Flexible and conformable thin film subdural electrodes for neural recordings – a new era in clinical practice

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Executive summary

Subdural strip and grid electrodes are used as a diagnostic tool in intracranial electroencephalography (iEEG) procedures in patients with drug resistant epilepsy (DRE) undergoing evaluation for potential surgical resection. The electrodes monitor brain activity to precisely localize abnormal brain tissue provoking seizures, as well as stimulate the brain to map functional cortical areas (e.g. speech, vision) to determine the relationship between the presumed seizing tissue and these cortical areas. Outside of the epilepsy field, subdural electrodes are used for monitoring brain activity in certain patients with acute severe traumatic brain injury and during intraoperative monitoring (IOM) in patients undergoing tumor resection.

Existing subdural electrodes, which have been around for decades, are made of silicon, are thick (~0.5 mm) and not conform well to the brain. The thickness, weight, lack of flexibility and conformability to the cortical surface have negative impact on the underlying cortical tissue, can result in fluid accumulation in between the electrode and brain or dura, and contribute to a heightened tissue inflammatory response.

These can result in increased number of post-operative complications and decreased quality of the neural recordings, all of which can greatly impact clinical decisions and outcomes.

To provide a solution to these problems, NeuroOne® had designed, developed and manufactured a new thin film electrode, the EVO® cortical electrode. By comparison with silicone electrodes, EVO electrodes are ~7 times thinner, ~8 times lighter, are characterized by greater flexibility, and demonstrate reduced tissue reaction in pre-clinical studies. The electrodes passed all biocompatibility, mechanical, electrical and electrochemical testing and were the first FDA cleared thin film electrodes for use in clinical practice for monitoring and stimulation of brain activity. To assess the initial clinical experience, NeuroOne conducted a post-market user feedback study. Data were collected from neurosurgeons (n=7) who used EVO electrodes in DRE patients undergoing evaluation for potential surgical resection or undergoing tissue (epileptic and/or tumor) resection. Users provided very high ratings, mostly 4 and 5 on a scale of 1-5, regarding the properties (thickness, flexibility, weight), features (ease of placement, conformability to the brain areas) and performance (qualitative signal recording quality) of the electrodes during surgical implantation.

In conclusion, the EVO cortical electrode is the first thin film electrode technology FDA cleared for use in clinical practice for monitoring and mapping brain activity. The properties of these thin, flexible polyimide electrode arrays may overcome many limitations of existing commercially available technology. Initial clinical use indicated that the technology is feasible for surgical implantation and demonstrates exceptional signal quality, greater flexibility, ease of placement and conformability to brain gyrations when compared to silicone based cortical electrodes.

Background

Drug resistant epilepsy - epidemiology and health care burden

Epilepsy affects about 1.2 % of the US population, which is ~3.4 million people, ~ 3 million adults and ~470,000 children [1]. Antiepileptic drugs (AEDs) are the first treatment choice, however, more than 30% of the patients continue to experience uncontrolled seizures despite trying two or more AEDs [2]. These patients became known as patients suffering from drug resistant epilepsy (DRE) or refractory epilepsy.

1/3 of the epilepsy patients fail drug treatment and are candidates for surgical options.

DRE takes a heavy toll on the patients, families, caregivers, health care system and socio-economic system. Quality of life and patient's ability to function independently are severely impacted [3, 4]. Seizures starting early in life may result in developmental delays, and impact cognition, learning, emotional development, behavior and social integration, often leading to a lifetime of disability [4, 5]. Social stigma, loss of employment, loss of independence such as inability to drive, further lead to isolation and contribute to well-known co-morbidities. Epidemiological studies have shown that co-morbidities including depression, anxiety, dementia, migraines, peptic ulcers, and arthritis are 8 times more common in people suffering from epilepsy than in the general population [3, 4]. The mortality rate is also 5-10 times higher than in the general population, due primarily to sudden unexpected death in epilepsy (SUDEP), accidents, and suicide [6-8].

The health care costs for patients with epilepsy are estimated at $28 billion per year [9], with direct costs per person ranging from $10,192 to $47,862 [10]. There is increased utilization of health care resources

and higher health care costs for DRE patients as compared to patients that respond to medication [2, 10]. In addition, loss of productivity and employment profoundly impacts the socio-economic system [11].

Surgical and neuromodulation treatment options for DRE patients

The most successful surgical treatment options for DRE patients are resective surgery and neuromodulation. Resective surgery involves the removal of abnormal tissue, while neuromodulation consists of stimulating brain circuitry that causes seizures to prevent or abort seizures. Other surgical options include ablation (e.g. Laser Interstitial Thermal Therapy, LITT), hemispherectomy, corpus callosotomy, and stereotactic radiosurgery).

The appropriate treatment critically depends on the location of the abnormal seizing tissue, called the seizure onset zone (SOZ), number of epileptogenic foci, and SOZ's proximity to functionally important brain areas, called eloquent cortical areas (e.g. speech, vision, movement, etc). These factors are identified based on a comprehensive patient evaluation, which can be a two-phase process. Phase 1 evaluation consists of non-invasive imaging and neuro-functional tests, such as a high-resolution magnetic resonance imaging (MRI), magnetoencephalography (MEG), positron emission tomography (PET), single-photon emission computed tomography (SPECT), video scalp electroencephalography (EEG), and a detailed neuropsychological assessment [12, 13]. If the SOZ cannot be clearly localized (for example due to imaging methods lacking the necessary spatial resolution), and/or different tests provide divergent results, and/or the presumed SOZ is located in close proximity to eloquent cortex or in an area inaccessible surgically (e.g. deep structures of the brain), the patients progress to phase 2 evaluation. This phase uses invasive intracranial electroencephalography (iEEG) tests. iEEG is a method to record electrical signals using electrodes that come in direct contact with the brain, providing anatomically precise information about neuronal populations at the millimeter scale.

The appropriate surgical treatment depends on the ability to precisely localize the epileptogenic tissue.

Two main types of intracranial electrodes are used, (a) subdural or cortical electrodes, consisting of strips and grids, placed under the dura using a craniotomy, and (b) depth electrodes, penetrating the brain to target deeper structures (e.g. hippocampus) and placed using stereotactic methods via a small burr hole. Electrode type and their placement are decided based on a hypothesis about the location of the SOZ, formulated based on the results of the phase 1 investigation. Once electrodes are implanted, patients are kept in epilepsy monitoring units (EMU) for a number of days (mean ± SD: 8.12 ± 3.49 days; range 2-29 days- [14-18]), until sufficient information about seizure type, frequency and precise localization is gathered for a clinical decision. [12, 13, 19].

Subdural strip and grid electrodes are main diagnostic tools used to precisely localize the epileptogenic tissue and map functional cortical areas.

At the end of phase 2 investigation, for patients with a clearly identified SOZ, resection is the most desirable treatment given the clinical outcomes. Studies have shown that seizure free rates in patients who underwent resection were 58-77% versus 0-8% in patients assigned to standard medical treatment with AEDs [20-23]. When there are multiple SOZs, or these areas are in close proximity to eloquent cortex, or in surgically difficult to reach areas, neuromodulation is a preferred option. Neuromodulation includes three modalities, vagus nerve stimulation (VNS), responsive neurostimulation (RNS), and deep brain stimulation (DBS). The efficacy rates, i.e. achieving seizure free rates or reducing the number of seizures

and/or their severity, are similar for all 3 modalities and range from 41-43% at 1 year and increase to 50-68% over the years (RNS [24] VNS [25], DBS [26], [26-32]).

Use of subdural electrodes outside of epilepsy indication

Monitoring and mapping of brain function with subdural electrodes has been shown to be beneficial in patients with acute severe traumatic brain injury (TBI) and patients undergoing tumor resection (not necessarily related to epilepsy).

In patients with severe TBI, strip electrodes have enabled identification of spreading cortical depolarizations, not detected with scalp EEG. These mass neuronal depolarizations are pathological brain waves triggered by ischemia, trauma and other noxious stimuli. They have adverse effects on the injured brain, effectively increasing the injured area, and are associated with poor clinical outcomes. Detection of these waves is critical for clinical intervention. [33-36]

Subdural strip and grid electrodes are useful tools for monitoring brain activity in:

- *patients with severe TBI*
- *patients undergoing tumor resection*

In patients undergoing tumor resection, strip electrodes are used during the intraoperative monitoring (IOM) to ensure that vital neural pathways are not affected by surgical resection. Strips are typically placed over the primary sensory and motor cortex areas, perpendicular to the central sulcus which divides these areas. The electrodes record somatosensory evoked potentials, which are electrical signals triggered by stimulation of a peripheral nerve (e.g. median nerve, tibial nerve). The signal waveform recorded by contacts located in the primary sensory cortex has opposite direction to the waveform recoded by contacts in the primary motor cortex. The anatomical location of the signal reversal is marked by the central sulcus. The method, called phase reversal, allows precise identification of the motor and sensory cortex areas and plays a critical role in monitoring of the integrity of the neural pathways carrying information from the periphery to cortex. [37, 38]

Problem

Legacy electrodes are thick, bulky, heavy, not flexible and do not conform well to brain convolutions

Subdural strips and grids electrodes represent a main diagnostic tool used for precise delineation of the extent of the epileptogenic zone and functional mapping of eloquent cortex. Electrodes are placed under the dura via a craniotomy and left in place for up to 30 days, to sample brain activity from large parts of the cerebral cortex.

Although these electrodes have been in the US market for decades (first FDA clearance 1985), their fabrication, materials and properties have hardly changed. Existing commercially available subdural electrode arrays are made of platinum or platinum-iridium discs (3 - 4.5 mm diameter) embedded within flat silastic sheets which are thick (>0.5mm), heavy (weight up to 4g for larger grids), and do not optimally conform to brain convolutions. **The consequences of these properties have an impact on complication rates, signal quality, and tissue immune response.**

- *Legacy subdural strip and grid electrodes are thick, bulky, heavy, lack flexibility and do not optimally conform to brain convolutions.*
- *These properties may result in increased complications, low quality recordings, and heightened tissue response.*

Electrode properties negatively impact clinical outcomes: complications, signal quality, tissue response

a) Lack of conformity to brain surface, bulkiness and reduced flexibility are linked to an increased number of complications [39]. A study appropriately entitled "**The Brain is Not Flat**: Conformal Electrode Arrays Diminish Complications of Subdural Electrode Implantation, A Series of 117 Cases", analyzed complication rates in patients implanted with subdural electrodes (SDEs) at one center over a period of 14 years, and directly linked the number of complications to the electrode properties. The electrodes did *"not reliably conform to the convex surface of the cortex*", which could promote fluid/blood accumulation in the spaces between electrodes and dura and between dura and skull. This accumulation can cause 'mass effect', putting pressure on the brain, which can result in increased intracranial pressure, intracranial hemorrhage, infections, and neurologic compromise. Changes to improve electrode conformability and decrease the effects of thickness/bulkiness dramatically reduced post-operative complications. One major change was to make incisions in the silastic sheet, to "*help the electrodes better conform to the cortex",* thereby *"minimizing potential spaces between the cortex and grid and grid and dura*". Another change included dural expansion using bovine xenograft, intended to decrease brain compression potentially from the thickness/bulkiness and weight of the electrodes and accumulated fluid. "*Our strategy of making a silastic sheet that holds the electrodes more pliably by making slits allows it to conform to the brain, which, with dural augmentation, prevents distortion of the cortex by SDEs and minimizes the potential subdural space. This practice was implemented from 2006 after an initial neurologic complication rate (17.7%, 3/17). Subsequent 100 implantations had a 4% (4/100) neurologic complication rate.*" yes. Complication from dura expansion, which can include infections and CSF leaks [40], were not reported in this study. Similarly, several other studies reported on the electrode effects of the brain, including mechanical compression exerted by the electrodes the brain. This can distort the surrounding tissue, compress the cortical veins resulting in cerebral edema, which lead to increase in intracranial pressure, bleeding (hematoma) and microinfarcts [41-44], [54]. In an effort to avoid or decrease these complications, some centers explant or elevate the bone flap for the duration of the monitoring in the EMU [43-45]. This practice, although having increased risks of infections, has been shown to reduce the rate of asymptomatic subdural hematomas and post procedure headaches [45].

b) Lack of conformity to brain surface, bulkiness and reduced flexibility can lead to decreased signal quality. Direct contact between the electrodes and neurons is desired for a high signal to noise ratio. Lack of conformability to the brain surface, accompanied by fluid accumulation under the electrodes, can result in noise and decreased signal quality. In addition, the brain exhibits micromotion from physiological sources, such as the cardiac rhythm and fluctuations in respiratory pressure, and behavioral sources, such as spontaneous head and/or trunk displacements (e.g. during seizures). Electrode flexibility and ability to move with the brain tissue have been shown to be an important factor in maintaining reliable tracking and recording stability [46-48]**.** Noisy, unstable or unreliable recordings may result in imprecise localization of the SOZ or delineation of the SOZ, or mapping of the functional cortical areas, which can impact clinical outcomes [49].

c) Lack of flexibility, weight and tissue compression due to thickness can contribute to heightened tissue response. Tissue immunological reaction to implanted electrodes is a complex process characterized by a multitude of biochemical and immunological reactions occurring in a timely fashion at the electrode-tissue interface [49-51]. The early (hours to weeks) response is characterized by an acute inflammatory response involving accumulation of immune system cells (macrophages, monocytes), blood-borne macrophages and edema, followed by activation and migration of microglial cells. [49-53]. Indeed, histopathological findings from tissue resected from epilepsy patients who had invasive EEG monitoring with SDG and/or sEEGs for a median of 7 days, have shown chronic inflammation with accumulation of lymphocytes and macrophages, contusion or acute/subacute infarct, acute inflammation,

acute hemorrhage, edema, and necrotizing vasculitis [54]. These findings were present in 75.7% of patients that had iEEG procedures, versus 18.5% of patients without iEEG.
Tissue reaction depends on multiple factors, including the electrode material, physical properties, such as stiffness, shape, texture and weight. It has been hypothesized that the mismatch between the hard biomaterial and soft brain tissue is a major contributor to the neuro-inflammatory response. Consequently, softer and more flexible biocompatible polymers, such as polyimide, are preferable. [49, 51-53, 55]
An important factor that can contribute to heightened tissue reaction is mechanical pressure exerted by the electrodes on the brain, especially when being compressed between the brain and skull plate. It is conceivable that the thicker the electrode the higher the pressure is. Compression of the cortical tissue compressed the cortical veins and interrupts cerebral blood flow, resulting in vasogenic edema and contributing to blood accumulation in the subarachnoid space [41-43]. Subarachnoid blood can induce an acute meningeal reaction characterized by the presence of an inflammatory infiltrate. Consistent with the presence of inflammation, the use of anti-inflammatory medication (e.g. dexamathasone) has been shown to improve clinical outcomes [41, 56].

Solution

New thin film subdural electrodes: EVO™ cortical electrodes

To overcome the issues with silicone electrodes, NeuroOne has developed a new series of thin film electrodes with improved properties, the **EVO™ cortical electrodes** (Fig 1).

EVO electrodes are thin (0.08 mm), very flexible and very light (0.05 g including the tail and connector). The electrodes are made of polyimide as a substrate with platinum contacts (3mm diameter spaced 10 mm apart). Various configurations are available to suit the clinical needs (Fig 1). EVO electrodes are fabricated using an automated process and have fewer components than silicone electrodes. These may result in better signal quality, reliability and scalability. The cable assembly is disposable, reducing the potential for losing signal due to re-sterilized cables. It also saves hospital time to sterilize and store cables. The cable connectors are compatible with standard headboxes, with no need to purchase additional equipment.

Fig 1. EVO cortical electrode specifications

- Number of Contacts: 2 - 16
- Contact Spacing: 10mm
- Contact Size: 3mm
- Electrode Contact Material: Platinum
- Electrode Substrate Material: Polyimide
- Thickness: 0.08mm
- Weight: 0.05 grams
- Tail Length: 12.70 inches
- Disposable Cables
- Zero force connection box
- Standard DIN42802 touch-proof connectors compatible with standard headboxes.

EVO™ subdural electrodes are very flexible, about 7 times thinner than silicone counterparts, and very light.

EVO electrodes' properties minimize tissue reaction, potentially reducing complications

Polyimide is a high-performance polymer characterized by increased flexibility as compared to silicone. Indeed, several measures of stiffness, including the Young's module (how easy a material can

deform), bending stiffness (resistance to deformation) and critical buckling load (force needed to bent the material), indicate that polyimide is much more flexible than silicone [52]. In addition, polyimide has been shown to have excellent thermal stability (>500°C), biocompatibility, mechanical toughness and chemical resistance [57-60]. These properties make polyimide an ideal material for the design of flexible electrodes.

In pilot preclinical studies, EVO subdural electrodes have shown to elicit reduced immunological response as compared to commercially available silicone electrodes. When implanted in a pig brain for 7 days, EVO subdural electrodes produced significantly less accumulation of macrophages and other immune system cells than silicone electrodes (Fig 2) [61, 62]. Similarly, when implanted for 28 days in sheep, EVO electrodes showed no or minimal tissue reaction, comparable to the control material (USDA high density polyethylene) (Fig 3) [63].

- *EVO™ subdural electrodes show minimal or no tissue reaction following up to 30 days implantation in pre-clinical studies.*
- *This could potentially reduce post-operative complications.*

The electrodes have a single tail exit, which has been suggested to reduce the possibilities for potential CFS leak and infection risks, thereby reducing the complications [39, 64]. It may also improve patient comfort.

Taken together, the minimal or reduced tissue reaction to EVO subdural electrodes and their single tail exit, have the potential to reduce complications and improve clinical outcomes.

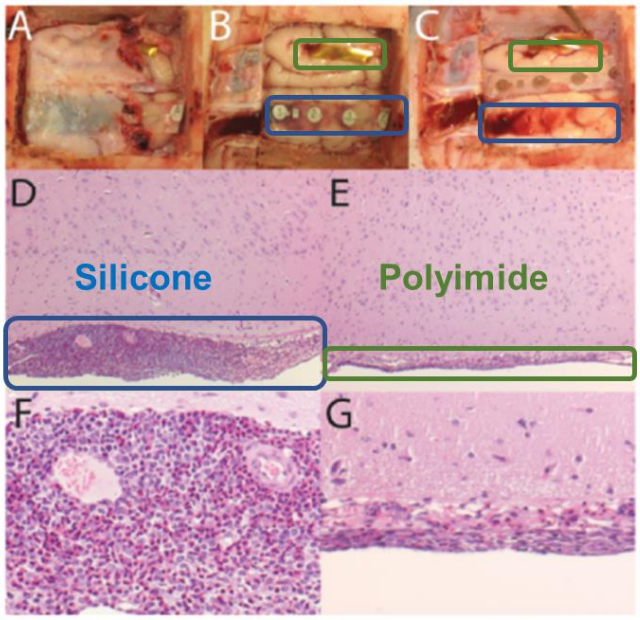

Fig 2. Reduced tissue reaction to polyimide v.s. silicone. Histological evaluation of pig brain tissue after 7 days of implantation of thin film and silicone subdural electrodes. **A.** Top view of a pig brain with dura partially exposed. **B.** Top view with dura removed to expose the electrodes. The silicon electrode is located on the lower part of the figure (blue box) and the thin film on the upper part (green box). **C.** Top view of the brain after the electrodes were removed. Blue and green boxes indicate the location where the electrodes were initially placed. Note pronounced patches of hemorrhages under the silicone electrode and minimal hemorrhage around the polyimide electrode. **D, E.** Hematoxylin & Eosin staining on tissue sections collected from directly underneath the electrodes, showing significantly more accumulation of immune system cells (lymphocytes & eosinophils) under silicone v.s. polyimide array. **F, G.** High magnification of the areas outlined by the blue and green boxes in D,E.

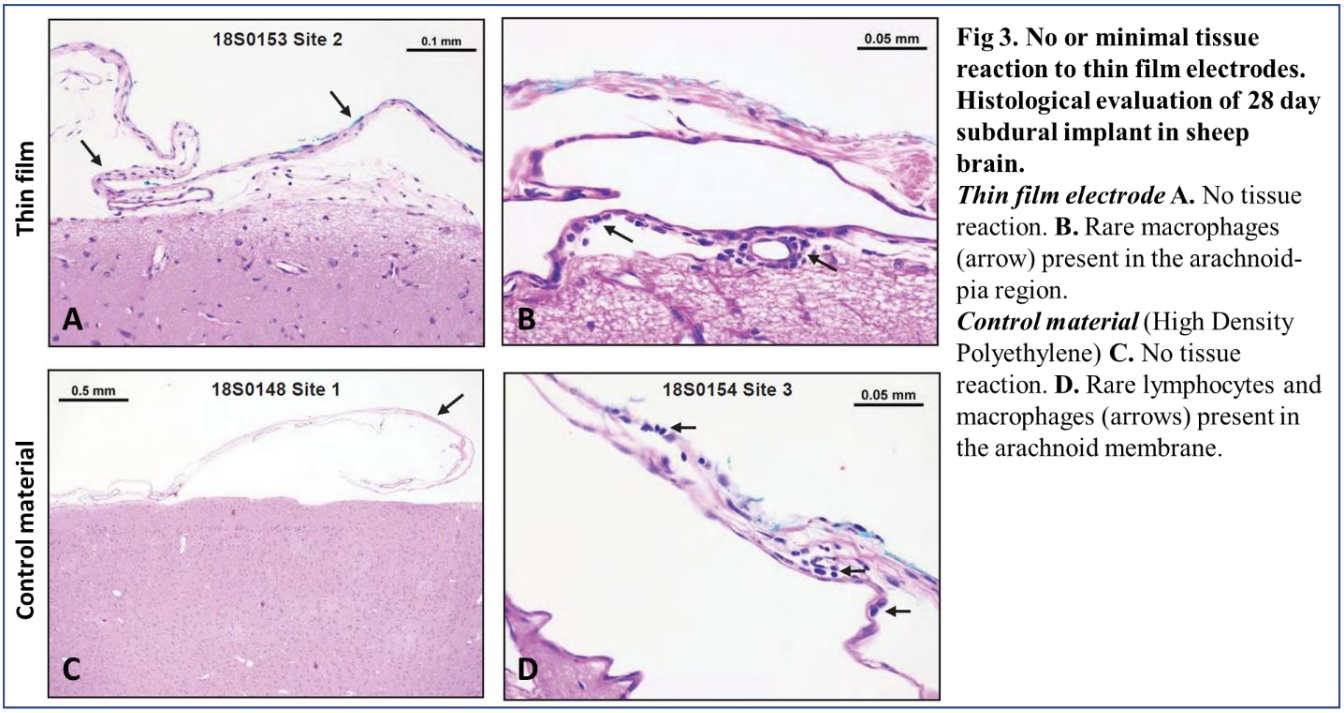

Fig 3. No or minimal tissue reaction to thin film electrodes. Histological evaluation of 28 day subdural implant in sheep brain.
***Thin film electrode* A.** No tissue reaction. **B.** Rare macrophages (arrow) present in the arachnoid-pia region.
Control material (High Density Polyethylene) **C.** No tissue reaction. **D.** Rare lymphocytes and macrophages (arrows) present in the arachnoid membrane.

Initial clinical use feedback

EVO subdural electrodes have successfully been tested in bench and pre-clinical studies and have passed all mechanical, electrical, electrochemical and biocompatibility testing, according to the International Electrotechnical Commission 60601 and the International Organization for Standardization (ISO) 10993 standards, resulting in FDA clearance for use in clinical practice.

To assess the initial user experience with these new electrodes, NeuroOne conducted a post-market study [63]. Data were collected using a questionnaire as well as unstructured oral feedback from surgeons and operating room staff during surgical procedures performed between November 23, 2020 and November 4, 2021. Data were collected from 14 centers, which included the Mayo Clinics in Rochester MN and Jacksonville FL, Stanford CA, Memorial Hermann Hospital in Houston, TX and others. 7 surgeons and OR staff members responded to questionnaires, while the remainders provided oral feedback only. A total of 60 electrodes of different sizes and shapes (e.g. 1x2, 1x6, 1x8, 2x8, 2x6, 4x4 arrays) were used in 25 procedures for:

(a) Monitoring and mapping in DRE patients undergoing evaluation for potential surgical resection. In these cases, the electrodes were kept in place for the duration of the monitoring phase (~8 days in average). In some patients, both subdural (EVO) and depth electrodes (commercially available) were placed during the same procedure.
(b) Monitoring and mapping in patients undergoing epileptic or tumor tissue resection. In these cases, the electrodes were used intraoperatively, for short period of times (~ 30 min to several hours).

The feedback questionnaire contained 6 questions, rated on a scale of 1 to 5, with 5 being the highest. The questions were intended to evaluate a) properties of the electrodes such as thickness, flexibility, weight, b) features such as ease of placement, conformability to the brain areas and c) performance, asking for a qualitative signal recording quality. (Table 1)

Users (neurosurgeons; n=7) provided ratings between 4 and 5 for most questions (Table 1), demonstrating remarkable user experience and illustrating the importance of a product that is flexible, light, easy to use in places that are not easily accessible, and conforms well to brain convolutions.

EVO™ subdural electrodes received exceptional user feedback during initial clinical use, with indications of greater flexibility, ease of placement and conformability to brain gyrations, when compared to silicone based cortical electrodes.

Table 1. Summary of post-market user feedback data

Question (Ratings scale 1-5: 1 lowest, 5 highest)	**Average** (range) n=7 users
1. Electrode thickness and flexibility	4.8 (5)
2. Lighter than current competitive electrodes	5 (5)
3. Cable connections simple, reliable	3.4 (1-5)
4. Ease of placement onto targeted locations	4.5 (3-5)
5. Conformability with the targeted anatomy	4.7 (3-5)
6. Recording quality and signal clarity	5 (5)

Conclusions

- EVO cortical electrodes are the only known FDA cleared thin film subdural electrodes.
- EVO cortical electrodes are thin, flexible and almost weightless
- Disposable cable assembly eliminates potential signal failures and saves hospital resources and time
- Compatibility with standard headboxes ensures no need for additional equipment
- In preclinical studies, EVO cortical electrodes have shown reduced tissue immunological response as compared to silicon counterparts
- Initial clinical use during surgical procedures received remarkable user feedback with indications of greater flexibility, ease of placement and conformability to brain gyrations, when compared to silicone based cortical electrodes.
- Signal quality was rated as excellent.

These properties have the potential to (a) reduce complications resulting from lack of conformability and tissue reaction, (b) allow placement in spaces with reduced accessibility, (c) be amenable to less invasive procedures, (d) reduce the size of the craniotomy, (e) shorten patient recovery. While it is too early to evaluate complication rates with these electrodes, we believe that the new thin film electrodes provide a much-needed solution in clinical practice that may ultimately benefit the patient.

Thin film subdural electrode technology for intracranial EEG is feasible for surgical implantation and may have the potential to minimize invasiveness of subdural recordings and improve surgical outcomes.

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