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Authors

Feinsinger, Ashley
Pouratian, Nader
Ebadi, Hamasa
[et al.](#)

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Ethical Commitments, Principles, and Practices Guiding Intracranial Neuroscientific Research in Humans

Ashley Feinsinger^{1,15}, Nader Pouratian^{2,15,16}, Hamasa Ebadi², Ralph Adolphs^{3,4}, Richard Andersen⁴, Michael S. Beauchamp⁵, Edward F Chang⁶, Nathan E. Crone⁷, Jennifer L. Collinger⁸, Itzhak Fried⁹, Adam Mamelak¹⁰, Mark Richardson¹¹, Ueli Rutishauser¹⁰, Sameer A. Sheth¹², Nanthia Suthana^{9,13}, Nitin Tandon¹⁴, Daniel Yoshor⁵ NIH Research Opportunities in Humans Consortium

¹Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California, 90095, USA

²Department of Neurological Surgery, UT Southwestern Medical Center, Dallas, Texas, 75390, USA

³Departments of Psychology and Neuroscience, California Institute of Technology, Pasadena, California, 91125 USA

⁴Department of Biology, California Institute of Technology, Pasadena, California, 91125, USA

⁵Department of Neurosurgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, 19104, USA

⁶Department of Neurosurgery, UC San Francisco, San Francisco, California, 94143, USA

⁷Department of Neurology, Johns Hopkins University, Baltimore, Maryland, 21287, USA, 15260, USA

⁸Department of Physical Medicine and Rehabilitation, University of Pittsburgh, Pittsburgh, Pennsylvania, 15260, USA

⁹Department of Neurosurgery, David Geffen School of Medicine at UCLA, Los Angeles, California, 90095, USA

¹⁰Department of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, California, 90048 USA

¹¹Department of Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, 02114, USA

Corresponding Author and Lead Contact: Nader Pouratian, MD PhD, Department of Neurological Surgery, UT Southwestern Medical Center, 8353 Harry Hines Blvd MC8855, Dallas, Texas, 75390, (214) 648-9320, Nader.pouratian@utsouthwestern.edu. Author Contributions

A.F. and N.P. led discussions, abstracted principles, and drafted, edited, and finalized the manuscript. H.E. documented discussions and edited the manuscript. All other authors significantly contributed to content and perspectives and edited the manuscript.

Declaration of Interests

SS is a consultant for Boston Scientific, Neuropace, and ZimmerBiomet. NP is a consultant for Abbott Laboratories. NT is a surgical committee member for the Medtronic SLATE trial.

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¹²Department of Neurosurgery, Baylor College of Medicine, Houston, Texas, 77030 USA

¹³Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, California, 90095, USA

¹⁴Department of Neurosurgery, University of Texas Houston, Houston, Texas, 77030, USA

¹⁵Equal Contribution

¹⁶Lead Contact and Corresponding Author

Summary

Leveraging firsthand experience, BRAIN-funded investigators conducting intracranial human neuroscience research propose two fundamental ethical commitments: (1) maintaining the integrity of clinical care and (2) ensuring voluntariness. Principles, practices, and uncertainties related to these commitments are offered for future investigation.

eTOC blurb

Investigators conducting intracranial neuroscientific research have real-world experience considering neuroethical challenges. Here, a consortium of investigators offer two overriding ethical commitments: 1. Maintain the integrity of clinical care and 2. Ensure the voluntariness of participation. Guiding ethical principles and practical examples of implementation, including areas of disagreement and future directions, are highlighted.

Keywords

Neuroethics; Ethics; Intracranial Research; Human Neuroscience; Human Neurophysiology; Investigators

Several neurosurgical interventions require intracranial electrodes for either diagnostic or therapeutic purposes, providing unique opportunities to conduct basic intracranial human neuroscience research (henceforth referred to as intracranial research). This research has significantly advanced our understanding of human brain function across multiple domains, including language, sensorimotor function, memory, and emotional and affective processing (Collinger *et al.*, 2014; Kirkby *et al.*, 2018; Mosher *et al.*, 2021). Notably, intracranial research is not intended to provide near-term therapeutic benefit to participants or other patients. While invasive human research is not unique to neurosurgery, the lack of therapeutic benefit, the vulnerability of patient populations with neurological or psychiatric diagnoses, the rarity of access to intracranial data, and the common occurrence of clinician-investigators necessitate ethical scrutiny. However, to date, non-therapeutic intracranial research has garnered little ethical discussion (Chiong *et al.*, 2018; Hendriks *et al.*, 2019; Mergenthaler *et al.*, 2021).

Two recent publications are of immediate relevance (Hendriks *et al.*, 2019, Chiong *et al.*, 2018). Hendriks *et al.* discuss ethical frameworks for neural device research aimed at developing novel clinical/therapeutic applications, which is distinct from the current focus. Chiong *et al.* address ethical considerations for intracranial electrophysiology research but

acknowledge the need for broader input to capture variability across institutions. Using Chiong *et al.* (2018) as an initial point of discussion, investigators from the Research Opportunities in Humans (ROH) Consortium, a group of more than 30 investigators funded by the NIH BRAIN Initiative to conduct intracranial research, developed explicit ethical commitments and areas of consensus related to intracranial research. We discuss these commitments, the principles they give rise to, and the associated practices used across settings, noting areas of uncertainty for future study. The goal for these contributions is to offer a framework for critically evaluating and refining future practices in intracranial research.

This work is the product of a series of discussions within the ROH consortium, which includes clinician-scientists (neurosurgeons and neurologists) and neuroscientists. Additionally, two NIH funded ethicists, who do not conduct intracranial research but interview patients-participants, participated in guiding the discussions and drafting this Neuroview. The common elements of ROH research are (i) the goal of scientific understanding of human brain function, (ii) absence of near-term therapeutic intent, and (iii) use of intracranial recordings and/or stimulation in human subjects requiring neurosurgical intervention. In some cases, research involves utilizing data recorded from therapeutically implanted devices, such as intracranial recordings during deep brain stimulator surgery (Mosher *et al.*, 2021). In other cases, recordings are obtained from patients undergoing clinically indicated surgeries with little or no modification of the clinical procedure, such as intracranial monitoring for epilepsy (Forseth *et al.*, 2020; Kornblith *et al.*, 2017). Finally, in some instances, patients undergo a neurosurgical procedure as part of an investigational device trial, such as implantation of a Utah array for brain computer interface (BCI) investigations (Collinger *et al.*, 2014).

Ethical discussions of this research should integrate input from all stakeholders, including patients, families, clinician-investigators, non-clinician investigators, non-investigator clinicians (e.g., epileptologists), funding and regulatory agencies, ethicists, device manufacturers, and society. Each group's experiences provide insight into different dimensions of the research. Without intending to privilege any one perspective, this report offers the ethical views of investigators who conduct intracranial research and whose perspectives are relatively under-represented in the literature. Investigators have substantial first-hand experience (i) practically managing ethical considerations, (ii) driving research from design to management, and (iii) interacting with other stakeholders. Because of these experiences, they can provide insights into how ethical principles might be formulated to best facilitate ethical practice across study contexts.

Ethical Commitments, Principles, and Practices

The ROH consortium offers the following two overarching ethical commitments as overt affirmations of their obligations and as foundations of an approach to ethical intracranial research:

1. Maintaining the integrity of clinical care and space.
2. Ensuring the voluntariness of participation in intracranial research.

These commitments, which align with the Belmont Report's principles of Beneficence and Respect for Persons, are further motivated by (i) the tension between exploiting a rare clinical opportunity and protecting a vulnerable participant population and (ii) the potential conflict created by the rewards, often in the form of grants, that drive this research. In the authors' view, the following principles and shared practices (as detailed in Table 1) are essential for conducting ethical intracranial research.

Maintaining the Integrity of Clinical Care and Space

Prioritizing the integrity of clinical care—maintaining that care be guided by fundamental clinical principles—requires practices to ensure that care is not compromised, purposefully or inadvertently.

1. Clinical care and research should be uncoupled, such that care be neither compromised by nor conditional on research participation, and this must be communicated to patients.

The temporal and spatial relationship between clinical care and research may raise concerns that care and research are interdependent, and that the decision to participate will influence care. For example, conducting experiments in the operating room (OR) during deep brain stimulator implantation or in the epilepsy monitoring unit (EMU) in patients undergoing intracranial monitoring for seizures can make it difficult for patients to distinguish the separability of the two efforts. We must not only assure patients that care is not conditional on participation, but also that the care of those who participate is guided by principles of best clinical practice. When clinical care is inherent to the research (such as implantation of intracranial arrays for BCI), it is particularly important to ensure optimal clinical care as part of the investigation.

Improving patient comprehension of the ways in which clinical care is distinct from research may promote this goal. Protocols for doing so may depend on the relative spatial and temporal correlation of clinical care and research, with closer correlations deserving explicit attention. All investigators agreed that the informed consent language must explicitly state that clinical care will not be compromised (regardless of participation).

Several programs separate clinical and research consents in time, space, and personnel, including having a non-investigator clinician obtain clinical consent or having someone other than the physician-investigator obtain research consent. Multiple centers have independently arrived at an approach akin to the “hybrid model,” in which the clinician-investigator introduces the research and risks but research consent and further discussion is obtained by a non-clinician investigator (Grady, 2019). When the surgical procedure is done for the purpose of research (e.g., implants for BCI research) (Collinger *et al.*, 2014), a more complex multi-step process was described, including pre-consent discussions of procedures with investigators, review of risks and benefits with the neurosurgeon, meetings with neuropsychologists, and a formal consent process with an investigator. These approaches do not preclude the clinician from being available to answer questions about risk, but still create separation.

In some cases, the clinician-investigator may be best suited to explain risks and help patient-participants understand the study in the context of the parent neurosurgical procedure. Investigators noted that absence of the clinician-investigator in the consent process may give the appearance of fragmentation between clinical and research teams. Moreover, in some jurisdictions, a physician must administer consent for any device study with greater than minimal risk. Ultimately, the approach to consent must be customized based on study factors, local resources, infrastructure, and regulations; a uniform approach should not be dictated, as long as the distinction between clinical care and research is explicit.

In addition to the written consent, some investigators suggest verbally conveying the separation of clinical care and research, repeating this at multiple times, as a reminder not only to patients, but also clinicians, investigators, and allied health professionals. Several investigators verbally re-consent immediately prior to initiating research studies (e.g., in the OR or EMU) to ensure that patient-participants understand their clinical care is not contingent upon participation before beginning. This is important, as the patient-participant may accumulate more information and opinions about their potential participation.

Additionally discussed but uncommonly used practices include reading out loud the parts of consent relating to this critical notion, seeking a verbal affirmation, or requesting a “teach back”. While others have discussed teach back (Mergenthaler, *et al.*, 2021), future work should focus on identifying study-specific considerations about teach back (including whether the efficacy of teach back varies and what content should be “taught back”) and include patient-participant input. A supplementary standardized video may be helpful, providing a purposeful timeout, an independent voice to amplify the separation, and communication to patient-participants that they are part of a larger research community.

2. While clinician-investigators have dual roles, their role as clinician should be placed above their role as investigator, and this duality must be communicated to patients.

Patients sometimes express, “I trust my doctors and the research team”, “they’ve done so much for me, I want to give back”, and “I will do anything to help my doctors”. These suggest that the dual role of clinician-investigator can affect motivation for participation. The need to provide the best clinical care for patients and the need to be scientifically productive in response to federal funding initiatives creates a conflict. Explicit discussion of these roles can emphasize that the clinician recognizes and prioritizes their role as the treating physician.

Disclosure of this duality should at least appear in the written informed consent, and many investigators also routinely include a verbal disclosure. One investigator noted, “It lends credibility to the fact that physician-investigators are thinking about this and trying to be principled about their role as a researcher and their role as a physician.” This acknowledgement also reassures others not involved in the research that clinician-investigators recognize the conflict and are committed to protecting the role as a clinician. Wording may include explicit dissociation, such as “I am telling you about this as a researcher, not as your doctor.”

While some have proposed that treating clinicians should not be investigators, the ROH (clinicians and non-clinicians alike) proposed that such prohibition would thwart progress, especially in some situations where the treating clinician is the most qualified person to carry out the research and understand the risks and benefits. Furthermore, clinicians have important relationships with patient populations, and prohibiting their participation in research may adversely affect patient welfare.

3. Non-clinician members of the research team who interact with patient-participants require instruction on bedside interactions with patients and on the surgical methods and risks.

Health professionals receive explicit training on maintaining respect for the clinical environment and patient communication. Non-clinician investigators may be responsible for discussing research procedures with clinical dimensions with which they are not familiar, and this introduces challenges for maintaining the integrity of clinical care. Non-clinician investigators who are interacting with patient-participants or who are otherwise working in clinical spaces should therefore receive formal training on conduct and communication in the clinical environment.

Few teams had implemented formal training for non-clinicians. Current practices include having non-clinician investigators observe clinical procedures and research studies before interfacing with patient-participants. Investigators endorsed the potential value of standardized training (such as standardized videos that are often used in the clinical setting) on topics ranging from bedside interactions to relevant surgical and research methods. A certification process was considered potentially valuable but requires further research.

4. The decision to use intracranial modalities in clinical care should not be influenced by scientific considerations unless the scientific study itself is the reason for the intracranial intervention.

The clinical decision about whether to use invasive methods should not be influenced by scientific considerations unless the intervention itself is driven by research. Investigators agree that it may be appropriate to modify the method (e.g., using modified electrodes with microwires, higher density arrays, or additional electrodes) with detailed informed consent. Other examples include temporary discontinuation of therapy (e.g., turning off a brain stimulator to enable research studies) or consumption of clinical resources that can modify clinical care (e.g., battery power or time in clinic or the OR). Critically, besides considering interval risks, the ultimate therapeutic goals of the surgery cannot be compromised by research-related modifications.

Several centers ensure that clinicians not involved in the conduct of research confirm the clinical need for intracranial interventions. For example, neurologists not involved in research convene to determine the clinical need for surgery. However, depending on the center and program, all treating clinicians may be involved in the research program. Alternative strategies include encouraging participants to discuss the study with other physicians and involving a Data Safety Monitoring Board (DSMB), which includes

physicians who are not invested in the research goals and are charged with guarding the participants' interests.

Ensuring the Voluntariness of Participation in Intracranial Neuroscientific Studies

Some of the practices above (e.g., assurance of care and research uncoupling, discussion of dual roles) are also motivated by a concern for patient misunderstanding and undue influence. These concerns are particularly relevant in this potentially vulnerable population. The remaining ethical principles and practices are intended to supplement those above to further promote voluntariness.

5. Informed consent procedures should be specifically designed to account for the potential for neurological injury, the high rate of clinician-investigators, and patient population vulnerabilities.

Given the surgical context in which these studies are carried out, targeted consent practices are essential for promoting voluntariness of participation. As previously detailed, practices for consenting include having both a written and verbal consent (and re-consent) and employing "hybrid consents." Many investigators also value providing an opportunity to involve family in the consenting process, to the extent that participants desire it, and giving participants a robust opportunity to discuss participation with non-investigator clinicians. Given the complexities of these studies, consent may require significantly more time.

In contrast to study and site-specific communications, standardized videos could provide an external voice on portions of the consent process, including the goals of the research, patient rights to withdraw, and the community involved in the research. Training videos are ubiquitous in medical care to ensure familiarity with and understanding of a broad range of topics, from financial conflicts of interest to personal protective equipment usage. It is important that standardized videos should not be used instead of personal discussions and that their value is verified, as done in other clinical areas (Christensen *et al.*, 2020). Limited resources were seen as the primary barrier to developing such videos.

6. Consenting to research may require different cognitive and decision-making capacities than consenting for care, and consent protocols may need to reflect this.

Consenting to clinically indicated surgery is rooted in a personal neurological or psychiatric concern, while consenting to participate in non-therapeutic research may require additional levels of abstraction. The latter requires understanding the purpose and benefits of the study, neither of which are rooted in the individual's condition, and which involve notions (e.g., societal benefit) that patients may not fully understand. The cognitive impairments often seen in patient-participants with Parkinson disease or epilepsy may differentially affect clinical vs. research consent capacity, and these patient population vulnerabilities may inadvertently lead to misunderstandings. No investigators reported using tools to separately assess capacity for research consent, but suggested practices include asking patient-participants to specifically express understanding of research-related risks and goals. Future work, including engagement with patient-participants, might better determine which

study features are most critical and how to assess abilities to comprehend those study features (e.g., benefits to society despite the lack of direct benefit).

7. Patients have the right to refuse or stop participation in research at any time and should be reminded of this right at appropriate intervals in meaningful ways.

Study participants have the right to refuse participation over any time frame and in any setting, whether before initial consent or at any time after consenting to participation.

This right is often explicitly detailed in the written informed consent and research participant bill of rights. Some expressed interest in standardized language that could be used across studies, but also acknowledged that institutional review boards may enforce certain local requirements that supersede this desire. Other practices include explicitly offering participants multiple opportunities to voluntarily withdraw, on a timescale relevant to the study, whether during regular intervals during a 20–30 minute intraoperative experiment or daily during an EMU stay. BCI studies often include multiple checkpoints over periods of weeks prior to the neurosurgical procedure, and for longer studies, some investigators have included informal and formal reconsent. Reconsenting or withdrawing opportunities may be particularly important for patient-participants in multi-day EMU stays, as their medical and psychiatric status can change quickly. Non-investigator clinician guidance is critical for understanding the continued appropriateness of participation of patient-participants in research. Further research is needed, in close concert with patient input, on the most effective ways to provide study-specific opportunities to withdraw.

Such opportunities may require different approaches, as simply repeating the right to withdraw may be insufficient. Understanding how patients can be made to feel comfortable withdrawing is crucial, particularly during research in the OR, where the context is unique and may add additional factors to their decision-making.

Promoting the right to withdraw also requires perceptiveness about hesitation or postponements. Postponements may be an indirect way of withdrawing, overshadowed by concerns of disappointing the clinic or research team, or they may be a sign that patients have unanswered questions and concerns. Investigators found value in having both clinician and non-clinician investigators engage in these discussions with patients, since patients may worry about disappointing clinicians but also more readily express clinical concerns to them. Practices for managing repeated postponements include asking permission to re-approach the patient for participation at a later time, offering an open-ended discussion about concerns, and offering patients an explicit opportunity to withdraw.

III. Conclusions and Future Directions

This Neuroview proposes an initial ethical framework for intracranial research from the perspectives of investigators. It aims to supplement other perspectives and provide practical implementations for discussion. Crucially, the framework acknowledges the need for study-specific practices as well as patient-participant input.

The focus on investigator perspectives is purposeful, in part because investigators must take responsibility for the ethical conduct of their research. This report is not inclusive of all investigator viewpoints nor exhaustive of neuroethical issues. Notably, the author-investigators are all NIH-funded US-based investigators, and future work should consider comparative perspectives across geographies. Further work should also include expanded input of non-investigator clinicians that care for these patient populations longitudinally (e.g., psychiatry, epileptology), and most critically, involve patients themselves. Looking forward, we hope to encourage collaboration between investigators and ethicists across multiple topics, including post-trial obligations, data-sharing, and the overall value of intracranial research.

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Highlights

- Intracranial neuroscience research in humans raises unique neuroethical issues.
- Neuroethical commitments and practices of investigators are poorly characterized.
- Commitments include protecting the clinical space and ensuring voluntariness.
- BRAIN-funded investigators provide guiding neuroethical principles and practical examples.

Table 1.

Ethical Commitments, Principles, and Practices for Basic Neuroscientific Intracranial Research

Commitment	Principles	Example Practices
Maintaining the integrity of clinical care and space	<i>1. Clinical care and research should be uncoupled, such that care be neither compromised by nor conditional on research participation, and this must be communicated to patients.</i>	Current 1. Separate clinical and research consents in time, space, and personnel 2. Multiple staged meetings to discuss research participation with both clinicians and non-clinicians. Proposed 1. Seek verbal confirmation and understanding of separation described in consent 2. Standardized videos to provide a consistent external voice describing the separation
	<i>2. While clinician-investigators have dual roles, their role as clinician should be placed above their role as investigator, and this duality must be communicated to patients.</i>	Current 1. Include explicit statements of this dual role (and conflict) in the written informed consent 2. Verbally disclose conflict during study recruitment
	<i>3. Non-clinician members of the research team who interact with patient-participants require instruction on bedside interactions with patients and on the surgical methods and risks.</i>	Proposed 1. Non-clinician investigators attend clinical procedures and research studies before interfacing with patient-participants. 2. Require standardized training courses or videos on bedside interactions and surgical and research methods.
	<i>4. The decision to use intracranial modalities in clinical care should not be influenced by scientific considerations unless the scientific study itself is the reason for the intracranial intervention.</i>	Current 1. Clinicians not involved in the research convene via multidisciplinary conference to determine need for intracranial monitoring. 2. Encourage participants to discuss study with non-research related physicians they see regularly
Ensuring the voluntariness of participation in intracranial neuroscientific studies	<i>5. Informed consent procedures should be specifically designed to account for the potential for neurological injury, the high rate of clinician-investigators, and patient population vulnerabilities.</i>	Current 1. Include disclosures in both verbal and written consent. 2. “Hybrid consent” process to address conflict of clinicianinvestigators. 3. Inclusion of family and caregivers in consent process when appropriate. Proposed 1. Standardized videos with external perspectives on basic study information to supplement other discussions.
	<i>6. Consenting to research may require different cognitive and decision-making capacities than consenting for care, and consent protocols may need to reflect this.</i>	Proposed 1. Additional intellectual capacity or cognitive assessments 2. Seek explicit confirmation of understanding of goals and risks of study
	<i>7. Patients have the right to refuse or stop participation in research at any time and should be reminded of this right at appropriate intervals in meaningful ways.</i>	Current 1. Offer multiple opportunities to withdraw, at regular intervals according to the design of the study 2. Include multiple check points for consent over period of weeks prior to surgical procedure Proposed 1. Seek acknowledgement of right to withdraw as part of “teach back” 2. Provide multiple opportunities to discuss concerns with clinical and non-clinical team, in addition to explicit withdraw opportunities.