverse events will be recorded. Epileptic seizures will be an adverse event of special interest and recorded regardless of serious or unexpected status.

Qualitative information regarding device tolerability and compatibility with ICU work-flow will be obtained from study subjects and ICU staff.

7.0 Study Design

This will be a prospective, observational, single site, first-in-man study of the SENSE device in up to 10 study subjects with primary spontaneous ICH. The treating clinicians will be blinded to the data collection and SENSE device scanning as described below.

All eligible subjects must have the diagnostic head CT scan (CT) demonstrating hemorrhage performed within 24 hours of symptom onset. While ICH and TBI patients may be evaluated in future studies, this early feasibility study is limited to primary spontaneous ICH patients only, given the relative homogeneity of this population compared with the TBI population.

Eligible subjects or legally authorized representatives will be approached for enrollment. After obtaining informed consent to participate in the study, the first study head CT will be performed to establish the hemorrhage volume; and the SENSE device will be placed on the subject within 15 minutes of this CT, or as soon as practicable, for initiation of monitoring. This repeat CT (after the diagnostic CT) is necessary since hemorrhage expansion (HE) occurs early in the clinical course, and the hemorrhage volume may have changed between the diagnostic CT and placement of the SENSE monitor.

After enrollment, routine clinical management will ensue in the emergency department (ED), hospital ward or intensive care unit (ICU) as appropriate. A standard of care head CT to evaluate for HE will be performed at 12 (±6) hours after the first study head CT. Finally, a study head CT will be performed at 72 (±12) hours to evaluate cerebral edema. Any head CT performed for clinical deterioration as standard of care between the first study CT and 72 hour study CTs will also be collected and analyzed.

The SENSE device will be placed on the subject's head, and two small ink dots will be marked on the head corresponding to a known location on the device to allow for the device to be removed and replaced consistently throughout testing. After the 12-hour scan, monitoring may be performed continuously or intermittently. For continuous monitoring, t~~T~~he SENSE device will be set to scan every 10 minutes until the device is removed after completion of the SENSE measurement corresponding to the 72 hour CT scan. For continuous monitoring, the SENSE device will be worn for the entire 72 hour monitoring period except for any temporary suspensions. If the SENSE device is removed to perform the CT or SENSE monitoring is temporarily suspended, the SENSE device will be replaced; and SENSE monitoring will resume within 15 minutes, or as soon as practicable, after each CT scan. For intermittent monitoring, the SENSE device will be placed on the patient for a minimum of 22 minutes every 6 (±1) hours until the 72-hour CT scan is obtained. A final SENSE measurement will be completed within 15 minutes before or after the 72-hour CT scan. A SENSE measurement obtained within 15 minutes ~~of~~ before or after each CT scan, or as soon as practicable thereafter, will be used for comparison with the corresponding CT scan for data analysis.

8.0 Subject Population

This is a single site study that will be conducted at the University of Cincinnati Medical Center (Cincinnati, OH). Up to 10 subjects will be enrolled and receive a headset for monitoring.

8.1 Inclusion Criteria

Subjects who meet all of the following inclusion criteria will be considered candidates for study enrollment:

1. Male or female patients age 22 years and older
2. Diagnostic head CT scan within 24 hours of primary spontaneous ICH symptom onset
3. ICH >3mL and <90mL, as measured by the ABC method
4. Signed written informed consent by study subject or, if subject is unable, by subject's next of kin or legal guardian
5. Willingness and ability to comply with schedule for study procedures

8.2 Exclusion Criteria

All subjects meeting any of the following criteria will be excluded from this study:

1. Female patients who are pregnant or lactating
2. Patients with any history of seizure or seizure at stroke onset
3. Presence or history of any other condition or finding that, in the investigator's opinion, makes the patient unsuitable as a candidate for the SENSE device monitoring or study participation or may confound the outcome of the study
4. Any intraventricular hemorrhage on the diagnostic (pre-enrollment) CT with planned placement of an intraventricular catheter
5. Secondary cause of ICH suspected (e.g., arteriovenous malformation, cavernoma, aneurysm, hemorrhagic transformation ischemic stroke, venous sinus thrombosis, trauma)
6. Planned withdrawal of care within 24 hours of enrollment
7. Planned surgical evacuation within 24 hours of enrollment
8. Current participation in a medical or surgical interventional clinical trial
9. Presence of subdural, epidural or aneurysmal subarachnoid hemorrhage on diagnostic scan

10. Planned continued use or prescribed use during the study of medications that, in the investigator's best clinical judgment, are known or suspected to lower the seizure threshold
11. Planned continued use of medications that, in the investigator's best clinical judgment, could increase the chances for subsequent uncontrolled hemorrhage
12. Planned or current use of continuous EEG monitoring

9.0 Study Procedures

Subjects enrolled in this study will complete the study as outlined below. All tests and measurements should be obtained in accordance with the procedures specified in this protocol. If it is not possible to perform a measurement or examination due to the individual's condition, the reason for not performing the test or measurement should be documented on the source documents.

ICH patients will be screened at the enrolling center based on the inclusion and exclusion criteria for the study. Those not meeting criteria will simply be clinically managed per standard of care and will not be enrolled in the study. Those who meet eligibility criteria will be approached for possible consent and enrollment. This must be done quickly as hemorrhage expansion occurs early in the clinical course; and the subject should be enrolled within 2 hours of the diagnostic CT, whenever practicable.

A consent process must be executed for all subjects entered in the study. Obtunded and aphasic patients are not automatically excluded from the study. If the next of kin or legal guardian (i.e., the individual legally empowered in the state where the consent is obtained) cannot provide consent, entry into the study will not proceed.

After enrollment, routine clinical management will ensue in the ED, hospital ward or ICU as appropriate.

[NOTE: The data from SENSE monitoring in this first-in-man study will be shielded from clinical staff and will in no way inform clinical management.]

9.1 Study Duration

The study duration is a total of up to 8 weeks which includes up to 72 (±12) hours for SENSE device and CT scan monitoring, and a follow-up phone call at 6 (±2) weeks.

9.2 Examination Schedule

The following examination schedule will be followed from screening through 6 (±2) weeks post-enrollment:

- **Diagnosis:** CT Scan 1 – standard of care; diagnostic head CT scan within 24 hours of symptom onset.

- **First Study CT:** CT Scan 2 – study CT; first study CT scan as soon as practicable after informed consent, followed by SENSE monitoring. Place SENSE device on subject's head within 15 minutes of completion of the first CT scan or as soon as practicable, with continuous SENSE monitoring until the SENSE device is removed to perform the 12-hour CT scan. If there is a delay in obtaining the first study CT scan, SENSE monitoring may begin after informed consent and before the first study CT scan to capture possible HE.
- **12 Hours:** CT Scan 3 – standard of care; CT scan 12 (±6) hours after first study CT scan, followed by continuous or intermittent SENSE monitoring. For continuous SENSE monitoring, replace SENSE device on the subject's head within 15 minutes, or as soon as practicable, after completion of the 12-hour CT scan and obtain continuous SENSE measurements until the SENSE device is removed to perform the 72-hour CT scan. If continuous SENSE monitoring is temporarily suspended or for any reason (e.g., unscheduled CT scan, EEG, patient care), resume continuous monitoring as soon as practicable. For intermittent monitoring, the SENSE device will be placed on the patient for a minimum of 22 minutes every 6 (±1) hours until the 72-hour CT scan is obtained. A final SENSE measurement will be completed within 15 minutes before or after the 72-hour CT scan.
- **72 Hours:** CT Scan 4 – study CT; end of study CT scan 72 (±12) hours after first study CT scan.
- **Unscheduled:** Unscheduled CT scan(s) may be obtained as needed throughout the study per standard of care as warranted by the treating team. Any head CT performed for clinical deterioration as standard of care between the first and 72 hour study CTs will be collected and analyzed. If SENSE monitoring has been temporarily suspended or is being performed intermittently, obtain a SENSE measurement within 15 minutes before or after the unscheduled CT scan whenever practicable, following the procedures above.
- **6 weeks:** Phone call with patient or surrogate to capture the presence or absence any adverse events that may have emerged after completion of the 72-hour SENSE device measurement period.

All eligible subjects must have the diagnostic head CT scan demonstrating hemorrhage performed within 24 hours of symptom onset.

Eligible subjects or legally authorized representative will be approached for enrollment after screening is completed and before the first study CT and SENSE measurements are obtained. After obtaining informed consent to participate in the study, a first study head CT will be performed to establish the hemorrhage volume; and the SENSE device will be placed on the subject within 15 minutes of this CT, or as soon as practicable, for initiation of monitoring. This repeat CT (after the diagnostic CT) is necessary since HE occurs

early in the clinical course, and the hemorrhage volume may have changed between the diagnostic CT and placement of the SENSE monitor. If there is a delay in completing the first study head CT, SENSE monitoring may be started after informed consent and before the first study head CT to obtain SENSE measurements during the time that HE is most likely to occur.

A standard of care head CT to evaluate for HE will be performed at 12 (±6) hours after the first study head CT. Finally, a study head CT will be performed at 72 (±12) hours to evaluate cerebral edema. Any head CT performed for clinical deterioration as standard of care between the first and 72 hour study CT will also be collected and analyzed. A SENSE scan will be performed ~~within1 hour before or~~ within 15 minutes, or as soon as practicable, before or after each CT scan, for the purpose of obtaining SENSE measurements at the same time as the CT scan to compare the output from the SENSE device with the CT scans.

SENSE monitoring should be obtained continuously after the first study CT scan and until the SENSE headset is removed for the 12 hour CT scan. After the 12 hour CT scan, SENSE monitoring should be performed continuously or intermittently until the SENSE headset is removed for the 72 hour CT scan. If intermittent monitoring is requested by the subject or the subject's physician at any time after the 12 hour CT scan, the SENSE device will be placed on the patient for a minimum of 22 minutes every 6 (±1) hours until the 72-hour CT scan is obtained. A final SENSE measurement will be completed 15 minutes before or after the 72-hour CT scan.

9.3 SENSE Device Monitoring Procedure

The device will be used according to the written Instructions for Use provided by the Sponsor. The device will emit and analyze signals of 40 seconds once every 10 minutes for up to a maximum of 72 (±12) hours, effectively minimizing the amount of RF radiation to which the subject is exposed while providing essentially continuous monitoring from a clinical point of view. This corresponds to a duty cycle (DC) of about 7%.

If the subject's condition is such that a SENSE device measurement cannot be obtained, the measurement may be omitted at the investigator's discretion; and the omission should be documented in the source documents.

The user interface requires the researcher to input the subject ID and headset ID so that the results can be entered into a database either via upload or manually. The research personnel will also sync the headset with the control box. Once these steps are completed, the research personnel can activate the device by hitting "Start Monitoring." The software will provide error messages if any required fields are blank.

Once activated, the device scans the subject according to the schedule selected per protocol. Before each scan, the device will run a diagnostic to ensure that all components are functioning normally. Data will be collected after each scan for subsequent analysis and correlation with clinical and imaging data.

The processing control unit will store the results from each subject's scans in a file on the device. If the subject ID is changed, the device will start a new file.

When the SENSE device is placed on the subject's head, two small ink dots will be marked on the head corresponding to a known location on the device to allow for the device to be removed and replaced consistently throughout testing. If the SENSE device is removed to perform the CT or SENSE monitoring is temporarily suspended for any reason (including whenever a routine EEG is performed) during continuous SENSE monitoring, the SENSE device will be replaced; and SENSE monitoring will resume within 15 minutes, or as soon as practicable, after each CT scan or other reason for suspension is finished. For intermittent SENSE monitoring, the SENSE device will be replaced and SENSE measurements obtained at 6 (±1) hour intervals. A SENSE measurement obtained within 15 minutes ~~of~~ before or after each CT scan, or as soon as practicable thereafter, will be used for comparison with the corresponding CT scan for data analysis. The purpose of obtaining SENSE measurements at the same time as the CT scan is to compare the output from the SENSE device with the CT scans.

Subjects requiring continuous EEG monitoring or other care that precludes placement of the SENSE device will have SENSE monitoring discontinued; and the subject will be terminated from the study according to the procedures described in Section 9.10, Early Termination if SENSE monitoring cannot be resumed during the remainder of the study.

9.4 CT Scan Procedures

Study eligibility intracranial hemorrhage volume will be estimated by clinical and/or research staff using the ABC method.[12] Subsequently, intracranial hemorrhage and edema volumes will be determined by a neuro-radiologist blinded to clinical data and SENSE device data. Quantification of volumes will be performed using computer-assisted methods. The blinded evaluator will be required to place seed-points within the volume of interest and adjust lower and upper intensity Hounsfield unit (HU) thresholds until the entire volume is correctly selected. In cases where the ICH volume cannot be differentiated from intraventricular hemorrhage (IVH) volume, the blinded evaluator will use freehand drawing tools in order to remove the IVH volume using his/her best

[12] Kothari RU, Brott T, Broderick JP, et al. The ABCs of measuring intracerebral hemorrhage volumes. Stroke. 1996 Aug; 27(8):1304-1305.

estimate. In this situation, the IVH will be determined using the original over-segmented volume that includes the combined ICH and IVH volumes, Vtotal, as IVH = Vtotal – ICH. This limitation is unavoidable as IVH has the same intensity as ICH and the two volumes often border each another. The volume (mL) and the affected part(s) of the brain will be measured from the segmented volume. Based on prior experimentation, it is anticipated there will be more difficulties in segmenting edema volumes as edema has more subtle HU intensity differences relative to normal tissue. Thus, edema segmentation will likely require more blinded evaluator effort (i.e., seed-points, freehand tools, etc.) The radiology report will be filed in the source documents for the study.

9.5 Study Evaluations

9.5.1 Pre-Monitoring Evaluations

These evaluations occur prior to the subject beginning study monitoring.

Screening: A history and physical examination will be performed by the treating physician, and routine evaluations (including a diagnostic head CT) and treatments for ICH will be performed in accordance with the institution's standard evaluation and treatment protocols and at the treating physician's discretion as deemed medically necessary. Screening will include completion of the NIH Stroke Scale and Glasgow Coma Scale.

Enrollment: If the diagnostic head CT is performed within 24 hours from ICH symptom onset, the patient will be evaluated for eligibility for the study. Informed consent will be obtained from the patient (if able) or surrogate (patient's next of kin or legal guardian).

9.5.2 Study Evaluations

The following study procedures will be performed at each of the following time points. If it is not possible to perform a measurement or examination due to the subject's condition or other reasons, the reason for not performing the test or measurement should be documented on the source documents.

- **Baseline:**
  - A first study head CT will be performed on every study subject immediately prior to initiation of SENSE device monitoring.
  - NIH Stroke Scale
  - Glasgow Coma Scale
  - SENSE device measurements within 15 minutes of first study head CT

scan, or as soon as practicable[13]
- Adverse event assessment

- **12 Hours (±6 hours):**
  - A standard of care head CT will be performed at 12 (±6) hours from first study CT to evaluate for hemorrhage expansion
  - NIH Stroke Scale
  - Glasgow Coma Scale
  - SENSE device measurements within 15 minutes of head CT scan, or as soon as practicable for continuous monitoring, or every 6 (±1) hours for intermittent monitoring
  - Adverse event assessment
- **72 Hours (±12 hours):** A study CT will be performed at 72 (±12) hours to evaluate cerebral edema.
  - NIH Stroke Scale
  - Glasgow Coma Scale
  - SENSE device measurements within 15 minutes ~~of~~ before or after head CT scan, or as soon as practicable
  - Adverse event assessment
- **7 days:** Adverse event assessment. After the subject is discharged from the hospital or through 7 days of hospital stay (whichever occurs first), the subject's inpatient medical records will be reviewed to detect any device related adverse events or epileptic seizures that may have emerged after the SENSE headset was removed.
- **6 weeks (±2 weeks):** A phone call with the patient or surrogate will be completed at 6 (±12) weeks to capture the presence or absence of adverse events that may have emerged after completion of the 72-hour SENSE device measurement period.

Changes from the screening or baseline medical history and concomitant medications should be recorded in the source documents. Changes that could affect the SENSE measurements or CT results should be recorded on the case report forms (CRFs), including head movements that may affect positioning of the SENSE device.

Other tests or measurements, including routine EEGs and head MRIs, may be performed as needed for management of the subject's medical condition(s) per ICH standard of care. Subjects undergoing continuous EEG monitoring without resumption of SENSE monitoring, or a neurosurgical procedure before study completion will be terminated

[13] SENSE device measurements may be obtained prior to first study head CT scan if there is a scheduling delay between informed consent and first study head CT.

early from the study (see Section 9.10, Early Termination). Subjects may also be terminated early from the study if the SENSE device interferes with another monitoring device or the subject requires placement of a monitoring device that interferes with the SENSE device or headset, and the interference cannot be resolved or SENSE monitoring cannot be resumed. Whenever practicable, any subject who is terminated early and was exposed to the SENSE device should have the Day 7 and 6 week safety evaluations performed to capture any adverse events that emerged after device exposure.

The results of non-study diagnostic tests (except MRI) will not be recorded on the CRFs. Non-study tests relevant to an adverse event will be included in the investigator's adverse event summary on the adverse event CRF. The results of any non-study head MRI will be recorded on the MRI CRFs for clinical comparison with the CT scans.

9.5.3 Adverse Events and Device Malfunctions

Adverse events and device malfunctions will be assessed at study entry and at the baseline, 12 hour, 72 hour and 6 week evaluation time points. If it is anticipated that a subject will die or be taken for a neurosurgical procedure before the 12 hour CT scan, the scan will be performed earlier if practicable and used to judge hemorrhage. If it is anticipated that a subject will be discharged from the hospital, die, or undergo a neurosurgical procedure after the 12 hour CT scan but before the 72 hour scan, the 72 hour scan will be performed earlier if practicable and used for analysis.

During the 72 hours of monitoring, adverse events of particular interest for this first-in-man study in an ICU setting include:

- Adverse tissue reactions from the headset, such as skin irritation, abrasion or other dermatological effects
- Discomfort of the head or neck from the headset
- Seizures (defined as clinical tonic-clonic activity that occurs during the 72 hours of SENSE monitoring)

Device malfunctions will also be assessed for the SENSE device. Such malfunctions could include:

- Failure of the device to operate
- Operator errors
- Interference with other devices, including SENSE device interference with other monitors (e.g., ICP monitor dislodges) or other monitor (e.g., intraventricular catheter placement) interferes with SENSE device monitoring or headset placement

9.6 Post-Study Procedures

Subjects will be discharged from the SENSE monitoring part of the study after the final

72 hour CT scan and SENSE measurements are complete. After completion of these 72 hour evaluations, all other management of the subject's medical condition(s) will be per ICH standard of care. Subjects will be discharged from the study completely after the 6-week phone call.

9.7 Safety Monitoring

The presence or absence of device related adverse events or complications, including epileptic seizures, occurring during the 72-hour SENSE monitoring period or emerging after the SENSE headset was removed (up to 7 days of hospital stay) will be documented.

A neurologist at the University of Cincinnati, who is not affiliated with the study or Sense Diagnostics, will serve as the independent safety monitor for this first-in-man study. The independent safety monitor will review adverse events and seizures for all subjects enrolled to detect any device related adverse events that may occur while the SENSE device is being worn or that emerged after exposure to the SENSE device. All adverse events, including seizures, determined to be device related will be recorded on the CRFs. The independent safety monitor will evaluate the incidence of seizures compared to the study stopping rules in Section 10.2 below to determine if early study termination is warranted.

9.8 Device Accountability

All use of the SENSE device will be under the direct supervision of the principal investigator or his/her designee. Records of device accountability will be maintained for the study.

9.9 Early Withdrawal

Subjects will be advised that they are free to withdraw from the study at any time. Subjects experiencing adverse safety events will be followed until the reaction has resolved. Appropriate supportive and/or definitive therapy will be administered as required. When a subject withdraws early from the study before completion of the 12 hour or 72 hour CT scan and SENSE measurement, or 6 week phone call, a final examination (including a final CT and SENSE measurement if before 72 hours) will be performed at the time of study withdrawal, whenever practicable.

9.10 Early Termination

The investigator may discontinue a subject if a serious adverse event occurs and it is in the subject's best interest not to continue in the study, or if the subject has continuous EEG monitoring initiated, is prescribed a medication that in the investigator's best clinical judgment is known or suspected to lower the subject's seizure threshold, is discharged from the hospital, dies, or undergoes a neurosurgical procedure before study completion. Subjects who are discontinued from the study due to either the SENSE

device interfering with another device or another device (e.g., intraventricular catheter placement) interfering with the SENSE device should have the reason for discontinuation recorded as due to an adverse event. When a subject is terminated early from the study before completion of the 12 hour or 72 hour CT scan and SENSE measurement, a final examination (including a final CT and SENSE measurement) will be performed at the time of termination, whenever practicable, and the 72-hour end of monitoring adverse event assessment will be completed. The 7 day and 6 week adverse event assessments should also be completed whenever practicable.

10.0 Data Analysis and Statistical Considerations

A detailed statistical analysis plan (SAP) will not be developed for analysis of the data for this first-in-man study due to the small sample size of 10 subjects. Data from the study will be tabulated and summarized using descriptive statistics, where applicable, for safety and efficacy or to optimize the device design or aid in clinical trial design.

10.1 Sample Size Justification

The purpose of this first-in-man investigation is twofold: 1) to provide preliminary safety and effectiveness and device usage information that can be used to design the pivotal study to support the eventual marketing application for the SENSE device; and 2) to optimize the device design. Hence, the number of subjects suggested for this clinical investigation is not based on a statistical evaluation of any objective efficacy or safety outcome measures.

10.2 Stopping Rules

Consistent with usual procedures for the conduct of first-in-man studies, a priori specific guidelines are described below for stopping the study when the threshold for an excess number of safety events is reached. Stopping rules are based on the methods proposed by Moye.[14]

The occurrence of seizures is the main adverse event of interest for this study. Seizures are defined as clinical tonic-clonic activity that occurs during the 72 hours of SENSE monitoring. Using the binomial observed event rate, the associated lower 90% confidence interval will be calculated for the observed event. The stopping decision is based on when the assumed true event rate, set at 16%,[15] falls below the lower 90% confidence interval for the observed rate which is dependent upon the number of subjects accrued.

Using these parameters, the study is stopped if there are:

- 3 subjects with occurrence of seizure after SENSE monitoring within the first 6 subjects
- 4 subjects with occurrence of seizure after SENSE monitoring within the first 10 subjects

[14] Fundamentals for investigators. Lemuel A. Moyé, Springer, New York, 2003. No. of pages: xxiii+436.

[15] Hemphill JC, Greenberg SM, Anderson CS, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association.Stroke. 2015 Jul;46(7):2032-60.

The table below shows the observed event rate and the lower 90% confidence interval for that rate for the number of subjects enrolled at the stage when the allowed number of observed subjects with seizure changes. The allowed number of subjects with seizure is based on the assumed event rate, 16%, falling below the 90% CI for the observed rate as stated above.

Table: Seizure Threshold Rates for an Assumed True Event Rate of 16%

Subjects Enrolled	Number of Seizures (S)	Observed Event Rate	Lower 90% CI for Observed Event Rate
6	3	0.50	0.16
7	3	0.43	0.12
7	4	0.57	0.26
9	4	0.44	0.17
10	4	0.40	0.14
10	5	0.50	0.24

The total RF energy exposure for the SENSE device over the 72-hour testing period proposed in this clinical study (1 mW for ~302 minutes) is equivalent to the energy exposure from a 36-second cell phone call. Nevertheless, the rate of seizures was selected as the adverse event of interest due to theoretical concerns from limited animal studies in the published literature evaluating the impact of cell phone usage and seizure activity.

Cinar et al.[16] studied the effects of electromagnetic waves (EMWs) on seizure activity in a mouse epilepsy model in which experimental groups of 10 mice were exposed to 900, 700, 500, 300 or 100 MHz EMWs for 20, 12, or 2 hours followed by intraperitoneal injection of pentylenetetrazole (PTZ) to induce seizures in all mice. Control group mice were injected with PTZ without exposure to EMWs. For the 900 MHz exposure (same as that used by the SENSE device), there were no significant differences between any of the experimental groups and PTZ-treated control at any exposure duration. Significant shortening of the initial seizure latency was observed at 500 MHz in the 2 hour exposure group, at 700 MHz in the 12 hour exposure group, and at 300 MHz in the 20 hour exposure group. No significant differences in the most severe seizure latency in any of the groups. The results of this study should be interpreted cautiously with respect to the SENSE device because: (1) the power level used in the study was not reported; (2) EMWs exposure without PTZ injection was not used as a control; (3) the sample size of mice studied (n = 10 mice) was too small to provide meaningful data; and, (4) the mice were exposed to 2 to 20 hours of continuous exposure, whereas the RF energy exposure

[16] Cinar N, Sahin S, Erdinc OO. What is the impact of electromagnetic waves on epileptic seizures. Med Sci Monit Basic Res. 2013 May 10; 19:141-145.

from the SENSE device is intermittent and with short durations (<1 minute per exposure).

Lopez-Martin et al. studied the effects of 2 hours of Global System for Mobiles (GSM)-modulated 900 MHz radiation (simulating cellular phone-type radiation) in a picrotoxin induced rat seizure model.[17] Rats pre-treated with subconvulsive doses of picrotoxin and exposed to radiation suffered seizures and had increased cerebral levels of neuronal activity marker c-Fos. However, rats exposed to radiation but not pretreated with picrotoxin did not suffer seizures and cerebral c-Fos levels were significantly lower. From this, the authors concluded cellular phone type radiation could induce seizures in rats with a picrotoxin induced lowering of the seizure threshold but not in rats exposed to GMS-type radiation alone. Carballo-Quintas et al. reported similar results in picrotoxin treated rats exposed to 90 minutes, 24, or 72 hours of 900 mHz electromagnetic field.[18]

Curcio et al. evaluated brain electroencephalogram (EEG) activity in 12 patients with focal epilepsy under acute real and sham exposure for 45 minutes of GSM-like electromagnetic fields in a double-blind crossover design. EEGs were obtained before, during, and after the GSM-like exposure.[19] Observed EEG spiking activity (spike count) tended to be lower under real exposure than sham exposure. Acute GSM exposure resulted in slight changes in EEG quantitative indices without reaching any clinical relevance. From this experiment, the authors concluded there was no evidence of an increased risk of incoming seizures for these patients as a result of using mobile phones.

Based on the evaluation of the published literature and the *in vivo* porcine studies conducted by researchers from Sense Diagnostics, an increase in the rate of occurrence of seizures resulting from exposure to the SENSE device in this clinical study is unlikely, and any increase in the rate of seizures above that which is expected in this patient population would be a clinically significant adverse event that could warrant stopping the clinical trial, especially since study candidates with a history of seizure activity are excluded from the trial. Thus, in the absence of any human clinical experience with the SENSE device, the selection of seizures as the adverse event of interest is justified for this study based solely on the published literature.

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[17] Lopez-Martin E, Relova-Quinteiro J, Gallego-G, et al. GSM radiation triggers seizures and increases cerebral c-Fos positivity in rats pretreated with subconvulsive doses of picrotoxin. Neurosci Lett. 2006 May 1;298(1-2):139-144.

[18] Carballo-Quintas M, Martinez-Silva I, Cadarso-Suariez C, et al. A study of neurotoxic biomarkers, c-fos and GFAP after acute exposure to GSM radiation at 900 MHz in the picrotoxin model of rat brains.

[19] Curcio G, Mazzuchi E, Della Marca G, et al. Electromagnetic fields and EEG spiking rate in patients with focal epilepsy. Clin Neurophysiol. 2015 Apr; 126(4):659-666.

10.3 Screening

The screening data for all subjects who are screened, but do not meet eligibility criteria, will not be analyzed or tabulated nor collected on the CRFs.

10.4 Subject Characteristics

The number of subjects included in the safety and/or effectiveness evaluations, subjects completing the study, and the reasons for any withdrawals will be tabulated by counts and percents. Continuous demographic data will be summarized using descriptive statistics. Categorical demographic data will be summarized using counts and percents. Abnormal medical histories and prior/concurrent medications obtained on the screening visit will be presented in data line listings.

10.5 Efficacy Criteria

Scheduled Exam Intervals: The change in received power ($P_{R)}$ measured by the SENSE device will be calculated and the accuracy of the SENSE algorithm will be tested for the SENSE measurements that correspond with the first, 12 hour, and 72 hour CT scans; and P_R will be compared to the hemorrhage volume on the corresponding CT scan. The change in P_R and CT hemorrhage volumes from the first study CT to 12 hours and from 12 hours to 72 hours will also be evaluated. Data will be summarized using descriptive statistics.

Unscheduled CT Scans: For any unscheduled CT scan that has a corresponding SENSE measurement, the SENSE P_R will be calculated and the accuracy of the SENSE algorithm will be tested; and the comparison to the hemorrhage volumes on the corresponding CT scan will be evaluated.

Although the sample size is small, the sensitivity and specificity of the P_R for monitoring changes in ICH will be estimated and evaluated for suitability as an outcome measure for determining the sample size for the pivotal study design.

10.6 Safety Criteria -- Adverse Events

The presence or absence of AEs and device malfunctions captured on the forced choice Complications/Adverse Events CRF and all other device related adverse events will be tabulated and summarized.

Seizures will be recorded and tabulated regardless of serious or unexpected status.

10.7 Other Outcome Measures

Qualitative and human factors information regarding device tolerability and compatibility with ICU work-flow obtained from study subjects and ICU staff will be summarized.

10.8 Study Success

This first-in-man study is not designed or powered to achieve pre-specified success or failure criteria.

10.9 Dropouts/Lost-to-Follow-up

Subjects may drop out at any time during the study. Effectiveness data from dropouts will be included through the last recorded subject measurement, except in those instances where missing data preclude the analysis of serial or comparative data points.

All subjects who have a SENSE device placed on his/her head will be included in the safety analysis. All subjects that sign a consent form but do not get a device assigned to them will be replaced.

10.10 Interim Analysis

Outcomes from the study may be tabulated to evaluate the progress of the study; however, an interim analysis will not be performed.

10.11 Poolability

A poolability analysis will not be performed for this single-site study.

10.12 Missing data

To assess the impact of missing data, a sensitivity analysis will be conducted. Under this analysis, the primary endpoints will be assessed in a worst case and best case scenario. For this study, the best case scenario is to use the last observation carried forward; and the worst case is to use the baseline value. Since the number of missing data points in this type of study is expected to be extremely small, it is anticipated that the sensitivity analysis will yield results similar to the main analysis.

10.13 Data Management

A unique personal identification number will be used to identify study subjects on all data forms and on all CRFs and electronic SENSE measurement data collected by the Sponsor. This will ensure proper compliance with HIPAA regulations. Instructions for completing the data forms will be addressed in detail in the CRF instruction guide. Data is expected to be entered onto the CRFs within 10 calendar days after SENSE monitoring is completed. The SENSE measurement data will be exported onto a USB drive or other electronic medium by the Sponsor at the conclusion of the SENSE monitoring for each subject. A file will be maintained of all relevant study documentation for a period of at least two years after the investigation is completed or discontinued and the FDA (Food and Drug Administration) has been notified by the Sponsor.

11.0 Ethical and Regulatory Considerations

The study is being conducted in accordance with the following GCP regulations:

21 CFR § 812 Investigational Device Exemption regulations;

21 CFR § 50 Protection of Human Subjects (informed consent) regulations;

21 CFR § 56 Institutional Review Boards; and,

21 CFR § 54 Financial Disclosure

All sites are located in the U.S., and no international sites are included in the study. Clinical monitoring is being conducted throughout the study in conformance with FDA's *Guideline for the Monitoring of Clinical Investigations* and *Guidance for Industry Oversight of Clinical Investigations – Risk-Based Approach to Monitoring.*

The clinical study will be registered on www.clinicaltrials.gov (ID Number to be assigned).

11.1 Informed Consent

In accordance with the provision of 21 CFR Part 50 and 21 CRF Part 50.25 (Elements of Informed Consent; Appendix B), each subject will provide written informed consent for participation in this study prior to the use of the investigational device.

The study will be explained to the prospective subject (or to the next of kin or legal representative for obtunded patients) by the investigator or his designee. The nature of the experimental product will be explained, including any possible adverse reactions. It will also be explained that the subject is free to terminate participation in the study for any reason. One copy of the signed consent form will be retained in the medical record, and one copy will be given to the subject.

11.2 Institutional Review Board

This protocol and the ICF will be approved initially and reviewed annually by an Institutional Review Board (IRB) constituted according to FDA regulations. Progress reports will be submitted at the completion of the study or at least once yearly, whichever comes first, to the IRB. Serious adverse events will be reported to the IRB and the FDA in accordance with applicable FDA regulations for serious adverse events.

11.3 Complications and Adverse Events

Device related adverse events should be recorded on the CRFs. For all adverse events and complications, a description of the event, date first observed, any action taken, relationship to device and ultimate outcome will be recorded. The ascertainment of relationship to the device will be performed by the independent safety monitor.

Any possible seizure related events that are observed by the investigator, or recorded in the chart notes or observed by nursing or medical personnel or reported by the subject, should be recorded and evaluated as a potential adverse event.

All device related adverse events should be recorded on the adverse event forms on the CRFs. Adverse device effects or events that are determined by the independent safety monitor to be neurologically threatening or result in a worsening of neurological status should be considered to be reportable according to the requirements of Sections 11.3.1, 11.3.2, and 11.3.3 below.

Observations that, after independent safety monitor review, are determined to be part of the normal clinical course that occur after an intracranial hemorrhage and unrelated to the SENSE device are not considered to be reportable events.

11.3.1 Serious and Unanticipated Adverse Device Effects

An unanticipated adverse device effect is defined as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects."

11.3.1.1 Sponsor Responsibilities

In accordance with 21 CFR Part 812.150(a)(1) and (b)(1), the sponsor shall promptly report the results of an evaluation of any serious and unanticipated adverse device effect to FDA, all reviewing IRB's and participating investigators (if any) as soon as possible, but not later than 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as the FDA requests. Complications and non-serious or anticipated adverse events should be

documented and tabulated but need not be submitted by the sponsor to the FDA as individual reports.

11.3.1.2 Investigator Responsibilities

Investigators should report all serious and unanticipated adverse events to the sponsor within 10 working days of first learning of the event. Those that are determined to be serious and unanticipated after independent safety monitor and sponsor review should also be reported to the IRB within 10 working days of first learning of the event. Should the IRB have more stringent time requirements, the reporting requirements of the IRB will be followed.

11.3.2 Non-serious or Anticipated Adverse Events

Non-serious or anticipated adverse events and complications should be documented on the CRFs and tabulated for reporting but need not be submitted as individual reports by the investigator to the sponsor or IRB. Should the IRB have different reporting requirements, the requirements of the IRB will be followed.

11.4 Monitoring

A monitor will be designated by the sponsor to oversee the progress of the investigation. The monitor may be an employee of the sponsor or a consultant to the sponsor. The monitor will meet with the investigator and staff before the study, during the study, and at other appropriate times to ensure compliance with the FDA's Good Clinical Practice (GCP) requirements and with the protocol specifications. All records pertaining to the study will be made available to the monitor at each review.

Study initiation and training activities may be conducted in a variety of formats prior to the start of the study, including centralized investigator meetings, web conferences, self-study of training modules on selected topics, and on-site initiation visits.

The monitor will review study activities periodically during the studyto identify any problems. Data will be verified for accuracy and thoroughness using the most appropriate source documents for all subjects. A monitoring report will be issued after each monitoring visit that summarizes current enrollment, activities reviewed during the monitoring visit, and any outstanding items or issues that require correction. The close out monitoring visit will take place at the completion of the study.

11.5 Source Documents / Case Report Forms

Adequate records will be maintained for the study including subject medical and surgical records, signed informed consent forms (ICFs), and device use records. All original source documentation will remain at the investigative site. Study data that are stored at the investigator site in any electronic medical records system, including measurements

that are obtained electronically (e.g., radiology or laboratory reports), will be printed and retained in the study files.

All study data will be recorded onto CRFs (electronic or paper) designed for the study. If paper CRFs are used, copies of the CRFs will be retained with the investigator's study files; and the original forms will be filed with the sponsor. The sponsor will enter the data from the paper CRFs into a database designed for the study.

The display screen for the SENSE device is disabled and the investigator is masked from the SENSE measurements. Data from the SENSE measurement device will be exported and stored on a USB or other electronic medium for analysis by the Sponsor. The Sponsor will provide the investigator with any available printouts from the SENSE device at the conclusion of the study for inclusion in the investigator's study files.

11.6 Deviation from the Protocol

The investigator will not deviate from the protocol without prior IRB and sponsor approval, unless such deviation is necessary to manage a medical emergency. The investigator will notify the IRB and the sponsor of any protocol deviation to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event any later than 5 working days after the emergency occurred. All other revisions and/or amendments to the protocol that affect subject treatment, study outcome, or subject safety should be submitted in writing to the IRB and the sponsor for approval prior to implementation, if the changes or deviations to the protocol affect the scientific soundness of the study or the rights, safety, or welfare of human subjects. In this case, the change should not be implemented until IRB and sponsor approvals are obtained. The investigator should maintain a record of all protocol deviations showing the dates of, and the reason for, each protocol deviation.

Changes that affect the scientific soundness of the study or the rights, safety, or welfare of human subjects may also require FDA approval, in addition to sponsor and IRB approval, prior to implementation. The sponsor and investigator will obtain such approvals, if required.

APPENDIX A: Study Flow Chart

Time	Screening	Baseline	~~Every 10 minutes for~~ 72 hour SENSE Monitorings	12 (±6) hours	72 (±12) hours	6 (±2) weeks
Assessments / Outcome Measures / Labs / Procedures	X	X		X	X	
Informed Consent	X					
History & Physical	X	X				
NIH Stroke Scale	X	X		X	X	
Glasgow Coma Scale	X	X		X	X	
CT scan	X	X		X	X	
Intermittent or Continuous SENSE Measurement		X	X	X	X	
Adverse event assessment	X	X		X	X	
Serious adverse event assessment	X	X		X	X	X
Phone call for safety monitoring						X

APPENDIX B: CFR 50.25 - ELEMENTS OF INFORMED CONSENT

BASIC ELEMENTS OF INFORMED CONSENT: In seeking informed consent, the following information shall be provided to each subject.

1. A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
2. A description of any reasonably foreseeable risks or discomforts to the subject.
3. A description of any benefits to the subject or to others which may reasonably be expected from the research.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the U.S. Food and Drug Administration may inspect records.
6. An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury.
7. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.