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Dartmouth College and Dartmouth-Hitchcock Medical Center
Committee for the Protection of Human Subjects

CPHS Study Plan for Full Committee Review

Template v. 5.13.2009

Instructions:
The following information in the format provided below is an application for Dartmouth-Hitchcock Health review. Read through each section and **respond to each item (even if to indicate NA - not applicable)**. Please also review the CHECKLIST for Full Committee Submission. We have provided some guidance information under each question.

Please define all acronyms at first use and attach a glossary if more than 3 acronyms are used in this application.

When revising a D-HH reviewed Study Plan for further review, please track the changes. To turn on tracking in this document in Microsoft Word:

1) Display the forms and reviewing toolbars.
2) Unlock the form by clicking on the lock icon on the forms toolbar.
3) Turn on change tracking by clicking the icon on the reviewing toolbar.
4) Lock the form by clicking again on the lock icon on the forms toolbar.

Attachments:
Complete and submit Attachment(s) if applicable to the research study.
Attachments may be downloaded from this webpage: http://www.dartmouth.edu/~cphs/tosubmit/forms/StudyPlanAttach

- ☐ Attachment A: Nonsignificant Risk Devices
- ☐ Attachment B: Placebo
- ☐ Attachment C: Genetic Research
- ☐ Attachment D: Employees and Students
- ☐ Attachment E: Illiterate Participants
- ☐ Attachment F: Research Involving Children
- ☒ Attachment G: Research Involving Individuals With Impaired Decision-Making Capacity (formerly referred to as incompetent)
- ☐ Attachment H: Request for Waiver of Participant Consent
- ☐ Attachment I: Request for Waiver of Participant Signed Consent Form
- ☐ Attachment J: Drugs or Biologics
- ☐ Attachment L: International Research
- ☐ Attachment M: Pregnant Women, Fetuses and Neonates

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Local Principal Investigator: **Barbara Jobst, MD**
Department: **Neurology**

Study Title: **Microelectrodes in Epilepsy**
Funding Source (Sponsor): **Department of Neurology Funds**

D-HH Study Plan Version Date: **30Mar2020**

1.Abstract.

Provide an abstract of the proposed research **in language that can be understood by a non-scientist**. The abstract should summarize the objectives of this project and the procedures to be used, with an emphasis on what will happen to the subjects. **(Maximum 250 words)**

The standard-of-care for medically refractory epilepsy is resective brain surgery. In certain patients, precise localization of the epileptic focus is done using intracranial EEG (iEEG) recording. In this type of EEG recording, electrodes are placed on the brain surface or inserted into the brain through an opening in the skull. In addition to standard electrode recording, several epilepsy centers have independently developed ultra thin microelectrode technology. Microelectrodes are only several micrometers thick and are uniquely useful because they are able to record the activity of single neurons in isolation. Such recording has tremendous clinical potential in epilepsy surgery and tremendous research potential in cognitive neuroscience. This IRB study plan outlines our clinical and research interests in the use of FDA approved, commercially available, dual macro-micro electrode system in patients who require intracranial EEG recording prior to epilepsy surgery.

2.**Objectives & Hypotheses:**

List your research objectives and hypotheses.

We have two fundamental objectives and hypotheses. Our first objective is to investigate the usefulness of microelectrode technology in epilepsy surgery. We hypothesize that microelectrode recording will provide unique and novel information on the specific epileptic potential of the implanted brain tissue. Our long-term aim is to improve our paradigms for epilepsy surgery. Our second objective is to investigate the activity of single neurons during specific cognitive tasks. We hypothesize that such analysis will help to predict possible cognitive deficits of epilepsy surgery and provide unique insight into the fundamental mechanisms of cognition and behavior.

3.**Introduction:**

a) Explain the background of this project so that we will understand why it is important to perform this research project. b) Summarize previously published data and pilot studies. Be sure to include a discussion of any data that do not support the study hypothesis. If a study similar to the one being proposed has already been completed, explain why the proposed study is necessary. c) For studies designed to compare or evaluate therapies, there should be a statement of the relative advantages or disadvantages of alternative modes of therapy. d) If not obvious, explain why human subjects are necessary. Include references for all published data cited. If a formal protocol for the study exists, page references to the protocol are acceptable.

Patients who have recurrent unprovoked seizures despite adequate treatment with antiepileptic medications have medically refractory epilepsy (1). This condition affects approximately 30% of all patients diagnosed with focal epilepsy in the United States. The standard of care for this group of patients is referral for epilepsy surgery. Epilepsy surgery has been well demonstrated to be an effective treatment option for these patients with high seizure freedom rates and low morbidity in properly selected patients (2). Each patient referred for epilepsy surgery undergoes a pre-surgical evaluation with a goal of precise localization of the epileptogenic region and determining the probable cognitive and functional morbidity for the surgery. The pre-surgical evaluation frequently requires the recording of seizures using intracranial EEG (iEEG). In this technique, specially designed electrodes are surgically implanted into target regions of the patient's brain by a trained neurosurgeon and epileptiform activity is recorded. IEEG recording has a long track record of being an effective method of seizure localization (3) with a complication rate of 2-4% (4,5). This method has been used successfully at the DHMC

Epilepsy Center on hundreds of patients since 1992. The recording of iEEG for conventional clinical applications is done using a standard macroelectrode system. A macroelectrode is either a soft plastic strip with multiple 5 mm disc electrodes or a rigid 10 cm needle electrode with multiple contacts along its length. Macroelectrodes are designed to record the summated activity of relatively large groups of neurons located in the vicinity of the electrode contact. Although macroelectrode iEEG recording is the mainstay of surgical epilepsy with established clinical indications, significant limitations are known.

Currently, several well-established epilepsy centers in the United States (for instance, UCLA and Mayo Clinic) are investigating the use of microelectrode systems in epilepsy surgery to supplement the standard macroelectrode recording. Microelectrodes are ultra thin filament electrodes with tip diameters of 3 to 10 micrometers which are able to record the activity of small groups or even single neurons, i.e. single unit potential recording. Supplementary microelectrode recordings are obtained using commercially available, FDA-approved, dual macro-micro electrode systems. These dual systems do not require the insertion of separate and additional microelectrode catheters but use the standard iEEG electrode to deliver the microelectrodes to the target brain regions. The major benefit of this novel design is that the rate of complications from such dual electrode systems is the same and for the standard iEEG electrodes.

The primary aim of supplementing standard iEEG recording with single unit recording is to obtain additional information about the epileptogenic potential of the brain region that is implanted. Initial research in this area was done in the 1980's at UCLA Medical Center where microelectrode recordings of epileptogenic brain tissue showed anomalous bursting patterns, coupled neuronal firing, and increased local inhibition (6, 7). At the same center in the 1990's high frequency oscillations called fast ripples were recorded in patients undergoing pre-surgical evaluation (8, 9) and Braquin et al Annals of Neurology 2002). Fast ripples are ultra-fast neuronal oscillations in the 80 to 1000 Hz range which have been proposed to be the exclusive signatures of epileptogenic cortex (10). Most recently, dual macro-micro system to record fast ripples and determined that they frequently appeared in the microelectrode recording and were not apparent in the standard macroelectrode recording (11). These findings suggest that fast ripples are generated by microscopic neuronal structures which are frequently too small to be recorded using the standard macroelectrode system. Therefore, single unit recording may offer clinically relevant information for epilepsy surgery.

A second yet no less important aim of recording single unit potentials is to gain better understanding of the role of the epileptogenic cortex in cognitive function. Once localization of epileptogenic cortex is established, the functional role of this cortex and possible cognitive deficits following resection must be established. Present paradigms require assessment of cognitive function during the electrical stimulation of macroelectrode contacts which can establish the eloquence of the underlying cortex. Recording of single unit potentials with microelectrodes during specifically designed neuropsychological tasks may offer unique insight into the function of epileptogenic cortex. For example, studies done at UCLA Medical Center have shown that the recording of single unit potentials during specific memory tasks has provided relevant information regarding the functional state of the hippocampus (12). Therefore, recording of single unit potential during specific cognitive tasks may provide important information on the functional integrity of the region of the brain where resection is planned.

A third aim of recording single unit potentials is to investigate the activity of single neurons during specific cognitive tasks. For instance, single unit recording from the hippocampus using the dual macro-micro electrode system during specific cognitive tasks has generated a novel insight into the organization of the human semantic memory system (13). Currently, patients at DHMC undergoing iEEG recording

may have depth electrodes in the orbitofrontal region, the insula, the amygdala, and the hippocampus. Investigation of single unit activity in these patients during performance of specific tasks may generate unique and novel insight into the function of these brain regions in behavior. For instance, investigation of the role of mirror neurons in social behavior may be done by recording the activity of insular neurons during observation of facial expression. Furthermore, single unit activity in the orbitofrontal region during Go-No Go tasks may offer novel insight into the role of this brain region in impulse control.

In summary, we have two concurrent goals for the use of microelectrode recording in patients undergoing iEEG for surgical treatment of medically refractory epilepsy. Our most salient goal is to augment the standard iEEG recording with additional microelectrode recording which may help to identify regions of epileptogenic cortex. Our second goal is to augment our ability to predict the cognitive risk of epilepsy surgery and investigate the role of the specific brain region in cognition and behavior. For these goals, we will utilize a safe, commercially available, FDA approved dual micro-macro electrode system. Our hypothesis is that such recording will elucidate specific characteristics of brain regions with epileptogenic potential, will offer novel insights into cognitive neuroscience, and help to predict neuropsychological outcomes of surgery.

References:

1. Kwan P, Brodie MJ. Early Identification of Refractory Epilepsy, NEJM 342 314-319, Feb 3 2000
2. Wiebe S, Blume WT, Girvin JP, Eliasziw M. A Randomized, Controlled Trial of Surgery for Temporal-Lobe Epilepsy. NEJM 345:311-318, August 2, 2001
3. Steven P, Ebersole J. Intracranial EEG in Temporal Lobe Epilepsy. Journal of Clinical Neurophysiology, September 1999 - Volume 16 - Issue 5 - p 399
4. Hamer HM, Morris HH, Wyllie E, Lüders HO. Complications of invasive video-EEG monitoring with subdural grid electrodes. Neurology 2002;58:97-103
5. Van Gompel JJ, Worrell G. Phase I trial: safety and feasibility of intracranial electroencephalography using hybrid subdural electrodes containing macro-and microelectrode arrays. Neurosurg Focus 25 (3):E23, 2008.
6. Babb TL, Brown WJ. Neuronal, dendritic, and vascular profiles of human temporal lobe epilepsy correlated with cellular physiology in vivo. Adv Neurol. 1986;44:949-66.
7. Colder BW, Wilson CL, Frysinger RC, Chao LC, Harper RM, Engel J Jr. Neuronal synchrony in relation to burst discharge in epileptic human temporal lobes. J Neurophysiol. 1996 Jun;75(6):2496-508.
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11. Greg A.Worrell,1 Andrew B.Gardner,3 S. Matt Stead,1,2 Sanqing Hu,1 Steve Goerss,4 Gregory J. Cascino,1 Fredric B. Meyer,4 Richard Marsh4 and Brian Litt3High-frequency oscillations in human temporal lobe: simultaneous microwire and clinical macroelectrode recordings. Brain February 7, 2008
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13. Gelbard-Sagiv H, Mukamel R, Harel M, Malach R, Fried I. Internally generated reactivation of single neurons in human hippocampus during free recall. Science. 2008 Oct 3;322(5898):96-101. Epub 2008 Sep 4.

4.**Design, procedures, materials and methods:**

Use a level of detail similar to what would be used when submitting an article for publication in a peer reviewed journal. Explain the study procedures, data collection, and analysis process. Please define terms and explain concepts which might be confusing to reviewers who are not expert in the area of the study. If a formal protocol for the study exists, page references to the protocol are acceptable.

Patient selection. Patients with medically refractory epilepsy are referred to DHMC for surgical evaluation. The first stage of the evaluation includes inpatient video EEG monitoring, epilepsy protocol MRI, and a neuropsychological evaluation. Following the initial evaluation, each patient's case is discussed in the epilepsy surgery conference. The conference is attended by all Dartmouth epilepsy neurologists and neurosurgeons. A consensus among all physicians is reached regarding further evaluation. Approximately 50% of patients require intracranial EEG (iEEG) recording prior to epilepsy surgery. If a patient requires iEEG, the strategy for the exact type of electrode implantation is determined at the same surgical conference. Subsequently, the need for iEEG monitoring is discussed with the patient in the outpatient clinic. Patients who meet clinical indication for iEEG recording will be asked to participate in the research study. If the patient agrees, certain standard electrodes will be substituted with the dual micro-macro electrodes during the iEEG recording.

Electrodes. Ad-tech is the largest manufacturer and supplier of intracranial electrodes for use in epilepsy surgery. Ad-tech standard macroelectrodes have been used at Dartmouth-Hitchcock Medical Center since 1992 in hundreds of iEEG cases. In addition to macroelectrodes, Ad-tech currently manufactures two types of dual macro-micro electrode systems that will be used in the study. The appropriate type of electrode system will be determined by the study team.

One system is designed to mimic the original macroelectrode design with the addition of ultra-thin microelectrodes. The original macroelectrode dimensions and properties are retained and additional microelectrodes are positioned at the tip. Leads for the macro and micro electrode recording are separate and are connected to two distinct recording systems. Safety information for the use of the dual electrodes is provided from a single retrospective study of 24 patients who underwent the dual electrode implantation at Mayo Clinic. The complication rate for microelectrodes was 4% compared to 6% for standard electrode systems. Attachment #1 and Attachment #2 address the safety of the electrodes.

The second system (Behnke Fried/Micro Inner Wire Bundle) consists of an outer macro contact depth electrode that accepts delivery of an inner micro wire bundle. The micro contacts extend past the tip of the macro depth electrode.

Data Recording. Recording of iEEG using macroelectrodes has been routinely performed at Dartmouth using the Natus system. Recording of microelectrode potentials will be done using a separate Digital Lynx system or the clinical Natus system. The two systems are distinct and will not share information. The Digital Lynx system is a state-of-the-art microelectrode recording system manufactured by Neuralynx. Neuralynx provides the highest quality microelectrode recording equipment. The Digital Lynx system is not FDA approved for clinical use. However, it has been fully tested and meets the 60601 medical safety standards, has the 60601-1 safety certification for medical devices, and has meets the 60601-2-26 safety standards for EEG equipment. This system is available for clinical use through the lab of Barbara Jobst. Attachment #3 addresses the safety of the Digital Lynx System.

Cognitive Tasks. Patients who agree to participate in microelectrode studies may be asked to participate in a study which involves a cognitive task. Each task will be specifically designed to elicit a specific cognitive function important to testing of the regions where electrodes are implanted. The task could be a memory task, such as remembering of word pairs if electrodes reside in the hippocampus. The task may involve perception of facial emotion, mimicry of facial movements, mimicry of planned movements, smell appreciation, taste appreciation, appreciation of disgust, or visual spatial analysis. The type of task that a patient gets will depend on the region of the brain that is implanted by the microelectrode.

Data Analysis. Data on neuronal discharge characteristics will be recorded using the 64 Chanel Digital Lynx system running Cheetah software. The characteristics of fast ripples, and the data on neuronal firing characteristics during specific cognitive tasks will by exported to Matlab software for statistical analysis. Data analysis will be done by either the study team at DHMC/Dartmouth College, or by collaborators at Columbia University.

5.Inclusion/Exclusion Criteria:

Please provide detailed description of inclusion and exclusion criteria. If a formal protocol for the study exists, page references to the protocol are acceptable.

Inclusion criteria:
1. 18-65 year old
2. male or female
3. right or left handed
4. IQ>70
5. medically refractory focal epilepsy requiring intracranial EEG for pre-surgical evaluation deemed medically necessary
6. no contraindications to intracranial electrode study
7. able and willing to participate in research

Exclusion criteria:
1. does not meet the inclusion criteria

6.Financial Considerations:

Disclosure of financial impact on the participant is critical to informed consent. Insurance cannot be billed for research-related services outside the standard of care or paid for by the funding agency for the study. The department, the study or the participant may be responsible for payment for research-related services. Participants should know which tests, visits, or procedures will be billed to them or their insurance and which ones will be paid by the funding agency for the study or the department.

a) List tests, visits, and procedures performed for only research purposes. These services are outside the standard of care. They would not be performed if the individual were not a research participant, and may not be billed to a health insurance plan.
Note: 6a information must also be in "How is this different . . ." section of the consent form.

There is no predicted extra cost to the patient if they choose to participate in the study. We will purchase the research portion of the dual micro-macro electrode system using research funds. Use of Digital Lynx system, collection of data, data analysis, creating and administration of neurocogntive tasks will be done during research time of individuals in the study. Nothing that is done outside the standard of care will be billed to the patients.

b) List the tests, visits, and procedures that may be standard care, but for which the funding agency for the study is paying.

None

c) Will the funding agency for the study be responsible for the above costs?
☐ Yes ☐ No
If No, describe who will be responsible (i.e., department or participant).
The Department of Neurology will be responsible for all research costs outside of standard of care.

PLEASE ENCLOSE THE DHMC BILLING GRID/PLAN. Also enclose the schedule of events or table listing all procedures from the sponsor protocol. A Billing Grid will not be applicable to this study as there is not a sponsor and all procedures are standard of care. There are only 2 points of contact with the patient regarding the study: 1. Consenting the patient after a routine office visit and 2. Standard of care surgical evaluation.

7.Statistical Methods and Review Statement:

a) Specify the primary endpoint, as well as other endpoint(s).

The primary hypothesis is that high oscillations (fast ripples) occur in epileptogenic cortex and are absent in non-epileptogenic cortex. Our secondary hypothesis is that single unit activity recorded from various electrode positions in the brain will correlate with specific cognitive tasks.

b) State the statistical analysis plan, including all hypothesis tests (e.g., t-test, chi-square), and estimation methods related to the primary endpoint. If a formal protocol for the study exists, page references to the protocol are acceptable.

The recording of high frequency oscillations will require only basic statistical analysis using chi-square testing. The analysis of neuronal discharge characteristics and temporal association with specific cognitive tasks will be done using Matlab.

c) Justify the sample size, using the concepts of power, type I error, and effect size if applicable. If a formal protocol for the study exists, page references to the protocol are acceptable.

We are planning to enroll up to 50 patients over an extended period of time. The power calculations and effect size, will depend on the cognitive task applied in the individual patient for the specific electrode array.

8.**Data and Safety Monitoring:**

Describe plans for data and safety monitoring to ensure the safety of subjects and the quality of the data. As described in federal guidance **"**… a variety of types of monitoring may be anticipated depending on the nature, size, and complexity of the trial. In many cases, the principal investigator would be expected to perform the monitoring function." This plan should include monitoring to determine:

The progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome. Monitoring should also consider factors external to the study when interpreting the data, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study.

Note: This section does not request information related to sponsor study monitor visits. This section requires a description of an adequate data and safety monitoring plan.

The safety of dual macro-micro electrodes will be assessed with every patient. Complete data analysis will be done with every patient.

9.**Genetics:**

Does any part of the study involve genetic analysis of biological specimens?

☐ Yes ☒ No

If yes, respond to **Genetics Attachment C**

10.**Instruments:**

Describe each instrument, if any, used to collect data in this study.

Attach copies of any questionnaires, surveys, or interview questions. If the research involves interviews that could evolve as the research progresses, include a list of discussion topics and any "starter" questions for each topic that can reasonably be expected to be covered. If a draft of a written questionnaire or survey is attached, it should be clearly labeled as such and a final version should be sent to Dartmouth-Hitchcock Health (D-HH) IRB for review before data collection begins.

11.**Deception.**

Will deception of participants, including withheld information, be used in this research?

☐ Yes ☒ No

If yes, complete a-d.

a) Describe the deception being used in this study:

b) Explain why deception is necessary in this research:

c) Describe the information provided to subjects when they decide to participate:

d) Describe how the subjects will be provided with additional pertinent information after participation (debriefing):

12.**Timetables:**

a) Indicate length of participant involvement in the study: **Each participant will be enrolled into the study for the duration of their iEEG monitoring, this is an inpatient admission of less than two weeks.**

b) Estimate how long it will take to enroll enough participants to complete this study: **This will be an ongoing study. We think we can enroll 2-3 patients per year.**

13.**Risks:**

The purpose of this section is to determine if subjects will be placed "at risk," which in general means exposed to the possibility of physical, psychological, social, economic, legal, dignitary or other harm as a consequence of any activity proposed in the research project.

a) What is the overall risk classification of the research?

- ☒ Minimal
- ☐ Greater than minimal
- ☐ Significant
- ☐ Unknown

Note: In the federal regulations on human subjects protection minimal risk means "The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

b) Describe any potential risks (physical, psychological, social, legal, economic, or other) and assess their likelihood and seriousness. Describe the procedures for protecting against or minimizing these risks, including risks to confidentiality, and assess their likely effectiveness. Please list risks from most severe/likely to least severe/unlikely.

The risk of participation in the study overall is only minimally greater that standard iEEG recording, although conclusive risk assessment is not available. The safety of dual micro-macro electrode systems has been annalyzed in a retrospective study done at the Mayo Clinic by Van Gompell et al. In this study, 24 consecutive patients underwent long-term iEEG monitoring with implanted dual depth and subdural grid and strip electrodes; both clinical macroelectrodes and research microelectrodes were used. The patients included 18 women and 6 men with an average age of 35 (range 21–65). The mean hospital stay was 11 days (range 5–20), with mean duration of implantation 7.0 days (range 3–15). Data from the 198 consecutive craniotomies for standard clinical subdural grid insertion (prior to surgery in the 24 patients described here) were used for comparison to investigate the relative risk of complications. The overall complication rate was 4.2% (only 1 patient had a complication), which did not significantly differ from the complication rate previously reported by the authors of 6.6% when standard subdural and depth intracranial electrodes were used. There were no deaths or permanent neurological deficits related to electrode implantation. In conclusion, he authors demonstrated the use of hybrid subdural strip and grid electrodes containing and standard clinical macroelectrodes. In this initial study in 24 patients, the complication rate is acceptable, and there does not appear to be increased risk associated with the use of hybrid electrodes compared with standard subdural and depth iEEG electrodes. Please refet to Attachments #1 and #2 for further details.

Digital Lynx system is not FDA approved. However, it has been certified to be UL/EN 60601-1 and 60601-22 compliant. Details are enclosed in attachment #3.

A theoretical risk of potential physical neuronal injury by direct contact of a microelectrode with a neuron exists. This type of injury has not been reported in humans with use of microelectrodes. Potential injury by direct microelectrode contact would most likely be limited to single neurons or very small populations of neurons. No neurocognitive effect would be expected by injury to such small populations of neurons.

14.**Risk/Benefit analysis:**

Describe why the risks to subjects are reasonable in relation to the anticipated benefits to participants and in relation to the importance of the knowledge that may reasonably be expected to result from the study.

The potential risk of this study is reasonable give the wealth of potential information which may be gained from this study. Potential benefits include improvement in prediction of neuropsychological outcomes, improvement in detection of epileptogenic brain regions, and novel understanding of neurocognitive mechanisms.

15. **Research Setting**

a) Is this a multi-center study?

☐ Yes ☒ No

If yes: Are you the lead investigator? ☐ Yes ☐ No

If you are NOT the lead investigator:

Name of lead investigator:

Institution where the lead investigator is located:

b) List all sites where research will take place and D-HH is the reviewing IRB (e.g. DHMC Alliance Hospitals, DHMC Clinics, WRJ VAMC):

DHMC - Lebanon

c) If you are the lead investigator of a multi-center study, list all sites where research will take place and D-HH is **NOT** the reviewing IRB: or check ☒ *N/A*

Note: Each site taking part in the research should have appropriate institutional or IRB oversight. A Site Agreement or Federalwide Assurance may be required. The D-HH office can assist you with these arrangements.

d) Does the study involve sites outside of the United States and Canada?
☐ Yes ☒ No
If yes, are arrangements for the international site(s) being made by a multinational pharmaceutical or device sponsor or a cooperative oncology working group?
☐ Yes ☐ No
If no, please **complete Attachment L**.

16.**Adequacy of Resources to Protect Subjects:**
a) Investigator (including co-investigators) has sufficient time to conduct and complete the research.
☒ Yes ☐ No

b) Adequately qualified (including experience, training, supervision, and familiarity with the protocol) staff are available for this research.
☒ Yes ☐ No.

c) Describe availability of psychological, social, or medical services, which include counseling or social support services, that may be required as a consequence of research participation.

Patients are routinely evaluated by neuropsychologists as part of routine work-up. As subjects will be inpatients during their participation in the study, epilepsy , neuropsychiatry, and psychology services will be available.

d) Describe psychological, social, or medical monitoring, ancillary care, equipment needed to protect participants (e.g. close proximity to resuscitation equipment or a plan for monitoring of emotional state during study procedures).

The study will be conducted inside the Epilepsy Monitoring Unit (EMU) at DHMC. This unit is specifically equipped to deal with complications of epilepsy and epilepsy surgery. The unit has continuous video EEG monitoring, meets safety standards for operating an EMU, has specially trained and qualified nurses who are able to treat seizures.

e) Describe other resources needed for the protection of subjects in the conduct of this research (e.g. language translation services).

None

f) Explain how the investigator has access to a population that would allow recruitment of the required number of subjects.

Patients who have medically refractory epilepsy are referred to the DHMC Epilepsy Center for surgical evalaution. Each year, between 10-15 intracranial EEG studies are performed. Patients will be recruited from among all patient who meet the inclusion criteria. We anticipate that 5-8 patients per year will be recruited to participate in the study.

17.**Participant Population:**

Certain populations are considered vulnerable to coercion and undue influence. These populations are provided with additional protections when participating in a research study. The populations include:

- prisoners
- human embryos
- fetuses
- elderly people
- people with an cognitive disability (also see #23 below)
- people with a disabling psychiatric illness
- people who are economically disadvantaged persons
- people who are illiterate

Refer to: Students, Employees **Attachment D**
Illiterate Subjects **Attachment E**

a) List vulnerable groups: or check ☐ *None*

People with a cognitive disability who meet the inclusion criteria, and are capable of performing the cognitive tasks, but are not capable of giving informed consent.

b) Describe additional protections: or check ☒ *N/A*

The informed consent process for potential participants with a cognitive disability who have a legal guardian will include the participant and their legal guardian. As the risks associated with this study are minimal, no other additional protections would be needed.

18.**Gender and Racial/Ethnic distribution:**

NIH guidelines state that research involving human participation should include minorities and both genders.

Note: If one gender or minorities are excluded or are inadequately represented in this research, particularly in proposed population-based studies, a clear and compelling rationale for exclusion or inadequate representation should be provided.

Will eligibility for the study be based on gender, race, or ethnicity? ☐ Yes ☒ No
If yes, explain:

19.**Pregnant Women:**
Are pregnant women eligible for enrollment into this study? ☐ Yes ☒ No
If yes, respond to **Research Involving Pregnant Women, Fetuses and Neonates: Attachment M**
If no, explain and include a process to determine pregnancy status. If a pregnancy test is required, note who will pay:

20.**Fetuses and Neonates:**
Are fetuses and neonates participants in the research?
☐ Yes ☒ No
If yes, respond to **Research Involving Pregnant Women, Fetuses and Neonates: Attachment M**

21.**Children:**
Are children eligible for enrollment into this study? Under state law, a child is a person less than 18 years old.
☐ Yes ☒ No
If yes, respond to **Children: Attachment F**
If no, present an acceptable justification for the exclusion:

Note: NIH guidelines state that research involving human participation should include children unless there is appropriate justification for their exclusion. The investigator should address the rationale for selecting or excluding a specific age range of children, or an explanation of the reasons for excluding children as participants in the research. When children are included, the plan should also include a description of the expertise of the investigative team for dealing with children at the ages included, of the available facilities to accommodate the children, and a sufficient number of children to contribute meaningfully to the study analysis.

22.**Women of Child-Bearing Capability**
Are women of child-bearing capability eligible for enrollment into this study?
☒ Yes ☐ No
If yes, describe potential harm to an unborn fetus from study activities and the process for determining pregnancy status if necessary. If a pregnancy test is required, note who will pay. If there is potential harm to an unborn fetus, the investigator should review with each individual a plan to avoid pregnancy. If the investigator regards these contraceptive plans as inadequate, the individual should be advised on how to achieve adequate contraception or should be excluded from the study.

All patients undergoing surgical work up for epilspsy have a pregnancy test done. Patients who are pregnant are excluded from epilepsy surgery and will not be included in this study.

If no, explain why this population is not eligible and how you will determine eligibility for each woman.

23.**Individuals With Impaired Decision-Making Capacity:**

Will participants potentially lacking capacity to provide informed consent be eligible to enroll in this study? ☒ Yes ☐ No

If yes, respond to **Research Involving Individuals With Impaired Decision-Making Capacity: Attachment G**

24.**Recruitment:**

Describe how subjects will be recruited for participation in this study:

Eligible participants may be identified from medical record information as a "preparatory to research" activity under the HIPAA Privacy Rule. Protected health information obtained as a preparatory to research activity may not be removed by a researcher from DHMC, including on mobile electronic storage devices. Contact with the identified participants, however, may not occur without prior D-HH approval of the recruitment plan for the study. This plan should describe how initial contact with participants will be made and by whom. Please note in general, individuals should not be contacted for recruitment into a research study by someone unknown to the individual.

a) Will subjects be recruited by searching records (e.g., school records, medical records)?
☐ Yes ☒ No
If yes, will this search include paper files?
☐ Yes ☐ No
If yes, where will these paper files be located?

If yes, will this search include electronic files?
☐ Yes ☐ No
If yes, who maintains these electronic files?

b) Will databases be utilized?
☒ Yes ☐ No
If yes, please specify types and locations of databases: **Patients will be recruited from the clinical patient pool of patients of the Dartmouth Epilepsy Program. No specific or pre-exisisting database will be searched.**

c) Will fliers or brochures be posted, mailed or otherwise distributed?
☐ Yes ☒ No

d) Will letters be sent to potential participants?
☐ Yes ☒ No
If yes, please provide the letter(s) for D-HH review.

e) Will referral be utilized for recruitment?
☐ Yes ☒ No
If yes, please be aware patients should first be informed about the study and agree to the contact before any referral.

f) Will any other method be employed?
☒ Yes ☐ No
If yes, please specify, in detail, what those methods will be:

Patients who are candidates for intracranial EEG monitoring for presurgical evaluaion of medically refractory epilepsy will be asked in the outpatient clinic or over the telephone by their clinician if they would like to participate in a clinical study. If they do, they (and their legal guardian, if applicable) will be provided with all pertinent study information.

g) Does the research plan include "finder fees" or incentives (bonus payment, gift certificates) offered to study personnel for enrollment of participants?
☐ Yes ☒ No
Note: As a rule, finder fees or incentives are not acceptable. Please justify any offered incentives. If incentives become available during the course of the study, please notify D-HH.

Attach copies of any proposed flyers, posters, pamphlets, print advertisements, and scripts for on-air advertisements or telephone calls. All recruitment materials should be approved by D-HH prior to use.

Note: Advertising should not use terms such as "new treatment," "new medication," or "new drug" without explaining that the test article is investigational. A phrase such as "receive new treatments" implies that research participants will be receiving newly marketed products of proven worth. Advertisements should not promise "free medical treatment," when the intent is only to say participants will not be charged for taking part in the investigation. D-HH will determine if the promise of treatment without charge is an inappropriate inducement for study participation. Advertisements may state that participants will be paid, but should not emphasize the payment or the amount to be paid. The advertisement should include: the name and address of clinical investigator and research facility; the condition under study or the purpose of the research; in summary form, the criteria that will be used to determine eligibility for the study; a brief list of participation benefits, if any (e.g., a no-cost health examination); the time or other commitment required of the participants; and the location of the research activities; and the person or office from whom to obtain further information.

25. **Consent Process:**

The Principal Investigator (PI) is responsible for ensuring all participants have provided informed consent to participate in this study unless the consent process is waived or altered by D-HH. The PI may authorize other appropriately trained individuals to obtain consent from participants.

Please file the consent form in the medical record of each research participant if study participation may affect other medical treatment.

Explain how informed consent to research participation will be obtained. Please describe the consent process, including information about:

- Who has been authorized by the PI to obtain consent
- The time interval between providing information potential participants about a study and having the consent form signed
- Any precautions taken to minimize the possibility of coercion or undue influence

- Plans for responding to a potential participant or a legally authorized representative who does not speak English, such as the use of a translator or a translated consent form
- Any aids used to simplify scientific or technical information, like a diagram
- Plans to accommodate the probable literacy level of potential participants

Dr. Barbara Jobst or a qualified, appropriately trained person designated by Dr. Jobst will be responsible for the consent process. All persons designated by Dr. Jobst to obtain consent will have completed the Protection of Human Subjects training, or the equivalent accepted by D-HH. The patients will be seen in the outpatient epilepsy clinic to discuss intracranial EEG monitoring prior to epilepsy surgery. The consent will take place at the same clinic visit. Patients who do not have a clinic visit scheduled prior to admission (usually due to travel distance) will be contacted by their clinicial via telephone. If they are interested, a consent form will be sent to them for review, and their signature obtained on the day of their admission. Undue coersion will be minimized by the team approach to determining who is a candidate for intracranial EEG study. That is, the decision for iEEG and implant plan is made during epilepsy surgery conference and requires the unanimous approval of all involved physicians. Only patients who require iEEG will be approach to participate in the study. We will not obtain research testing on patient who cannot understand or speak English. We may show patients actual examples of the electrodes used for routine clinical care and the dual electrodes to help them make the decision.

Patients who are not able to provide informed consent will be considered for participation in the study if: 1) they meet the inclusion criteria; 2) they are interested in participating in the study and; 3) in the judgement of the research team they are capable of performing the cognitive tasks. In those instances the patient and their legal guardian will both participate in the informed consent process, with the legal guardian signing the consent form.

☐ I intend to obtain consent for research participation but I am requesting a waiver for the use of a *signed and dated* consent form. Please respond to the criteria listed in **Attachment I** and include an information sheet based on the D-HH template.

☐ I am requesting an alteration of the consent process to exclude certain information that is ordinarily required. A list of the essential elements of consent to research participation is available on the CPHS website: http://www.dartmouth.edu/~cphs/tosubmit/ConsentElements.html.
Please respond to **Attachment H.**

☐ I am requesting a waiver of the entire consent process and use of a consent form. Please respond to **Attachment H.**

Explain why any alteration or waiver to the consent process or form is necessary.

b) Authorization: Explain how an authorization for research use of protected health information (PHI) will be obtained. PHI is individually identifiable health information obtained from a health care provider or insurance plan. In general, the HIPAA Privacy Rule permits the use or disclosure of PHI for research purposes only with an authorization from each participant whose PHI will be involved. Only when certain criteria are satisfied can D-HH grant a waiver of authorization or of the use of a signed and dated authorization form. A waiver of authorization is necessary for recruitment procedures when patient information is used to identify and contact potentially eligible research participants. A single

form may combine the essential information for both consent and an authorization. The D-HH consent template contains this combination and is available on the D-HH website.

Check all that apply:
☐ This study does not involve PHI.
☒ A single form combining an authorization with the consent form and based on the CPHS template is included with this application.
☐ A separate authorization form is included with this application.
☐ I am requesting a waiver of authorization for only the recruitment procedure. Please respond to **Attachment H.**
☐ I am requesting a waiver of *signed and dated* authorization. Please respond to **Attachment I.**
☐ I am requesting a waiver of authorization for the use or disclosure of PHI in this entire study. Please respond to **Attachment H.**

In your explanation of the consent process above, please include information about obtaining authorization for the research use of PHI.

26.**Privacy and Confidentiality**:
Describe the plans to protect the privacy of subjects and maintain the confidentiality of the data.

Note: Under certain circumstances, an invasion of privacy or breach of confidentiality may present a risk of serious harm to subjects (e.g., as when the research obtains information about subjects that would, if disclosed by the researcher, jeopardize jobs or lead to prosecution for criminal behavior). Under other circumstances, an invasion of privacy or breach of confidentiality can be a moral wrong

a) Will any study activities involve an interaction or reveal information for which protection of participant privacy is necessary?
☒ Yes ☐ No
If yes, please identify the activities and describe the plan to protect the privacy of participants. For example, a plan for protection of privacy might consist of conducting the assent process for an adolescent minor in a private setting, rather than in the presence of the minor's parent.

Data recorded during the study will include the names of patients, their dates of birth, medical record numbers, and results of testing. This information will be kept on DHMC servers. Data sent from DHMC to collaborators at Columbia University will be de-identified. Access to the data will only be available for investigators involved in the study.

De-identified EEG data collected for this study will be shared with other academic institutions, and added to public databases of EEG data. Data shared in this way will not include any identifying information.

b) Will the data collected in the course of the study be considered sensitive, e.g., include information about a mental health disorder, HIV status, or SS#?
☐ Yes ☒ No
If yes, provide the rationale for why these data are needed:

If yes, could any of these data, if disclosed, damage financial standing, employability, insurability, or reputation?

☐ Yes ☐ No

If yes, will a Certificate of Confidentiality be obtained?

☐ Yes ☐ No

Any person engaged in research collecting information about illegal conduct from human research subjects may apply for a Certificate of Confidentiality. NIH provides detailed instructions for investigators wishing to make an application at http://grants.nih.gov/grants/policy/coc/index.htm.

c) Describe specific physical, administrative, and technical safeguards employed to protect confidentiality of data, e.g., coding with the removal of identifiers, limitation of access to data, use of locked file cabinets, protection of computer-based data systems.

Sensitive patient information will be stored on DHMC servers.

d) Will data that identify individual subjects be published or in any way be disclosed to third parties other than project personnel?

☐ Yes ☒ No

If yes, please explain here and incorporate the information in consent form:

27.**Responsibility for costs of injury or illness related to research:**

Will the sponsor or other funding agency be responsible for costs of injury or illness related to the research?

☐ Yes ☒ No

If applicable, describe whether or not the sponsor will be responsible for investigational device removal if required:

Use of microelectrodes is generally considered safe. A single retrospective annalysis of the use of the dual macro-micro electrode system has shown no significant complications above that for the use of macroelectrodes. Specific macroelectrode complications do occur. If any complications such as infection or hemorrhage occur, they will be attributable to the macroelectrode part, and not the microelectrode. Therefore, the cost of complications should be covered by the health insurance plan as these would be expected to occur in standard electrode patients.

If the sponsor or other funding agency will not be responsible for costs of injury or illness related to research, please complete:

a) The reasons why the sponsor or funding agency is not accepting responsibility for research-related injury.

We anticipate that any complications will be related to the implant or admission generally, and not specific to the research portion of the electrodes or the study tasks.

b) Summary of risks as related to potential costs that could be incurred as a result of research-related injury or illness.

c) Describe reasons for requesting that DHMC or Dartmouth College provide coverage for research-related injury or illness, which is not standard policy.

28.**Participant Remuneration:**

Will participants be paid for their time, reimbursed for travel or meal expenses, or receive any sort of "gift" for participating in this study?

☐ Yes ☒ No

If yes, please describe in detail:

Note: Participant remuneration is not considered a benefit of being in a research study. D-HH will consider the amount of payment in relation to the time needed and any inconvenience to participants. Payment, reimbursement, or gifts should not be in an amount that would be coercive to the participant population.

If study is to be done at the VA, specific questions need to be answered if a participant is being paid "in excess of reimbursement for travel." Please contact the D-HH office if you need more information.

All patients involved in the research study will be inpatients undergoing intracranial EEG monitoring. Participants will not be paid for participation in the study. There will be no additional travel expenses.

29.**Investigational Drug or Biological Agent:**

Respond to items below or check ☒ No investigational drug or biological agent involved.

Are all agents approved by the FDA for the specific indication for which they are used in this study?

☐ Yes ☐ No

If no, respond to a and b:

a) Briefly discuss the plan for the storage, dispensing, handling, and disposal of investigational and FDA-approved drugs, devices, and biologics. When these activities are being done by the investigator, include a description of the procedures for inventory control and documentation.

DHMC Investigational Pharmacy is managing all study drugs.

☐ Yes ☐ No

If No please describe management plan below.

b) Check and respond to one of the following statements:
☐ If this study is being done under an Investigational New Drug (IND) application to the FDA please provide: IND # (Investigational New Drug): # ☐ and specify who holds the IND#: ☐

OR

☐ If the drug or biologic agent used in this study is not FDA approved for the indication in this study, but an IND # has not been obtained, please **complete Attachment J.**

30.**Placebo vs. Standard Care:**
Does any part of the study involve use of a placebo or procedures that are inconsistent with the standard of care at DHMC?
☐ Yes ☒ No
If yes, respond to **Placebo: Attachment B**

31.**Medical Device:**
Respond to items below or check ☐ No devices involved.

Is this device approved by the FDA for this indication?
☒ Yes ☐ No

If no or if FDA approval is pending, respond to a, b, and c

a) Is the device provided free of charge by the sponsor?
☐ Yes ☐ No

b) Where are the devices used in the study stored? Who controls their use?

c) Respond to (1), (2), (3), or (4)

(1) If this study is being done under an Investigational Device Exemption (IDE) from the FDA please provide: IDE#: # ☐ or check here if the IDE is pending: ☐
Also check the FDA Device HCFA Reimbursement Category:
☐ A ☐ B2 ☐ B3
Please note: D-HH will not approve a study before an IDE # has been received.

OR

(2) If 510(k) notification for the device has been sent to FDA check here ☐ and either: provide a copy of the documentation verifying 510(k) clearance, or check here if 510(k) clearance is pending ☐.

OR

(3) If the device is exempt from IDE requirements, check here ☐ and provide a copy of a letter from the FDA or sponsor stating that the device is exempt from IDE requirements under 812.2(c).

OR

(4) If you are requesting a **nonsignificant risk** determination for the device from D-HH, please check here ☐ and complete **Attachment A**.

Please note: D-HH may approve, disapprove, or require modifications in a protocol that has been approved or cleared by the FDA.

32.**Conflict of Interest Review:**

Dartmouth College, Dartmouth-Hitchcock Clinic, and Mary Hitchcock Memorial Hospital have adopted a policy on Conflict of Interest in Human Subject Research. Copies of the policy are available on the Dartmouth College, Office of Sponsored Projects web site at http://www.dartmouth.edu/~osp/policies.html.

Definitions:

"Conflict of interest" occurs when an independent observer may reasonably question whether an individual's professional actions or decisions are influenced by considerations of the individual's private interests, financial or otherwise.

Conflicting financial interests do not include:

- salary and benefits from Dartmouth College, Dartmouth-Hitchcock Clinic, and Mary Hitchcock Memorial Hospital;
- income from seminars, lectures, teaching engagements, or publishing sponsored by federal, state, or local entities, or from non-profit academic institutions, when the funds do not originate from corporate sources;
- income from service on advisory committees or review panels for governmental or non-profit entities;
- investments in publicly-traded mutual funds;
- gifts and promotional items of nominal value; and
- meals and lodging for participation in professional meetings.

"Principal investigator or other key personnel" means the principal investigator and any other person, including students, who is responsible for the design, conduct, analysis, or reporting of research involving human subjects.

Instructions:

To assist institutional review of the proposed research for conflicts of interest, please respond to the question below.

With regard to this proposed research study, does the principal investigator or other key personnel, or any of their spouses, domestic partners, or dependent children, hold a financial interest that would reasonably appear to affect or be affected by the proposed study, including but not limited to the following interests?

a. compensation for services (e.g., consulting fees or honoraria), or in-kind payments, other than from the researcher's primary employer, in the prior calendar year or projected over the next twelve months;

b. royalty income or the right to receive future royalties under a patent license or copyright, when the proposed research is directly related to the licensed technology or work;

c. equity interests (e.g., stocks, stock options or other ownership interests), including equity holdings where the value cannot readily be determined by reference to public prices;

d. intellectual property rights (e.g., patents and copyrights), and royalties from such rights;

e. gifts or funds available to the researcher from the sponsor of this study beyond the current project;

f. funding expected to significantly exceed the projected costs of conducting this study; or

g. another financial or private interest that may present a conflict of interest.

☒ No: The Principal Investigator or other key personnel **do not** have any financial interests listed in a. - g. above.

☐ Yes: The Principal Investigator or other key personnel **do** have financial interests listed in items a. - g. above.

Only if you have answered yes to the question above about study-specific financial interests for a member of the research team, please provide the following additional information.

Name of each individual with a listed financial interest: ☐

Each individual on the above list should complete a Conflict of Interest Disclosure Form for Human Subject Research. The disclosure should include only those financial interests that are specifically relevant to this research study.

The Conflict of Interest Disclosure Form for Human Subject Research is available on the CPHS website at the following url:

http://www.dartmouth.edu/~cphs/tosubmit/forms/

Please complete and sign the Conflict of Interest Disclosure Form for Human Subject Research form. In an envelope marked "Confidential", send the form to the Director of the Office of Sponsored Projects, using the following address:

CPHS/COI-HS, Hinman Box 6254.

Attachment G
Research Involving Individuals With Impaired Decision-Making Capacity

Introductory Information:

*When a subject lacks capacity to give informed consent, the investigator should obtain written permission from a **legally authorized representative** prior to enrolling the subject in a research study. Federal Regulations define **legally authorized representative** as an "individual or judicial or other body*

authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research" (45CFR46.102(c)). Neither Federal Regulations nor New Hampshire State Law provide specific information about who may or may not qualify as a ***legally authorized representative*** *in a research setting. For the purposes of this policy statement, the options of defining a legally authorized representative include:*

a) Durable power of attorney for health care (DPAHC),
b) Court appointed legal guardian
c) Next-of-kin.

A strict interpretation of NH state law does not provide for the use of next-of-kin as a surrogate decision maker for investigational activity. The argument for allowing next-of-kin to consent to participation in research activity for an individual who lacks capacity to consent is that, without such an option, it is often impractical or impossible to conduct important medical research on conditions where results with the best current therapy are suboptimal. When investigational therapy represents the best treatment option or when risks to the subject are small in relation to the potential benefit of research to society, a policy which creates a major obstacle to the conduct of important research activity is ethically unsound.

With the above issues in mind, the Dartmouth CPHS has established the following policy for research studies that may involve adult subjects who lack capacity to give informed consent to participation in a research study. ***Please carefully review all items.***

Submission requirements:
When initially submitting a protocol for review by the CPHS, the investigator will inform the CPHS in the appropriate section of the CPHS Study Plan (item #18) if the study may involve subjects who lack capacity to give informed consent to participate in the study being proposed.

In addition, when a study may involve subjects who lack capacity to give informed consent, the investigator will use the form provided below to inform the CPHS of the requested options to provide permission for an individual who lacks capacity to participate in the research study and respond to specific CPHS questions.

For all requests:
Even with the permission of a DPAHC, or court appointed legal guardian, the D-HH will not permit a subject who lacks capacity to give informed consent to participate in a research study that offers little chance of DIRECT BENEFIT to the research subject over what they could receive outside the research setting and involves a meaningful increase in the risk of harm or discomfort, regardless of the potential gain to future subjects or society in general.
Please complete a) and b):

a) *Does participating in this study offer the subject a chance of direct benefit over what they could receive outside the research setting?*

There is little chance that data gathered using the microelectrodes will inform decisions being made about epilepsy surgery for the participant or otherwise directly benefit the patient.

---

b) *Is there an increase in the risk of harm or discomfort for the subject over what they would experience outside the research setting?*

To the best of our knowledge, the risk associated with implanting electrodes that include microelectrode contacts is no greater than that associated with implanting standard electrodes.

The risk associated with the memory, speech and thinking tasks that participants will perform is very minimal. Participants can decline to continue the tasks at any time.

When there is a meaningful chance of DIRECT BENEFIT to the research subject over what they could receive outside the research setting, D-HH will make a judgment decision about who may consent to participation in the study. The options include: DPAHC, court appointed legal guardian, and a properly motivated next-of-kin.

Please indicate the option(s) requested to allow for consent if a subject is incompetent to provide consent:

Durable power of attorney for health care (DPAHC)	☐ *YES*	☒ *NO*
Court appointed legal guardian	☒ *YES*	☐ *NO*
Next-of-kin.	☐ *YES*	☒ *NO*

<u>If a study requests the use of Next-of-Kin as the legally authorized representative, Please complete a) through e) below:</u>

a) Could the subject receive the same management that they will receive in the research study outside the setting of a research protocol?

b) Will participation in the study increase the risk of harm or discomfort compared to what is expected with the management that the subject will receive if they do not participate in the research study?

c) Will participating in the study increase the chance that the subject will experience a favorable outcome compared to what is expected with the management that the subject will receive if they do not participate in the research study?

d) What is the magnitude of the benefit that future patients, or society in general, may experience as a result of the subject participating in this study?

e) The process of appointing a legal guardian may take several months. Would this type of delay compromise patient care?

_____

_____

The CPHS will use the responses to the items a) – e) when discussing the option of allowing Next-of-Kin to enroll subjects into a research study.

Signature section of the consent form:

Below is the signature line to use when individuals lacking decision-making capacity may be enrolled into a research study. As described above, use of the next-of-kin option requires special CPHS approval:

_____

Participant Signature and Date *Printed Name*

If participant lacks capacity to provide informed consent, sign below as appropriate:

_____ *Durable*

Power of Attorney for Health Care and Date *Printed Name*

or

_____

Court Appointed Legal Guardian and Date *Printed Name*

or

_____

Next-of-kin and Date *Printed Name*

Decision by the CPHS:

The CPHS decision will be relayed to the investigator via the CPHS approval letter.