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A Qualitative Analysis of Ethical Perspectives on Recruitment and Consent for Human Intracranial Electrophysiology Studies

Authors: Joncarmen V. Mergenthaler; Winston Chiong, MD, PhD; Daniel Dohan, PhD; Josh Feler; Cailin R. Lechner; Philip A. Starr, MD, PhD; Jalayne J. Arias, JD, MA Word Count: 3084

Department of Neurology, University of California, San Francisco, San Francisco, CA, United States

Joncarmen V. Mergenthaler, University of California, San Francisco, Department of Neurosurgery, San Francisco, CA, USA

Winston Chiong, University of California, San Francisco, Department of Neurology, San Francisco, CA, USA

Daniel Dohan, University of California San Francisco, Philip R. Lee Institute for Health Policy Studies, San Francisco CA, USA

Josh Feler, Yale University, School of Medicine, New Haven, CT, USA

Cailin R. Lechner, University of California, San Francisco, Department of Neurology, San Francisco, CA, USA

Philip A. Starr, University of California, San Francisco, Department of Neurosurgery, San Francisco, CA, USA

Jalayne J. Arias, University of California, San Francisco, Department of Neurology, San Francisco, CA, USA

Corresponding Author:

Jalayne Arias
675 Nelson Rising Lane, Suite 192
San Francisco, CA 94158
Phone: 415-353-3597
Jalayne.Arias@ucsf.edu

Abstract: Intracranial electrophysiological research methods, including those applying electrodes on the cortical surface or in deep structures, have become increasingly important in human neuroscience. They also pose novel ethical concerns, as human studies require the participation of neurological patients undergoing surgery for conditions such as epilepsy and Parkinson's disease. Research participants in this setting may be vulnerable to conflicts of interest, therapeutic misconception, and other threats to valid recruitment and consent. We conducted semi-structured interviews with investigators from NIH-funded studies involving recording or stimulation inside the human skull. We elicited perspectives on study recruitment and consent procedures, and analyzed transcripts using a modified grounded theory approach. We interviewed 26 investigators from 19 separate intracranial electrophysiology studies, who described two study types: opportunity studies (n=15) and experimental trials (n=4). Respondents described significant heterogeneity in recruitment and consent procedures, even among studies employing similar techniques. In some studies, clinician-investigators were specifically barred from obtaining consent, while in other studies clinician-investigators were specifically required to obtain consent; regulatory guidance was inconsistent. Respondents also described various models for subject selection, the timing of consent, and continuing consent for temporally extended studies. Respondents expressed ethical concerns about participants' vulnerability and the communication of research-related risks. We found a lack of consensus among investigators regarding recruitment and consent methods in human intracranial electrophysiology. This likely reflects the novelty and complexity of such studies and indicates a need for further discussion and development of best practices in this research domain.

Keywords: Neuroethics, research, neurosurgery, informed consent

Introduction

Recent advancements in neuroscience have expanded the use of intracranial electrophysiological research methods, such as electrocorticography and electrical stimulation mapping (Engel et al. 2005; Jorgenson et al. 2015; Chang 2015; Panov et al. 2016). Circuit-based treatments for patients with neurological and psychiatric disorders increase the potential uses for invasive application of intracranial procedures, driving an emerging area of research. Intracranial electrophysiology research involves electrodes placed on the cortical surface (as in electrocorticography and electrical cortical stimulation) or within the brain parenchyma (as in stereotactic EEG and deep brain stimulation). Studies typically take place in the clinical setting (Chiong, Leonard, and Chang 2018; Hendriks et al. 2019) with patients undergoing surgical intervention for neurological conditions such as epilepsy, brain tumors, or Parkinson's disease. This setting enables valuable opportunities for advancing neuroscientific research related to complicated neurological and psychological conditions.

Invasive intracranial studies introduce novel perspectives on familiar research ethics issues – particularly in the context of recruitment and informed consent (Cook, Espinoza, and Leuchter 2014; Krook-Magnuson et al. 2015; Greely et al. 2018). Many of these ethical concerns, including voluntariness and therapeutic misconception, stem from the potential blurring between clinical care and research procedures. Neurologists or neurosurgeons who are also scientific researchers may experience conflicts between their clinical duties and scientific responsibilities (Chiong 2006). As described by prior authors, there are potential conflicts of interest risks resulting from incentives that encourage clinicians to recruit or refer their patients to research (Dickert et al. 2013). The clinician-research dual roles may also invite "therapeutic misconception" if patients believe that research procedures are directed at their own clinical benefit rather than for the sake of generalizable knowledge (Appelbaum, Roth, and Lidz 1982; Kim et al. 2009).

Voluntariness, a cornerstone of a valid research informed consent, may be threatened given the blurring between clinical care and research or by participants' desperation for treatment. Intracranial studies raise questions about participant voluntariness if patients fear that refusing to consent would interfere with clinicians' motivations to promote their medical wellbeing. This concern is sometimes phrased in terms of coercion or undue influence, but overt threats of harm and cognitive distortions are usually not present (Largent et al. 2013). In trials of novel electrophysiological interventions, patients with serious neurological illness who are desperate for new treatment options may fail to fully evaluate research risks.

The extended duration of intracranial studies introduces questions about the timing of consent procedures and whether continuing consent is required throughout the study. While some intraoperative research procedures during surgery are time-limited, other studies involve extraoperative recording and

stimulation with temporary or chronically-implanted electrodes (Chiong, Leonard, and Chang 2018). When subjects are repeatedly approached to participate in research protocols during extended inpatient monitoring or multiple outpatient appointments, consent for continuing research participation may be required (Wendler and Rackoff 2002).

Ethical concerns in intracranial electrophysiology research parallel those in other domains of human clinical research, including clinical trials in pediatric oncology and other high-risk research areas conducted in close relationship with clinical care (de Vries, et al. 2011). The unique relationship between neurosurgeons and patients may make indebtedness and vulnerability more acute for surgical interventions. Unlike treatment options where the intervention is medical, a neurosurgeon is intimately involved in patient care. Ultimately, a neurosurgeon is responsible for surgical procedures on a patient's brain – the source of identity. In intracranial research, the limited available options for treatment plans for complex neurological and psychiatric conditions may further challenge subjects' voluntariness when considering participation in research. The unique circumstances of human intracranial electrophysiological research present additional novel complexities. First, other clinical trials are used to investigate the safety or effectiveness of potential therapies and may include the prospect of improved treatment for a patient's illness. Intracranial electrophysiological studies are often directed at basic questions in neuroscience, which animal models may be inadequate to address. These basic questions may be unrelated to a patient's indications for surgery. This may hinder a valid consent if participants misunderstand the rationale for research. Additionally, if participants perceive a potential benefit, this affects their self-interested and altruistic motivations for participation. Moreover, while participants in clinical trials are broadly familiar with risks such as medication adverse effects or standard study, procedures such as randomization or safety monitoring, intracranial electrophysiological studies often involve neuroscientific and neurotechnological elements that are wholly unfamiliar.

While electrophysiology intracranial research is expanding, little is known about current practices in recruiting and obtaining consent for research participation or about researchers' experiences and ethical perspectives on such research. This article reports on a qualitative study of NIH-funded research teams engaged in human intracranial electrophysiology studies using semi-structured interviews. The results from this study document and characterize respondents' descriptions of their study protocols and their ethical observations and experiences. This study collects the qualitative lived experiences of researchers that expand beyond study protocols and procedures as described in an institutional review board application. These interviews provide critical insight on ethical challenges researchers face in implementing study procedures. This is a first step, by understanding current practices and challenges, towards developing guidance for researchers and regulators for the conduct of such studies.

Materials and Methods

This study used semi-structured interviews with investigators and study team members of active intracranial electrophysiology studies to understand the implementation of study protocols and procedures. Semi-structured interviews allow for unprompted responses and a dialogue to understand implementation of the study designs. Through in-depth interviews, respondents provided rich narratives regarding the challenges associated with recruitment and consent, as well as their perspectives on the ethical challenges associated with invasive intracranial electrophysiology studies.

Sample population

We identified active intracranial electrophysiology studies that were recruiting human subjects or had completed enrollment through the RePORTER database and BRAIN initiative reports. Forty-five of 502 screened studies met preliminary eligibility criteria for inclusion (Supplementary Tables A1-2). We invited principal investigators (PI) of all 45 studies via email or in-person to participate in the study or suggest an appropriate study team member. Study team members of 25 studies expressed interest in participating in an interview. Study team members from three studies could not be scheduled for an interview and three studies were ineligible because the research involved only non-human primates.

Interview guide

Semi-structured interviews followed an interview guide, including prompts, focused on two open-ended substantive domains, descriptions of procedures and practices: (1) to identify and recruit potential research subjects, and (2) to obtain informed consent. In a third domain, the interview guide elicited respondent's ethical concerns about consent and recruitment. In addition, the interview guide collected respondents' demographic information. Experts in ethics and qualitative research, including co-investigators of this study, reviewed the interview guide and then pilot tested and refined the guide in interviews with intracranial electrophysiology researchers at our institution. (Supplementary Table A3).

Interview procedures

We conducted interviews between May and September 2018. Interviews were conducted either in person, while attending a prominent neurosurgical conference, or via telephone. Following a review of transcripts for differences between interviews conducted in person versus via telephone, we did not identify any biases in the results based on how the interview was conducted. Respondents provided verbal consent to participate in the interview and demographic data collection. Interviews were conducted either in person or via telephone according to the respondent's preference. All interviews took place in a private setting to protect the respondent's confidentiality. Respondents provided verbal consent prior to enrolment.

Interviews were audio recorded for transcription. Interviews lasted 10-60 minutes; variation depended on the complexity of the study and the depth of responses provided by respondents. The University of California - San Francisco Institutional Review Board approved this study.

Data management and analysis

Interview audio recordings were transcribed by a professional service. We reviewed the transcripts for accuracy and removed personally identifying information. We then uploaded all transcripts into NVivo, software that assists with transcript coding, to facilitate qualitative data analysis.

For analysis, we used a modified grounded theory approach featuring the use of constant comparison to identify similarities and differences among consent processes by different investigator teams. Our analysis sought to theorize how teams' consent processes reflected investigators' understandings of consent, the nature of studies conducted, and the context in which teams carried out the research. This process involves an iterative process of data review, discussion, and coding (Creswell 2007; Lingard, Albert, and Levinson 2008). We met and collectively read several transcripts to identify key ideas and themes that respondents expressed in their interviews. By reading and discussing multiple transcripts, we arrived by consensus at a set of key themes to examine in the full set of interview transcripts. These themes became the codes, and we then used NVivo to label relevant portions of each interview with an appropriate thematic code. To minimize bias and to validate the coding process, two coders reviewed each transcript and met to resolve discrepancies by consensus.

To generate results, we used the coded NVivo database to identify codes that recurred in multiple interviews and retrieved transcript segments that had been tagged with those codes. We read, discussed, and wrote memos about these coded segments to arrive at a consensus about how to interpret these data. The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. The authors will consider requests for additional materials from the corresponding author, JJA, with restrictions. The data are not publicly available due to the sensitivity of the data and potential for identifying respondents or their institutions.

Results

We conducted interviews with 26 respondents reflecting researchers' perspectives on 19 intracranial electrophysiology studies. Of these 19 studies, 7 studies were represented by more than one respondent in our sample. Interviews with more than one representative of the study provided clarifying perspectives regarding procedures given the diverse role of respondents. Respondents included principal investigators and other study team members from multiple academic research institutions across the United States (Table 1). Most respondents reported that their study was led by a researcher with clinical training (i.e., a neurologist or neurosurgeon), as opposed to basic science or technical training (Table 2).

Respondents provided insight on the structure of the study, the relationship between study procedures and clinical care, and the recruitment procedures from screening through consent.
[Table 1]

[Table 2]

Classification of studies

We identified two classifications of intracranial electrophysiology studies: opportunity studies (n=15) and experimental trials (n=4). Opportunity studies involved the addition of experimental procedures to a clinically indicated surgical intervention. Opportunity studies included research protocols conducted intraoperative or post-operative to the clinically indicated procedure. For example, an opportunity study might add intraoperative electrode recording for research purposes to deep brain stimulator placement for Parkinson's disease or postoperative recordings taken during monitoring for epilepsy. Intraoperative studies were diverse with respect to recording techniques used (ECoG strips or penetrating micro-wires), the number and duration of recording sessions, and if recordings were paired to behavioral tasks. Post-operative studies were performed while electrodes were temporarily implanted in order to monitor for epileptic activity. These recording sessions could take place once or more per day while the patient remained under observation for epilepsy and were sometimes paired to visual-motor tasks. Generally, opportunity studies introduce a marginal increase in risk over the risk associated with the clinical intervention itself. The opportunity studies, as described by respondents, did not provide or intend to provide a direct clinical benefit to the subject. For example, one study was described as "*a study that's conducted in the operating room with patients with Parkinson's disease who are undergoing deep brain stimulation surgery where we temporarily place an ECoG strip electrode and record*." Some opportunity studies in our sample involved the addition of research procedures to clinically indicated interventions that were only available at a limited number of tertiary research hospitals via a Humanitarian Device Exemption (HDE).

In experimental trials, investigators tested novel electrophysiological devices or techniques as interventions for subjects' neurological or psychiatric impairments as stand-alone procedures. These subjects would be unlikely to receive neurosurgery if not for enrolment in research. Participants in experimental trials are exposed to *de novo* risk, because they do not have established clinical indications for surgery. The experimental trials described in our study offered the prospect of clinical or functional benefits for patients for Parkinson's disease, psychiatric and other neurological disorders. These potential clinical or functional benefits extended beyond the benefits accessible to patients, but for research participation. As one investigator described, *"Everything [is done outside of standard care]*." The experimental trials in this sample were governed by Investigational Device Exemptions unique to each

study. These studies require subjects to return to the research site for study visits to ensure adequate relief and safety of the research device, as well as to download physiological data from the implanted neural pulse generator. Implanted devices can be programmed to capture physiologic data during behavioral tasks (often movement related) performed during the research visit or while the patient is at home.

Recruitment Practices

Respondents described heterogenous recruitment and consent procedures (Table 3). Multiple pathways for subject recruitment were described, including: (1) internal sources from the same clinic or hospital, (2) external sources such as local physician referrals, (3) websites such as Clinicaltrials.gov, or (4) patient support groups. Generally, prospective subjects for opportunity studies were identified during clinical evaluation for their upcoming treatments. These respondents described that not only were individuals identified as eligible during clinic visits, they may also introduce the study to prospective subjects during a clinic visits, "I talk to the patients in my clinic about the study [. . .]" (Table 3). This perspective is in contrast with a perspective provided by a respondent, of an experimental trial, who emphasized the value of clinicaltrials.gov for recruitment, stating that it is "not dependent on providers who increasingly are less reliable [. .]" (Table 3). Meanwhile, experimental interventions often had a higher number of interested candidates than they were able to accommodate, particularly if the experimental intervention was for a condition without established clinical therapy. In these cases, research teams employed multiple levels of subject screening, and in many cases expected prospective subjects to initiate contact. For example, one respondent described a lengthy multi-step process for individuals who express interest in the study. In that study, the respondent reported that the prospective subjects first complete a screening interview for "obvious exclusion criteria", after which the study requests the last five years of medical history and then completes an in-person interview. This respondent reports that at the time of the interview they had screened approximately 4,000 candidates and only conducted 150 in-person interviews. Additionally, for this study, due to the investigational device exemption (IDE) status the candidate must be Medicare eligible or be able to cover costs associated with the surgery.

Consent Procedures & Practices

Respondents described different models for which study team member (PI, research coordinator, co-investigator, etc.) sought consent, methods for obtaining consent, and processes for continuing consent. We found that the team member who obtained subjects' consent varied between studies. We have described in Figure 2 who obtained consent by study classification. In some studies, consent was obtained by the PI alone. One respondent, a PI for an opportunity study, reports the process of providing information regarding the study during a the pre-surgery medical work-up for the scheduled clinical procedure and then seeking consent themselves the day prior to admission. In other studies, the research coordinator seeks consent without PI involvement. In an experimental trial, the respondent described a process where the research

coordinator conducts an initial phone screen and then obtains consent in-person before any clinical-research team members (e.g., neurologist, neurosurgeon, neuropsychiatrist) evaluates the prospective subjects. In one study, consent was sought by a research nurse who was not otherwise involved in the research. Lastly, other studies implement collaborative models between the PI and a research coordinator. In these studies the PI and the research coordinator obtain subjects' signatures on the consent together or alternatively the PI or research coordinator to follow up individually to obtain signatures after an initial joint meeting with the prospective subject. Rationales for the selection of which team member sought consent were varied, including considerations of logistical convenience and availability (given the complex timeframe of pre-surgical planning), the need to offer expert advice to prospective subjects, the desire to avoid excessive influence on patients' decisions, the aim of facilitating recruitment, and requirements from regulators.

Continuing consent practices varied by the type of study protocols and procedures (intraoperative versus extraoperative). Respondents from intraoperative studies reported obtaining additional verbal consent from subjects prior to beginning research procedures or proceeding between intervals of behavioral tasks. Respondents from 4 studies with extended extraoperative research procedures reported formalized time points after the initial written consent to seek verbal agreement for continuing research participation. Others described less-formal approaches to confirming consent to continue, awaiting fluctuations in subjects' mood or performance on behavioral tasks. In studies utilizing an implanted electrophysiological device (including all 4 experimental trials and several opportunity studies), respondents did not report a process for continuing consent unless there was a significant change in the protocol or unless the subject expressed an interest in leaving the study.

[Table 3]

Respondent ethical concerns

Respondents self-reported ethical concerns in multiple domains, including the voluntariness of subjects' consent and the potential risks associated with the research procedure. In reference to voluntariness, respondents conducting opportunity studies raised concerns about vulnerabilities associated with the established patient-physician relationship and pre-surgery stress at the time of consent (Table 4). One respondent stated:

> "I also understand that they're in a position where they feel like maybe they should do this because they're getting surgery, and so maybe it's part of their obligation. And so, the question is, does that make them vulnerable or not?"

Respondents conducting experimental trials expressed that patients' desperation in the absence of established treatment options for their conditions may adversely affect voluntariness when considering participation in a study considering potential risks. In recognizing the potential concern, respondents

described efforts to preserve voluntariness, such as designating another team member to seek consent. For example, a respondent described the role of the importance of the research nurse, who was not otherwise involved in the study, seeking consent: “They have no incentive to enroll or not enroll somebody in the studies” (Table 4). Similarly, another respondent framed preserving voluntariness in terms of avoiding coercion and assuring the prospective subject that enrollment in the study “has completely no bearing on their clinical care.” Others reported challenges with ensuring subjects’ understanding that research interventions were not directed at their clinical benefit (particularly in opportunity studies) or were not known to be efficacious in these subjects’ case (in experimental trials).

The heterogeneity of intracranial electrophysiological techniques described by respondents was reflected in a spectrum of reported risks from minor (boredom or anxiety from testing procedures) to serious (seizure or brain damage). Some risks, such as those due to extending operating time, were difficult to enumerate because research participation did not add a new hazard but amplified an existing hazard. One respondent describes the difficulty in quantifying the additional risk for extended surgical time, but highlighted “the longer you're on the table, the more chance there is for things to go wrong” (Table 4).

Respondents reported a broader concern with institutional and standardized guidance on managing ethical challenges associated with intracranial electrophysiology research. Respondents perceived an absence of standard approaches to recruitment and consent practices and limitations on institutional review boards (IRBs) guidance. For example, respondents described inconsistent or no guidance on ethical issues (e.g., which team members should seek consent). Several respondents expressed a desire to know more about other research groups’ recruitment and consent practices.

[Table 4]

Discussion

This study captured respondents’ perspectives and experiences with ethical challenges associated with implementing research protocols for human intracranial electrophysiology research. Results from these interviews have identified two classifications of studies, opportunity studies and experimental trials. Advisory bodies in neuroethics have recognized that opportunity studies have unique ethical features requiring special consideration (Amadio et al, 2018). To our knowledge, none have made this distinction between opportunity studies and experimental trials or analyzed the implications of this distinction for participant consent and investigator conduct. Each classification raises distinct ethical concerns among researchers, with associated differences in recruitment and consent procedures. While procedures and expressed ethical concerns reflected this distinction, we also found heterogeneity in the implementation of recruitment and consent procedures among human electrophysiology studies of the same classification.

Importantly respondents recognized the need to mitigate ethical concerns, including risks associated with subjects' vulnerability. Despite our analytical approach and attempt, we did not identify a unified theory of consent and recruitment in these studies.

The approach to which study team member sought subjects' consent was one of the most significant variations reported by respondents. Studies reporting practices that required clinician-investigators' involvement in seeking consent drew from a perceived or actual need to provide expert advice about the study procedures and the relationship between research and clinical management. Alternatively, some respondents reported that clinician-investigators were barred from seeking consent given concerns that the patient-physician relationship would compromise patients' abilities to make voluntary decisions about research participation. Respondents described inconsistent guidance and requirements on this and other points by IRBs. Respondents raised concerns about subjects' vulnerability within the consent procedure. While patients undergoing neurosurgery are not specifically categorized as a vulnerable class of research subjects, the special features of this research context raise concerns for situational vulnerability. In other vulnerable populations (such as cognitively impaired older adults and prisoners), some groups have developed "teach-back" or "teach-to-goal" approaches to informed consent that have been shown to enhance understanding of study information without imposing undue burdens on subjects or researchers (Sudore et al, 2006; Ahalt et al, 2017). This method includes the combination of a consent form, written at an appropriate education level, and the use of comprehension questions with targeted education. In one model, education is repeated until comprehension is achieved – measured by the comprehension questions (Sudore e al, 2006). This method could be well suited to the complexity of invasive intracranial electrophysiology studies, given the technical procedures involved and the potential blurring between clinical management and research.

A particularly complex topic is whether clinician-investigators should themselves seek consent from their own patients for research participation. These members of the research team are often best positioned to provide the necessary expertise and have an established relationship with patients undergoing surgical treatment for serious neurological illness. This allows the clinician to offer medical and scientific opinion and integrate a patient's values. However, a position as the patient's clinician could also exert unintended influence over patients' decision-making. A traditional view of clinical research ethics discourages such "dual-role consent." More recently, however, authors have advocated for its appropriateness in selected circumstances (Shah et al. 2015; Morain, Joffe, and Largent 2019). Prior work in pediatric oncology research has evaluated similar challenges and addressed the ethical challenges associated with the dual role (de Vries et al. 2011). In evaluating the ethical issues associated with clinician-researchers seeking consent for enrolling subjects, de Vries et al propose that clinician-researchers be clear as to how the researcher/subject relationship differs from the clinician-patient relationship, use separate

consent documents, and for research studies without a therapeutic goal that investigators emphasize voluntariness. Respondents in our study reported taking similar approaches to preserve voluntariness. Elsewhere we have argued that clinician-investigators will in many cases be the best sources of advice for patients. Regardless of which member of the study team obtains consent, other protections should be instituted to preserve voluntariness, including: appropriate training of the study team around potential conflicts, and meaningful assurances to patients that research participation is not a condition of their clinical care (Chiong, Leonard, and Chang 2018). A "hybrid" approach has been advocated for intracranial electrophysiology, in which a clinician investigator is responsible for ensuring that consent is informed, and another team member is responsible for ensuring that consent is voluntary (Grady 2019). Further development of innovative models for consent are needed in this domain of research.

While there is precedent in establishing procedures and interpreting legal doctrine for a valid research informed consent, our results showed that respondents perceived a lack of standardization. This lack of consensus among researchers and IRBs may reflect heterogeneity in institutional policies and state law or the novelty and complexity of human intracranial electrophysiology studies. Despite this, questions regarding consistency among IRBs on a range of issues have been well documented over the last three decades (Abbott a& Grady 2011). In the context of intracranial studies, it is important that IRBs include members with the necessary expertise and familiarity with the standard surgical clinical treatments and electrophysiological protocols and trials used for research. This project adds to the evidence base regarding current practices and may guide discussion of opportunities for refining and establishing standardization for consent processes and oversight.

Our findings should be interpreted in the light of our project's limitations. As with most qualitative interview-based research, our sample size (26 respondents) was small compared to most quantitative investigations. However, this sample size is consistent with standards for qualitative research. Additionally, respondents represented a significant proportion of all research studies meeting our inclusion criteria, at academic research institutions within the United States. In-person interviews were conducted at a neurosurgical conference (The American Society for Stereotactic and Functional Neurosurgery, 2018). As a result, neurosurgeons may be overrepresented in our sample. More broadly, our interview findings may be subject to response bias. For example, researchers' perceptions about ethics or ethical challenges associated with their own study may have influenced responses to our requests for interview.

The results from this study offer insight into current recruitment and consent practices in invasive electrophysiology studies in the United States. The results highlight the potential ethical concerns raised by this novel area of research, including ethical concerns raised by the respondents. The promotion of ethical procedures for recruiting participants to these studies could benefit from standardized approaches to

recruitment that reflect the classification of the study, opportunity or experimental. Additionally, innovative approaches to informed consent should be considered to capture clinician-investigator expertise while maintaining participant voluntariness.

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Disclosure of Interest

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References

Abbott, L., & Grady, C. (2011). A systematic review of the empirical literature evaluating IRBs: what we know and what we still need to learn. *Journal of Empirical Research on Human Research Ethics: JERHRE*, 6(1), 3–19. https://doi.org/10.1525/jer.2011.6.1.3

Ahalt C, Sudore R, Bolano M, Metzger L, Darby AM, Williams B. Teach-to-goal to better assess informed consent comprehension among incarcerated clinical research participants. AMA J Ethics. 2017 Sep 1 [cited 2019 Apr];19(9):862-72. DOI: 10.1001/journalofethics.2017.19.9.peer3-1709. PMCID: PMC5762181

Amadio, J., Bi, G. Q., Boshears, P. F., Carter, A., Devor, A., Doya, K., ... & Jun, B. O. (2018). Neuroethics questions to guide ethical research in the international brain initiatives. Neuron, 100(1), 19-36.

Appelbaum, P.S., L.H. Roth, and C. Lidz. 1982. The therapeutic misconception: informed consent in psychiatric research. *International Journal of Law and Psychiatry* 5(3-4): 319–29.

Chang, E.F. 2015. Towards large-scale, human-based, mesoscopic neurotechnologies. *Neuron* 86(1): 68–78.

Chiong, W. 2006. The real problem with equipoise. *American Journal of Bioethics* 6(4): 37–47.

Chiong, W., M.K. Leonard, and E.F. Chang. 2018. Neurosurgical patients as human research subjects: ethical considerations in intracranial electrophysiology research. *Neurosurgery* 83(1): 29–37.

Cook, I.A., R. Espinoza, and A.F. Leuchter. 2014. Neuromodulation for depression: invasive and noninvasive (deep brain stimulation, transcranial magnetic stimulation, trigeminal nerve stimulation). *Neurosurgery Clinics of North America* 25(1): 103116.

Creswell, John W. 2007. *Qualitative inquiry and research design: Choosing among five approaches, 2nd ed*. Thousand Oaks: Sage.

de Vries, Martine C., Mirjam Houtlosser, Jan M. Wit, Dirk P. Engberts, Dorine Bresters, Gertjan JL Kaspers, and Evert van Leeuwen. "Ethical issues at the interface of clinical care and research practice in pediatric oncology: a narrative review of parents' and physicians' experiences." BMC medical ethics 12, no. 1 (2011): 18.

Dickert, Neal W., Scott D. Halpern, and Javed Butler. "Incentivizing recruitment and retention to address enrollment challenges in clinical research." Circulation: Cardiovascular Quality and Outcomes 6, no. 3 (2013): 367-370.

Engel, A.K., C.K.E. Moll, I. Fried, and G.A. Ojemann. 2005. Invasive recordings from the human brain: clinical insights and beyond. *Nature Reviews Neuroscience* 6(1): 35–47.

Grady, C. 2019. A hybrid approach to obtaining research consent. *American Journal of Bioeth*ics 19(4): 28–30.

Greely, H.T., C. Grady, K.M. Ramos, W. Chiong, J. Eberwine, N.A. Farahany, L.S.M. Johnson et al. 2018. Neuroethics guiding principles for the NIH BRAIN Initiative. *The Journal of Neuroscience* 38(50): 10586–88.

Hendriks, S., C. Grady, K.M. Ramos, W. Chiong, J.J. Fins, P. Ford, S. Goering et al. 2019. Ethical challenges of risk, informed consent, and posttrial responsibilities in human research with neural devices: a review. *JAMA Neurology* 76(12): 1506–14.

Jorgenson, L.A., W.T. Newsome, D.J. Anderson, C.I. Bargmann, E.N. Brown, K. Deisseroth, J.P. Donoghue et al. 2015. The BRAIN Initiative: developing technology to catalyse neuroscience discovery. *Philosophical Transactions of the Royal Society B: Biological Sciences* 370(1668): 20140164.

Kim, S.Y.H., L. Schrock, R.M. Wilson, S.A. Frank, R.G. Holloway, K. Kieburtz, and R.G. de Vries. 2009. An approach to evaluating the therapeutic misconception. *IRB: Ethics and Human Research* 31(5): 7–14.

Krook-Magnuson, E., J.N. Gelinas, I. Soltesz, and G. Buzsáki. 2015. Neuroelectronics and biooptics: closed-loop technologies in neurological disorders. *JAMA Neurology* 72(7): 823–829.

Largent, E., C. Grady, F.G. Miller, and A. Wertheimer. 2013. Misconceptions about coercion and undue influence: reflections on the views of IRB members. *Bioethics* 27(9): 500–7.

Lingard, L., M. Albert, and W. Levinson. 2008. Grounded theory, mixed methods, and action research. *The BMJ* 337: a567.

Morain, S.R., S. Joffe, and E.A. Largent. 2019. When is it ethical for physician-investigators to seek consent from their own patients? *American Journal of Bioethics* 19(4): 11–8.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. The Belmont Report: ethical principles and guidelines for the protection of human subject of research. *Federal Register* 44(76): 23192–7.

Panov, F., E. Levin, C. de Hemptinne, N.C. Swann, S. Qasim, S. Miocinovic, J.L. Ostrem, and P.A. Starr. 2016. Intraoperative electrocorticography for physiological research in movement disorders: principles and experience in 200 cases. *Journal of Neurosurgery* 126(1): 122–31.

Shah, A., K. Porter, S. Juul, and B.S. Wilfond. 2015. Precluding consent by clinicians who are both the attending and the investigator: an outdated shibboleth? *American Journal of Bioethics* 15(4): 80–2.

Sudore RL, Landefeld CS, Williams BA, Barnes DE, Lindquist K, Schillinger D. Use of a modified informed consent process among vulnerable patients: a descriptive study. J Gen Int Med. 2006 Aug;21(9):867-73. PMCID: PMC1831581

Wendler, D., and J. Rackoff. 2002. Consent for continuing research participation: what is it and when should it be obtained? *IRB: Ethics and Human Research* 24(3): 1–6.

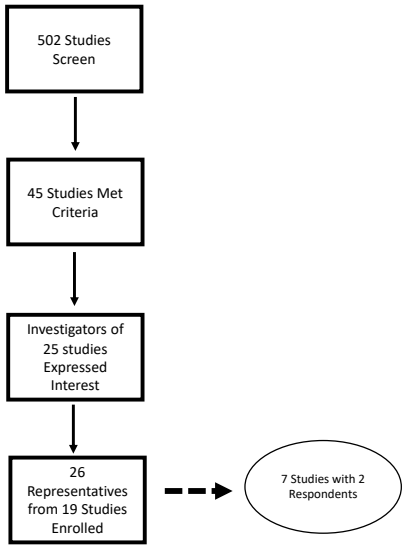

Figure 1. Recruitment procedure to identify eligible participants.

Table 1: Characteristics of respondents (n=26)	
Gender, male/female	18/8
Geographic region (United States)	
West	9
Midwest	2
Northeast	5
Southeast	10
Research role	
PI (principal investigator)	15
non-PI	11
Respondent training background	
Neurologist	4
Neurosurgeon	11
Other clinician	8
Non-clinician PhD	3
Race/Ethnicity (1 reported multiple)	
White Non-Hispanic/Latino	21
Asian Non-Hispanic/Latino	4
Hispanic/Latino	2

Table 2: Characteristics of unique studies (n=19; one study had two co-principal investigators)	
Principal investigator training background	
Neurologist	4
Neurosurgeon	10
Other clinician	2
Non-clinician PhD	4

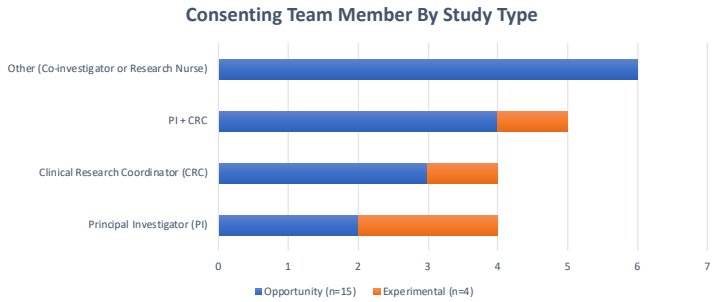

Figure 2. Study team member obtaining consent opportunity and experimental studies
Of the 19 principal investigators studies surveyed, we were able to conduct interviews with 7 additional study team members identified by the PI of the study. Minor differences in reporting consent practices were found: when a PI and CRC was interviewed on a study where a CRC and PI obtained consent, one team member indicated that both were simultaneously involved in consent, while the other said that one or the other may obtain consent independently. The Other row includes studies where one or more researcher apart from the PI or CRC are involved in the consent process. This category included a research nurse that was the only person responsible for consent in the study.

Table 3: Selected quotes from respondents about recruitment and consent procedures	
Recruitment for opportunity studies	• "So when they come to see our physician and once they're deemed eligible for surgery, our physician that will be performing deep brain stimulation will mention the study to the patients and/or provide the consent form to them or I will provide the consent form to the patients after the physician has mentioned the study to them. And then patients have some time between when they're seen in clinic and their surgery to think about if they would like to participate in the study." – research coordinator • "I talk to the patients in my clinic about the study, and if they're interested in participating then one of the research coordinators will get in touch with them ahead of time, sometimes in the clinic, sometimes by phone. Then we review a consent form with them, again, before surgery in the pre-op area during the training process and have them sign the consent there." – co-investigator
Recruitment for experimental trials	• "I think *[ClinicalTrials.gov]* probably just simply reaches more people. It's a website, and not dependent on providers who increasingly are less reliable because of the turntable requirement for medicine these days. It's a burden for our colleagues to help recruit because it means an additional discussion, and it slows down their clinics." – principal investigator • "*[Patients]* call us…. We always wait for them to make contact with us. We're not proactively calling patients out of the blue without knowing them." – principal investigator
Rationales for clinician involvement in obtaining consent	• "It's the person who has the most expertise in conducting the experiments that are being consented for." – principal investigator • "The way we work is there's myself and a PhD neurophysiologist and we run this project together. So he's not a clinician. He's a PhD researcher, but we work closely together. So we do it together so that way, they can understand from both the research side as well as the clinical side what they're being asked to participate in." – co-investigator • "If the first person that they talk to about a brain surgery study is not a doctor, there's an uphill battle to fight, so. And now, they're already getting brain surgery, so there's a little bit of a tension there, but if the physicians are the first ones to mention it, then it helps a lot." – research coordinator
Rationales for clinician exclusion from obtaining consent	• "Well, I have conflict of interest because it's my procedure and I have a patent related to it." – principal investigator • "These studies started at *[previous institution]* and moved over to *[present institution]*, where I am. That was, I think, not a requirement, but a strong suggestion, that the caregiver not be the consenter." – co-investigator • "We realized that the investigators, the psychiatry, psychology, neurosurgery have to be involved in the process to be able to adequately explain all the details. But for the purposes of both efficiency and lack of coercion, we felt like it was good to have the coordinator who is not involved in the patient's care in any way be the one that actually obtains the consent." – co-investigator
Consent for continuing participation	• "So they're given a presentation where they might do a hundred trials of this, it's a button pressing task. In between those, I'll say, 'How are you doing? Are you comfortable? Shall we go ahead and do another one? Are you ready?' And if they give any indication or if I just get a feeling that they're a little bit exhausted by it, I may say, 'We can stop this anytime, if you're ready.' And certainly, if they seem put out, I may stop it. If I don't feel comfortable that they're comfortable." – co-investigator

	• "Yes, but that's challenging with the DBS study because they do have a device in their head… We haven't had anybody actually want to do *[explantation surgery]*. We've had people complain about the amount of travel and about the number of tics they still have, but we remind them, 'Like we told you, you don't have to do this.' Then, when push comes to shove none of them have opted to withdraw." – research coordinator

Table 4: Selected quotes from respondents about ethical concerns	
Special vulnerability of patients as research subjects	• "It's definitely the case that, in a sense, the patients are very nice and they're very willing to work with you to help the research efforts. But I also understand that they're in a position where they feel like maybe they should do this because they're getting surgery, and so maybe it's part of their obligation. And so, the question is, does that make them vulnerable or not?" (opportunity study) – co-investigator • "I think a lot of the patients that have this disorder, once they get to the DBS, they're pretty severe, and they would come in the next day or the next week. I mean they would want to come in fast. I mean, those people that want to come are pretty desperate." (experimental trial) – co-investigator
Unique risks	• "We're adding an extra piece of hardware, so that's extra time which is a fuzzy distinction. I mean it's kind of a surgical risk, but they wouldn't be encountering it if they weren't in the study, and so we talk about that and just the idea that the longer you're on the table, the more chance there is for things to go wrong, but the characterization of those risks is essentially what the surgical risks are." (opportunity study) – research coordinator
Preserving voluntariness	• "And so we try to tell them and comfort them as many times as possible that, again, the decision to participate in the research has completely no bearing on their clinical care." – co-investigator • "So the research nurses, by the way, who are obtaining the consent, they are actually not involved in the actual research itself. …I mean, they know generally what the infrastructure is involved, but they have no incentive to enroll or not enroll somebody in the studies." – co-investigator
Therapeutic misconception	• "I think that the critical thing here is that there is no direct benefit to the patient and their disease. Their participation is really benefiting scientific understanding. So that needs to be fairly explained to the patient." (opportunity study) – co-investigator • "And I think you have to be really clear-- I think people can assume because you are doing intraoperative research that you are somehow doing an experimental operation and that is absolutely not the case." (opportunity study) – co-investigator • "What we don't know is who are patients who are not appropriate for this procedure. So when that comes up, in terms of what's the likelihood of getting well, or a patients' therapeutic misconception that they will get well, they have to temper that." (experimental trial) – principal investigator
Inconsistent regulatory guidance	• "Well, they've told us different things on different IRB protocols. So to be perfectly honest with you, I can't remember what it is on this one." – co-investigator • "So at our institution, our IRB believes that since this is an invasive procedure, a surgical procedure that has inherent risk due to the invasiveness, that the informed consent must be performed by a surgeon who actually understands the risks and can explain the risks to the person enrolling in the study. We have recently have gotten an amendment to our protocol so that I, as the surgeon, can tell the patient about the study and the related risks and then the rest of the informed consent can be done by a research assistant who is trained in the risks and I'm immediately available in case additional questions come up regarding the risks of the study. I say it's controversial because I know other sites insist that the consent cannot be done by the surgeon because there's a conflict of interest there, so it's kind of interesting." – co-investigator

	• "They have in the past expressed the desire that only physicians be the ones to consent patients, and in studies with adaptive DBS or DBS and other indications, that has been the case in the past, but it is not for this study the case." – research coordinator