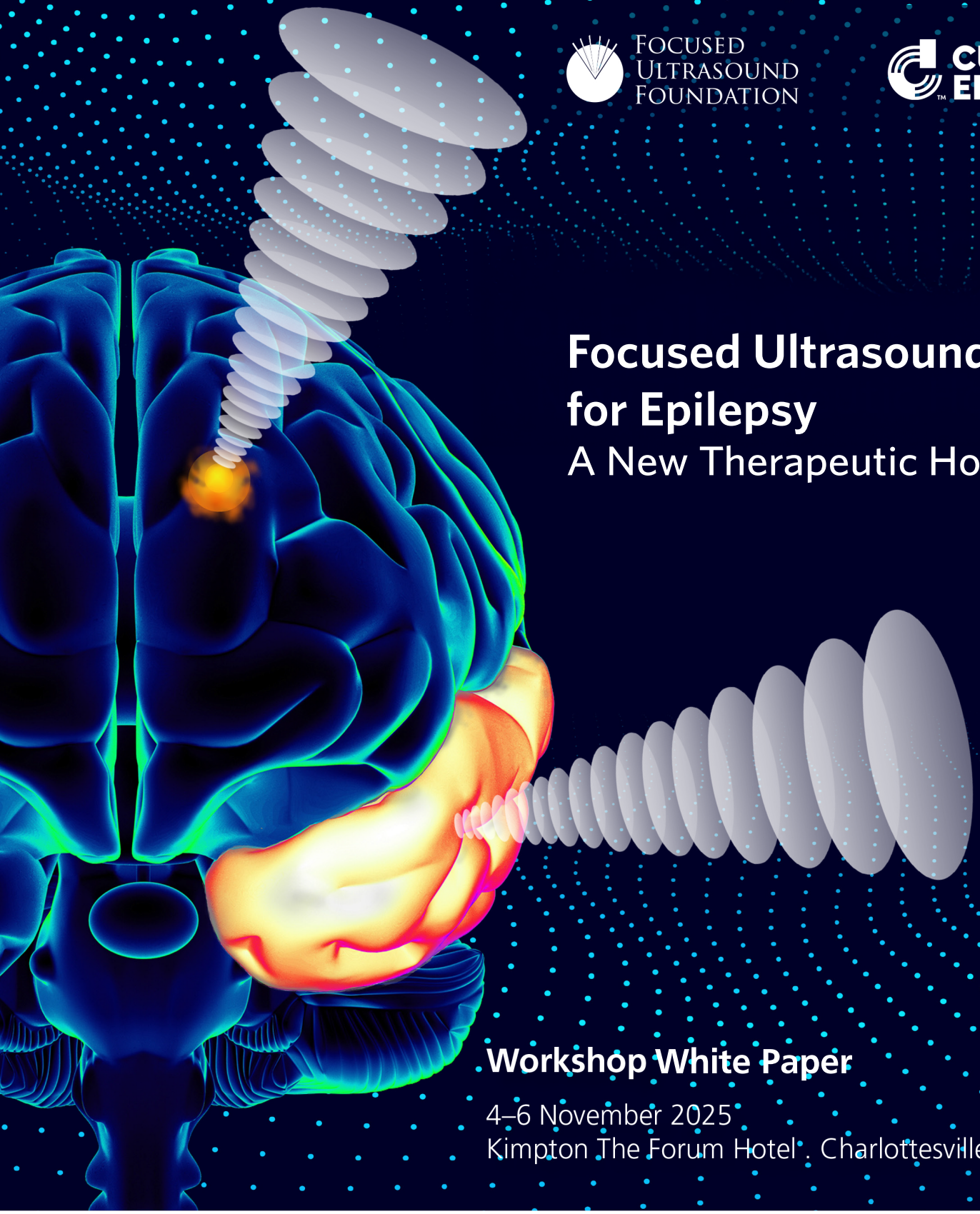
Focused Ultrasound Foundation

CURE EPILEPSY



# Focused Ultrasound for Epilepsy

## A New Therapeutic Horizon

**Workshop White Paper**

4–6 November 2025
Kimpton The Forum Hotel . Charlottesville, VA

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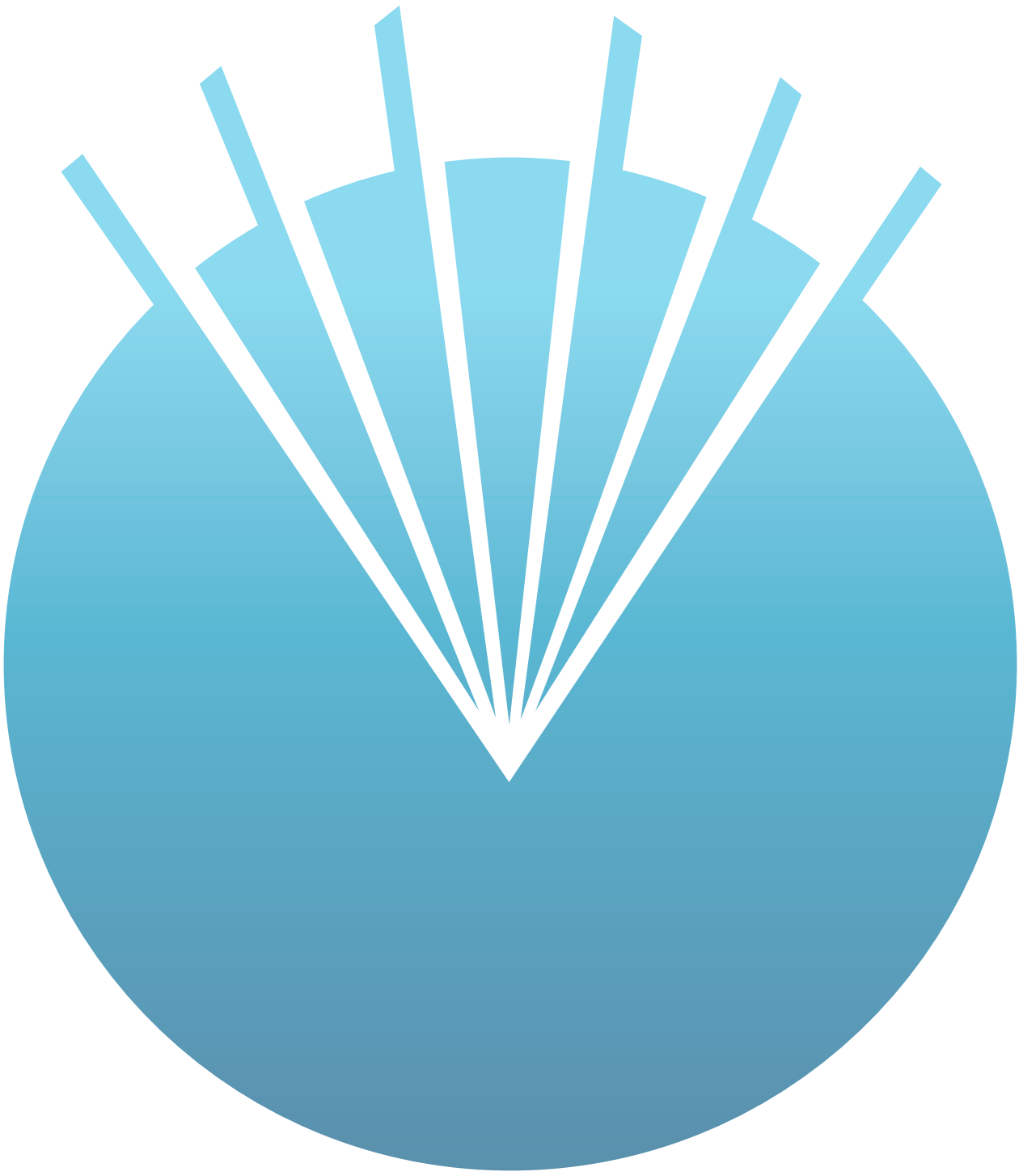

# Contents

# Executive Summary

The Focused Ultrasound Foundation along with CURE Epilepsy hosted the first workshop on focused ultrasound (FUS) for epilepsy on November 5-6, 2025, in Charlottesville, VA. This workshop assembled a diverse group of experts from academia, industry, government, and the not-for-profit sector. We would like to thank our industry partners including Insightec, NaviFUS, and SPIRE therapeutics.

Epilepsy affects over 65 million people worldwide, with one-third of patients remaining refractory to existing anti-seizure medications. Current options, including resective surgery, and neuromodulation, are often invasive and limited by incomplete seizure focus localization. FUS offers a non-invasive alternative with potential for ablation, neuromodulation, and blood-brain barrier (BBB) opening. Workshop participants identified promising indications for ablative FUS, such as periventricular nodular heterotopia and hypothalamic hamartoma, while neuromodulation approaches could address non-lesional modulatory effect incurring tissue damage. BBB opening (BBBO) offers opportunities for targeted drug and gene delivery, expanding therapeutic possibilities.

Consensus highlighted the urgent need for standardized and transparent reporting of neuromodulation parameters. Safety considerations include mechanical index limits, thermal rise thresholds, and patient-specific stopping rules. Regulatory engagement and adherence to iTRUSST[1] guidelines were emphasized.

Patients emphasized the profound impact of uncontrolled seizures on quality of life, including memory loss, disability, and social isolation. They expressed a strong willingness to participate in research and adopt new therapies that could restore independence, especially a non-invasive option like LIFU.

### Path Forward

Future directions include a roadmap to advance preclinical studies in chronic epilepsy models, explore veterinary applications, and initiate early feasibility trials in well-defined patient populations, such as in those with temporal lobe epilepsy. The FUS Foundation will explore forming working groups to optimize parameter settings, identify BBB opening studies, create a unique clinical trial design, and define patient-focused device usability criteria. A comprehensive table documenting all ongoing clinical trials with their specific FUS parameters will be created in accordance with iTRUSST reporting standards.

# Opening Remarks

### Introductions

**Suzanne LeBlang**, MD welcomed participants to the workshop. She thanked the Epilepsy Workshop Steering Committee: **Ellen Bubrick**, MD; **Rees Cosgrove**, MD; **Robert Fisher**, MD, PhD; **Nathan Fountain**, MD, **John Rolston**, MD, PhD; **Steven Schachter**, MD; **Michael Sperling**, MD; **Iris Hongchae Baek**, PhD and **Laura Lubbers**, PhD. She also thanked the meeting sponsors: Insightec, NaviFUS, and SPIRE Therapeutics.

**Laura Lubbers**, PhD stated that epilepsy affects 3.4 million Americans and 50 million people globally. Approximately one-third of patients do not respond to existing treatments, which often carry significant side effects. Uncontrolled epilepsy increases the risk of sudden unexpected death from 1 in 1,000 to 1 in 150 cases per year. New therapies and approaches are urgently needed, particularly for drug-resistant epilepsy. This workshop explored the use of FUS as a potential therapeutic option for epilepsy.

### Why Do We Need Focused Ultrasound?

**Robert Fisher**, MD, PhD stated that epilepsy is a major neurological disease affecting 1% of the world's population. While two-thirds of patients have epilepsy that can be controlled with medications, around 1/3 do not. This makes the absolute number of people with uncontrolled epilepsy exceed the number of all patients with brain tumors, multiple sclerosis, and muscular dystrophy combined, making it far from a solved problem. Currently available treatments in the US include 27 medications, surgical procedures like resective surgery and laser treatments, and neuromodulation techniques such as vagus nerve stimulation, responsive neurostimulation, and deep-brain stimulation (DBS). Some of these treatments are quite invasive, and surgical and neuromodulation approaches are typically limited to patients with well-identified and relatively fewer seizure foci. Transcranial magnetic and direct current stimulation are incisionless but efficacy has not yet been documented in pivotal trials and have limited depth penetration with spatial resolution. These limitations highlight the urgent need for new, non-invasive, focused technologies.

### Patient Interview

**Nathan Fountain**, MD introduced one of his patients, **Kelly Falk**, who discussed her journey with epilepsy. Ms. Falk experienced her first seizure at the age of 15 while driving with her learner's permit. She lost her vision and had a grand mal seizure, falling out of the car when it stopped. Initially, medication controlled her seizures, but this success was temporary. She began experiencing simple and complex partial seizures that went undiagnosed for some time, during which she continued working and driving.

After switching to an epilepsy specialist, she tried numerous medications over the years. The frequency and severity of her seizures eventually made it impossible to work or drive, forcing her onto disability about 15 years ago. A crucial part of her life has been finding joy in painting and selling her artwork.

In addition to trying many medications with various side effects, Ms. Falk's treatment journey also included having a vagus nerve stimulator implanted (which caused severe side effects and was removed) and ultimately receiving a responsive neurostimulator about three years ago. This device successfully eliminated her grand mal seizures, which made a considerable

improvement in her quality of life. However, she continues to struggle to control her simple and complex partial seizures.

One of the most challenging aspects of living with epilepsy is severe memory loss. She cannot remember her first seizure or many significant life events. In 2016, she experienced status epilepticus after falling down a flight of stairs, resulting in substantial memory loss from her childhood and that entire year. Many of her "memories" are accounts others have told her.

Managing epilepsy has become a full-time job. She hopes to become seizure-free and eventually pursue training as a massage therapist. However, she faces an unusual fear: after 15 years without working or driving, she worries about rebuilding her life and identity as a seizure-free person. Despite these challenges, she maintains hope as she works to accept and find happiness in her current situation.

Ms. Falk estimates that she has tried approximately 30 different epilepsy medications, including several experimental drugs in clinical trials. She is currently taking four medications. She mentions her willingness to participate in research studies and try new treatments, which reflects her contribution to medical knowledge while searching for solutions.

# What are the Clinical Unmet Needs?

**Moderators:** **Jeff Elias**, MD; **Nathan Fountain**, PhD; and **Michael Sperling**, MD

**Panelists:** **Eyiyemisi Damisah**, MD; **Augusto Grinspan**, MD; **John Stern**, MD; and **Nitin Tandon**, MD

This panel discussion explored clinical applications of FUS for epilepsy treatment, covering patient needs, technical capabilities, and future directions.

Panelists highlighted specific types of epilepsy well-suited for current FUS ablation. Periventricular nodular heterotopia was emphasized as an ideal candidate due to its wallpaper-like structure lining the ventricles, which is challenging to treat with traditional surgery or laser ablation. Published results show 80% to 90% seizure-free rates with laser treatment, but FUS has the potential to achieve comparable outcomes while avoiding invasive catheter insertion into the brain. Hypothalamic hamartoma has been repeatedly cited as an ideal lesion for non-invasive treatment. However, panelists noted that current technology is more effective for smaller lesions, while larger lesions remain technically challenging.

Approximately 600,000 people have surgically remediable focal epilepsy yet only 3,800 to 4,000 epilepsy surgeries occur annually in the United States. This tenfold gap represents the actual unmet need. The group discussed whether the emphasis should be on replacing laser ablation, arguing that developing large-volume ablation capabilities would take a decade or more, while 40,000 to 45,000 patients go untreated every year to avoid invasive surgical procedures. Many patients decline traditional temporal lobectomy but accept less invasive options. FUS has the potential to appeal to many patients because of its non-invasive nature.

It's important to distinguish between high-intensity focused ultrasound (HIFU) for ablation and LIFU for neuromodulation. HIFU creates small lesions (approximately grain-of-rice-sized), limiting coverage of larger areas like the hippocampus. However, LIFU can cover 1.5 centimeters per sonication, allowing treatment of the entire 4.5-centimeter hippocampus with three sonications. A 2020 study showed that LIFU of the thalamus could inhibit generalized epilepsy in rat models, suggesting the potential to treat generalized epilepsy by targeting key network nodes.[2]

FUS approaches for epilepsy could be considered through multiple frameworks: high-intensity ablation versus low-intensity neuromodulation, and whether to target specific areas, entire networks, or modulatory nodes like subcortical nuclei. Broadly, the field can be framed around treating clear-cut lesions or modulating distributed networks. Networks may be altered either by modulating structures or by lesioning key network nodes.

In contrast, when addressing specific seizure foci in the traditional surgical sense, the goal would be to create a lesion that destroys the underlying pathology. Current ultrasound ablation technology produces tiny lesions, while modulation approaches can target larger tissue volumes.

The patient population for ablation may be small. However, neuromodulation could reach more patients with focal and generalized epilepsies distributed throughout the brain, where lesioning is not possible. Although FUS's ability to reach deep structures like the hippocampus, amygdala, and parahippocampal gyrus non-invasively is valuable for temporal lobe epilepsy, many patients have extratemporal disease. Superficial targets may not respond to FUS, as obliquely directed emitter beams may reflect off the skull and deliver little energy to the brain. The field must eventually develop the ability to target neocortical regions, which will require advances in addressing skull-related challenges and in superficial targeting, since many patients have seizure foci that are not deep but are in the neocortex.

When asked about FUS versus DBS, it was noted that DBS carries a 1% to 2% risk of serious complications from electrode insertion, a 10% infection rate, usually superficial but requiring hardware removal, and potential mood and memory problems.[3] LIFU eliminates risks of hemorrhage or infection, offering significant advantages if it proves effective.

There was a suggestion to reframe the discussion around what FUS uniquely offers (non-invasive ablation, temporary neuromodulation, and focal BBB opening) and its limitations (many systems cannot accommodate the general anesthesia needed for pediatric hypothalamic hamartoma cases, and special coils are required for patients with vagus nerve stimulators). Framing the discussion around technology's capabilities, rather than starting from specific clinical indications, may be more helpful.

Panelists discussed using FUS for non-invasive brain mapping to identify seizure foci, potentially replacing the highly invasive intracranial electroencephalography (EEG) currently used. Several participants noted this possibility. This could involve testing multiple targets to determine optimal electrode placement for neuromodulation or to guide ablation therapy. However, it was pointed out that distinguishing what calms a particular brain region from what makes it hyperexcitable requires careful study for each brain target.

The discussion concluded with an acknowledgment that biological approaches are advancing rapidly, including phase 3 trials of GABAergic stem cell implants for bilateral hippocampal epilepsy and gene therapy for focal cortical dysplasias. These treatments address the underlying biology rather than ablating pathological brain tissue. Panelists emphasized that FUS must clearly define where it fits alongside these emerging biological therapies and demonstrate reliable seizure freedom, not just reduction, to change patient lives meaningfully.

Three main themes emerged from the discussion:

1. Exploring FUS neuromodulation for seizure mapping could identify which patients would benefit from various therapies, enable earlier treatment, and reach patients who refuse surgery but would consider less invasive options.
2. As an ablation tool, FUS can treat focal lesions without any incisions and offer a nonsurgical alternative for the many patients that will not consent for traditional surgery
3. FUS BBBO should be explored for potential assistance with gene and cell therapy delivery.[4]

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# What Do We Know About What Low-Intensity Focused Ultrasound Does to the Brain?

**Moderators:** **Iris Hongchae Baek**, PhD and **Ellen Bubrick**, MD

**Panelists:** **Alexander Bystritsky**, PhD; **Charles Caskey**, PhD; **Cheng-Chia Lee**, MD, PhD; and **Kim Butts Pauly**, PhD

The session explored how FUS affects brain tissue at multiple scales, from ion channels to neural networks. While the ideal approach remains finding and treating the primary seizure focus when possible, this field has evolved from viewing epilepsy as a purely focal disorder to understanding it as a network disorder. Kim Butts Pauly presented patch-clamp experiments showing that FUS affects mechanosensitive ion channels, particularly non-voltage-dependent K2P potassium channels that cause hyperpolarization.[5] The experiments demonstrated state-dependent effects: FUS decreased neuronal excitability at low current injection but increased it at higher current injections. The research suggests FUS acts as a subtle modulator of neuronal excitability rather than directly triggering action potentials. Further research is needed to better define expression patterns of these channels to identify effects in excitatory and inhibitory neuronal populations.

The brain is not only composed of neurons but also of astrocytes and other cell types. Neuronal networks are also increasingly recognized as playing a role in brain pathology. Multiple speakers stressed that epilepsy is increasingly understood as a network disorder rather than purely focal, complicating treatment approaches. The thalamus received particular attention as a key structure in epilepsy networks, though speakers noted epilepsy rarely originates in this brain region. The thalamus contains over a dozen distinct nuclei that are part of different networks, offering opportunities for targeted modulation. FUS has an advantage in targeting specific thalamic sub-regions to avoid side effects.

The discussion revealed that FUS effects may be primarily driven by non-neuronal cells rather than by neurons themselves. Preliminary data suggest that the strongest signals were from microglia and astrocytes, not neurons. Both cell types express mechanosensitive channels. The BBB opening capability was highlighted as promising for drug delivery and potentially gene therapy applications.

### .Questions

**Q: Are FUS effects directionally specific? Would perpendicular sonication affect neurons differently?**

Dr. Butts-Pauly explained that this is not fully understood. Some studies suggest that shear forces across membranes matter, while others indicate that pressure alone is sufficient to cause effects. Both radiation force (causing displacement and shearing) and direct pressure at the focus likely contribute. The differences in tissue stiffness between gray and white matter would also affect mechanical responses.

**Q: How does the fundamental frequency of 43 MHz used in the animal experiments relate to the parameters that would be used for epilepsy patients?**

Dr. Butts-Pauly said that frequency has emerged as a critical issue, as most preclinical work uses frequencies (like 43 MHz in patch-clamp studies) that cannot penetrate the human skull. Clinical applications require lower frequencies (0.5-0.65 MHz), but mouse brains are too small for adequate focal spots at these frequencies. Duty cycle was

identified as potentially crucial, with different groups using duty cycles ranging from 1% to 50%. The pressure amplitude and pulse-repetition frequency also need to be optimized. The comparison to DBS was made, where 130 to 150 Hz stimulation became standard without a complete mechanistic understanding.

**Q: What duration of effect is needed for brain mapping applications?**

No clear consensus emerged. It depends on the readout (EEG changes, seizures, etc.). Some participants reported only seconds for local effects and days for clinical EEG responses. Further research is additionally needed on safety.

**Q: How do we know that astrocytes are modulated by FUS, and what information do we have about that modulation?**

- FUS modulation of astrocytes through experiments with cultured astrocytes showed calcium signaling when FUS is applied. Blocking specific ion channels, particularly transient receptor potential canonical (TRPC) channels, stops this modulation, confirming the mechanism. Rodent studies have also demonstrated changes in neurotransmitter concentrations. Beyond direct neuromodulation, the potential of BBB opening for particle delivery was highlighted. Since FUS is inherently a poor way to interact with brain cells (which weren't designed for this purpose despite having mechanosensitive ion channels), BBB opening enables cellular-level interactions at specific brain locations that is not possible with other methods. This could allow delivery of stem cell therapy or other neuroprotective components, or genetic modification using designer receptors and drugs. Such an approach could create personalized drugs with no off-target effects that only affect specific brain regions, offering a powerful technique for conditions like epilepsy, where hyperactivity in particular brain areas or networks is the underlying problem.
- Spatial transcriptomic analysis and histology of healthy and diseased mouse brains suggests that the strongest signals from FUS were not neuronal but from microglia and astrocytes, which express the same mechanosensitive channels in both rodents and humans.

**Q: Does FUS have suppressive or excitatory effects?**

- The consensus suggested primarily suppressive/inhibitory effects, though context dependent. Reduction in spiking activity has been repeatedly observed across studies. Patch-clamp data showed both decreased and increased excitability depending on the neuron's initial state. Multiple speakers' noted effects are subtle and state-dependent rather than simply excitatory or inhibitory.
- Studies measuring neurotransmitters (glutamate, GABA, dopamine, and serotonin) showed that FUS alone produces only a temporary, minor rise in glutamate. However, when FUS is applied during ketamine administration, the neurotransmitter response amplifies significantly, with low-dose ketamine (0.75 mg/kg) producing effects closer to those of high-dose ketamine (10 mg/kg). This suggests FUS doesn't directly activate neurons but rather modulates how the brain responds to other stimuli, likely through effects on glia and microglia rather than neurons.

**Q: What should preclinical scientists do to speed up clinical translation?**

Multiple responses emphasized the need to identify optimal parameter sets at different brain locations, conduct studies at clinically translatable frequencies, develop better targeting methods through the skull, and identify biomarkers for rapid assessment of effects. The comparison to DBS was made, suggesting that the field may need to determine empirically effective parameters before fully understanding the mechanisms.

**Q: Will FUS neuromodulation require a single standardized set of parameters like the 140 Hz typically used in DBS, or will parameters need to be personalized and adjusted for each patient?**

Parameters will need to differ by brain location, even within the same patient, because different regions, like the hippocampus (which is hyperexcitable), behave differently than areas like the frontal lobe, both electrically and clinically, and the skull anatomy also varies by location.

**Q: Is the duty cycle the key determining factor for excitation versus inhibition?**

There was no definitive answer. One group found that 30% was the most effective for reducing spike activity in their models compared with lower duty cycles (1%, 5%, 7%) under neuromodulation conditions. The field lacks consensus, and different applications may require different duty cycles.

# How Do We Define the Optimal Neuromodulation Target?

**Moderators:** **Suzanne LeBlang**, MD and **Michael Sperling**, MD

**Panelists:** **Kathryn Davis**, MD, PhD; **Nitin Tandon**, MD; **Jasmine Thum**, MD and **Chengyuan Wu**, MD

Some patients with epilepsy have focal networks amenable to procedures like laser ablation or FUS, while others have highly distributed networks that will never suit focal approaches. The hippocampus and anterior nucleus (part of the Papez circuit) remain appealing targets for initial assessment due to their established role in temporal lobe epilepsy. However, individual patient connectomes exhibit significant heterogeneity.

Multiple bottlenecks limit surgical intervention beyond stereoelectroencephalography (SEEG) capacity alone. The epilepsy management unit (EMU) represents a major constraint due to limited bed availability and throughput problems. However, other issues include competing departmental priorities focused on research metrics rather than surgical volume, and significant patient barriers exist, including financial constraints, travel difficulties, social factors, psychiatric comorbidities, and mistrust of providers. The gap between academic medical centers and community practices serving less privileged populations creates additional disparities.

Participants discussed using normative connectome databases (such as the Human Connectome Project) in combination with patient-specific imaging to identify perturbations in functional and structural networks. This approach could non-invasively distinguish between focal and distributed epilepsy patterns, helping to guide appropriate therapies and potentially obviating unnecessary SEEG in some cases. However, concerns arose about applying population-level data to individual patients, with some noting that this approach has limitations even in well-understood movement disorder networks. The consensus favored patient-specific imaging z-scored against normative backgrounds rather than relying solely on population data.

A major theme was the use of FUS as both a diagnostic and a therapeutic tool. The non-invasive nature could enable testing multiple targets sequentially to identify optimal locations before committing to permanent interventions like DBS or resection. Interventions could include acute interictal spike suppression and temporary reduction of seizures. This could serve as a "bridge therapy" to assess the effectiveness of network modulation before device implantation, particularly appealing to surgery-averse patients. FUS offers significant advantages over invasive procedures such as electrode placement or resection because it enables non-invasive neuromodulation that can be adjusted and retargeted as needed. Participants also raised capacity issues at surgical centers and expressed interest in treatment methods that could bypass existing bottlenecks. Rather than replacing existing treatments, this approach could expand the overall patient population by offering options to those who currently decline surgical interventions, as FUS has successfully done in movement disorders.

Differences in the use of FUS between adult and pediatric epilepsy were noted. Pediatric epilepsy surgery differs fundamentally from adult surgery, being predominantly extratemporal and developmental rather than temporal. Focal cortical dysplasia type 1 is particularly challenging to diagnose and often produces large networks that require extensive modulation or ablation. The anterior nucleus of the thalamus holds less interest in pediatric cases, as most are not limbic based, with the centromedian and pulvinar nuclei being more relevant targets.

The duration of FUS effects varies dramatically across targets and indications. Essential tremor showed effects lasting approximately 30 minutes with 15 seconds of stimulation, while

depression required 5 minutes repeated multiple times daily over a week to see effects lasting 2 weeks. The mechanism likely requires inducing plasticity for sustained benefits, operating across numerous time scales including immediate effects during sonication, frequency-dependent optimization during treatment sessions, repetition schedules for sustained effects, and potential consolidation treatments. This differs markedly from movement disorders, where immediate operating room effects are visible, while epilepsy neurostimulation typically requires weeks to months to show benefits.

The centromedian nucleus may be a potential target for FUS ablation, although concerns have arisen about its role in consciousness circuits and potential cognitive side effects from ablation. The thalamus contains over a dozen functionally distinct nuclei, making precise targeting critical. Some advocated for non-destructive neuromodulation of these structures rather than ablation. For idiopathic generalized epilepsy specifically, thalamic targets like the centromedian nucleus offer promise, though practical barriers exist. The choice of target will depend on the treatment goal.

Significant heterogeneity exists across treatment centers in SEEG approaches, surgical techniques, and decision-making about who receives invasive monitoring. The field needs improved consortium-based data sharing and standardization. This includes reclassifying epilepsies into discrete subtypes rather than treating each as unique and developing population-based non-invasive methods to define large-scale versus small-scale networks.

Multiple centers must collaborate since no single institution can gather sufficient data quickly enough before techniques evolve. Even when the seizure onset location is precisely identified, FUS sensitivity varies significantly across brain regions and structures, reflecting differences in cellular composition, which creates challenges for effective neuromodulation. This variability in sensitivity across brain tissues means that researchers need to better understand how FUS parameters translate to other neuromodulation techniques, such as DBS, and account for these inherent sensitivity differences when developing treatment protocols.

Current reliance on seizure logs and diaries remains problematic for assessing treatment efficacy. Alternatives under exploration include responsive neurostimulation (RNS) long-episode detection, ambulatory EEG with remote reading, resting-state fMRI measuring entropy and excitatory-inhibitory balance, and potentially motor threshold testing with scalp stimulation to assess short-term changes in network inhibition. Wearable ultrasound devices with EEG recording capabilities are in development, and there's already clinical data on transient neuromodulation for movement disorders that provides insights into safe protocols and duration effects, though epilepsy applications would be different. The challenge remains in finding reliable biomarkers that predict long-term outcomes from short-term interventions.

# What Are the Best FUS Neuromodulation Parameters to Move into Clinical Trials?

**Moderators:** **Iris Hongchae Baek**, PhD; **Ellen Bubrick**, MD; and **Robert Fisher**, MD, PhD

**Panelists:** **Kim Butts Pauly**, PhD; **Alexander Bystritsky**, PhD; and **David Moore**, MSc

Uncertainty about optimal targets and parameters for FUS to treat epilepsy poses a challenge for developers of clinical trials and for device manufacturers. Data from preclinical studies informed preliminary clinical trials and suggested some benefits The challenge is avoiding a scenario in which clinical effectiveness depends on identifying the exact combination among numerous FUS parameters. One hope is that pulsed effects can provide meaningful clinical benefits that can be optimized through trials rather than requiring perfect parameter selection upfront. Parameter optimization for FUS must be tailored to the disorder and the brain circuit, since animal studies do not translate reliably to humans. Early safety studies demonstrated promise, including one patient with frequent seizures who had no seizures between treatment and surgery, but more human research is needed to establish effective protocols.

Robert Fisher presented a few slides on the work of Hao-Li Liu and colleagues at the National Taiwan University using pulsed FUS in the rat kainic acid epilepsy model. FUS reduced spikes and seizures in the rat model.[6] This effect also lasted up to a month after a single FUS treatment with three 5 to 10-minute sonications over 25-40 minutes. FUS was also neuroprotective, resulting in less hippocampal atrophy. FUS resulted in less anxiety and more exploration, improved memory, and increased social behavior. The optimal parameters identified were 30% duty cycle, 2.8 W/cm2, and a mechanical index of 0.25, which performed best among the tested groups and was selected for clinical trials. Higher parameters (0.75 MI) began to show inflammatory effects in the normal hippocampus.

The epilepsy FUS community should standardize on a few specific parameter sets with fixed pulse-repetition frequency and duty-cycle values to enable better comparison among studies. The current literature reports a range of parameters, making it difficult to determine optimal protocols. While acknowledging that this would somewhat lock researchers into those parameters, the group recognized that standardized modes would be better than the current situation, in which different groups use different parameters, preventing clear conclusions about what works best.

The discussion highlighted the challenge of parameter optimization in FUS for epilepsy, comparing it to drug dosing trials, where it is necessary to find an effective dose before conducting efficacy studies. With multiple parameters creating a multidimensional space, complete optimization would require an enormous number of trials, suggesting that hope lies in identifying meaningful parameter combinations (such as Reynolds numbers in fluid mechanics) rather than optimizing individual parameters. The group considered approaches in which two parameters were varied simultaneously while holding the others fixed, like isobologram studies in drug research.

Multiple speakers emphasized that understanding biological mechanisms is crucial for parameter selection. One researcher described the neuronal intramembrane cavitation excitation model that supports the idea that inhibitory effects may predominate when FUS preferentially engages thalamic reticular inhibitory neurons, across a range of duty cycles (5-30%). The discussion explored potential biomarkers for real-time parameter optimization, including coupling FUS with transcranial magnetic stimulation (TMS) to test inhibition of

motor or sensory evoked potentials. This could provide a way to verify parameters before clinical treatment, similar to how animal studies use quantifiable endpoints, such as seizure thresholds.

Beyond theoretical concerns, researchers discussed real-world implementation issues, including:

- Patient tolerance: duration limitations due to the need for patients to remain immobile.
- Anatomical variability: skull bone angles and thickness affecting targeting and heating.
- Safety monitoring: reports of scalp burns in some single-element transducer studies emphasize the need for proper equipment and protocols.
- Coverage optimization: debate about whether to target the entire hippocampus versus specific sub-regions.

Attendees acknowledged the conflict between commercial interests and scientific transparency. One participant argued that companies have legitimate reasons to protect proprietary parameters and that the company's success might depend on specific parameter sets. However, this creates problems for reproducibility and field advancement.

The importance of reporting neuromodulation parameters in research was discussed. Transparent parameter reporting is crucial not only for finding effective treatment doses but also for patient safety and preventing other companies from repeating the same errors. Organizations like the FUS Foundation could help reinforce existing safety guidelines and reporting standards. The International Transcranial Ultrasonic Stimulation Safety and Standards Consortium (ITRUSST) consortium's standardized reporting guidelines emerged as a potential solution, requiring researchers to report device specifications, focal spot characteristics, pulsing parameters, and amplitude metrics. Outcome reports are important. However, participants noted that compliance remains inconsistent, with some suggesting that journal editors and grant reviewers should enforce these standards more rigorously. It was also noted that reporting parameters or biomarkers provide clinically actionable insights for clinical translation. The discussion also touched on regulatory challenges, with representatives from the US Food and Drug Administration (FDA) indicating that they are developing guidance documents but are facing resource constraints. At some point in the future, there may be a workshop on FUS reporting standards.

A question was raised about whether intensity is the appropriate parameter for dose escalation in neuromodulation, given that studies have demonstrated opposite effects at lower versus higher intensities, including animal research. Discussion participants noted that the probability of successful neuromodulation appears to correlate with radiation force (proportional to pressure squared) rather than pressure alone, and that peripheral nervous system studies show clear relationships between radiation force and the ability to initiate or suppress action potentials. However, there is uncertainty in the field, emphasizing that neuromodulation likely depends on combinations of parameters rather than a single variable. Comprehensive reporting of parameters across studies would enable comparative analysis to determine whether phenomena are driven by radiation force, pressure, or other factors. The integration of reported data with computational models was identified as a promising approach to advance understanding of the underlying mechanisms, including the role of mechanosensitive ion channels.

Several concrete proposals emerged:

- Focusing optimization efforts on the most critical 2 to 3 parameters rather than attempting comprehensive exploration.
- Using computational modeling and AI approaches to guide parameter selection.
- Establishing quantitative biomarkers that could be measured across studies.

The discussion concluded with recognition that this is a broader challenge in neuromodulation, not unique to FUS. One participant noted that even established fields like DBS still lack standardization, with companies using proprietary parameters. More than one parameter set may be effective; DBS at low frequencies is more efficacious in some patients than are high frequencies. The consensus was that while perfect optimization may be impossible, the field needs coordinated action to move beyond the current scattered approach toward more systematic parameter exploration and standardized reporting, balancing scientific rigor with the need for practical clinical advancement.

# What Safety Issues Should Be Reported in Clinical Studies with FUS Neuromodulation?

**Moderators:** **Ellen Bubrick**, MD and **Shayan Moosa**, MD,

**Panelists:** **Jean Francois Aubry**, PhD; **Gabriela Cantarero**, PhD; and **Matt Myers**, PhD

The FDA typically assembles a review team for a submission, depending on the scientific nature of the application. A clinician with relevant patient population expertise and a subject matter expert in FUS are recruited to evaluate submissions. Safety issues are related to the power level. The discussion emphasized that FDA safety assessments focus primarily on mechanical and thermal safety parameters. For mechanical safety, peak negative pressure is the most critical parameter, while thermal safety guidelines recommend staying below a 2-degree temperature rise. Participants stressed that while specific parameters such as ISPTA and the mechanical index provide useful benchmarks, computational modeling offers the highest level of evidence for safety assessment. The FDA has published guidelines for performing and reporting computational studies, with the rigor of validation requirements increasing proportionally to proximity to safety thresholds and the mechanical index level.

A significant portion of the discussion addressed the distinction between significant risk and non-significant risk determinations. The FDA clarified that risk determinations do not weigh benefits, which are considered only during marketing submissions. The ideal pathway involves investigators first consulting their institutional review board (IRB), which can determine non-significant risk without FDA involvement, determine significant risk, and proceed directly to an Investigational Device Exemption (IDE), or request FDA risk determination when lacking in-house expertise. Several attendees noted that their IRBs routinely defer to the FDA for risk determinations, even when they have FUS expertise, a practice acknowledged as common. There was some discussion on the use of academic versus private IRBs and whether there was a distinction between them.

Parallels were drawn with TMS development, illustrating how regulatory approaches evolve as evidence accumulates. Initially, TMS studies required significant oversight, but as the safety profile became clearer and parameters were established, the FDA adopted a more flexible approach. LIFU is currently in an earlier, more conservative phase, in which the FDA requests close monitoring and annual reporting to build its internal safety database. Leadership changes and accumulating evidence both influence when regulatory posture shifts from conservative to more permissive.

Participants emphasized the importance of disease-specific safety parameters and clearly defined stopping rules. Once a study receives a significant risk determination (whether from the FDA or a local IRB) and enters the IDE pathway, the FDA focuses on implementing risk-mitigating measures rather than enforcing hard parameter limits, with the level of monitoring and safety requirements (such as imaging, behavioral assessments, and stopping rules) increasing proportionally as studies approach potential safety thresholds for concerns like cavitation or thermal injury. The goal is to enable scientific exploration while ensuring that potential benefits outweigh risks through comprehensive safety monitoring appropriate to each study's specific risk profile. The FDA strongly encourages sponsors to demonstrate expertise by outlining specific criteria for individual-patient stopping rules and overall study stopping rules. This proactive safety planning assures that patient safety is prioritized and that investigators have appropriate expertise. Risk determinations can vary based on patient population and clinician judgment, with the same procedure potentially deemed a significant risk for vulnerable

populations. Reviewers lack the extensive clinical experience found in established fields; their assessments may reflect caution rather than purely empirical evidence.

The patient perspective emerged as an important consideration. Patients with epilepsy may have a willingness to accept risks for potential treatment benefits, emphasizing that patients with refractory conditions often value the opportunity to participate in trials despite risks. The FDA confirmed that patient perspectives significantly factor into risk-benefit analyses for marketing submissions.

Throughout the discussion, FDA representatives emphasized their supportive role. They encouraged open communication, noting that brief conversations often clarify ambiguities more efficiently than lengthy email exchanges. The FDA's primary goal is to advance technology to patients as quickly as possible while ensuring safety.

# What Are the Future Directions?

**Moderators:** **Jeff Elias**, MD; **Nathan Fountain**, PhD; and **Michael Sperling**, MD

**Panelists:** **Raag Airan**, MD, PhD; **Vibhor Krishna**, MD; **John Snell**, PhD; and **Peter Warnke**, MD

This panel discussion explored future applications of FUS technology in the treatment of epilepsy, focusing on ablation techniques and BBB manipulation.

John Snell from Histosonics introduced histotripsy as an alternative to conventional thermal ablation. Unlike continuous-wave thermal devices, histotripsy uses very short, high-pressure pulses (10-20 microseconds) to create bubble clouds that mechanically fractionate tissue, reducing the need for extended skull heating and cooling. This approach offers several advantages; for example, it can treat 1 to 3 cubic centimeters per minute, which is faster than current thermal methods that ablate minuscule volumes with lengthy cooling intervals between treatments. The technology can also approach bone within 10 millimeters, expanding the treatment envelope beyond that of current thermal devices. However, the technique does cause peripheral BBB disruption around lesions and faces limitations near bone surfaces due to focal degradation of image quality. Clinical availability was estimated to be within 2 to 3 years, noting that working prototypes already exist and the remaining challenges are primarily engineering rather than scientific.

The panel discussed how FUS fits within the broader landscape of epilepsy treatment. It was noted that while mesial temporal lobe epilepsy can be treated with surgery, it represents only a fraction of epilepsy cases. Many patients have seizures originating outside the hippocampus, making technologies capable of safely treating cortical regions particularly valuable. Other patients have generalized onset seizures, in which case a network neuromodulatory approach could be useful. The issue of targeting certain regions with FUS safely was raised. Overheating of the bone will remain a challenge for the targeting of certain brain regions. The discussion revealed recruitment challenges in clinical trials: one center received hundreds of inquiries but found only one appropriate candidate. Panelists emphasized designing trials that address unmet needs rather than competing directly with proven procedures.

The panel debated whether FUS ablation would replace laser interstitial thermal therapy (LITT) in epilepsy. For smaller lesions, such as hippocampal sclerosis, LITT appears effective, with early results comparable to those of surgical series. However, larger lesions may still require open resection. FUS ablation for large thalamic targets still remains challenging with technical constraints.

The use of FUS for temporary brain mapping before permanent ablation was also discussed. The concept involves creating reversible functional lesions to predict surgical outcomes. Development of an ultrasound-triggered liposomal anesthetic capable of transiently inactivating targeted brain regions for 45 to 60 minutes would allow functional assessment before permanent treatment. Panelists agreed that non-invasive mapping could revolutionize neuroscience and surgical planning, enabling testing of different brain regions across multiple sessions. However, they acknowledged current limitations in rapidly assessing seizure networks, as traditional EEG monitoring requires extended observation periods, because suppression of spikes does not perfectly predict suppression of electrographic or clinical seizures. Future advances in EEG analysis might enable faster network identification separate from actual seizure occurrence.

The discussion explored BBB opening for targeted drug delivery in epilepsy. While hundreds of patients with brain tumors have received this treatment, epilepsy applications remain

investigational. However, most antiepileptic drugs already cross the BBB, limiting the advantage of focal opening, unless doing so limits whole-brain toxicity. The panel identified ideal candidates as large, water-soluble molecules, such as monoclonal antibodies, that generally cannot penetrate the brain.

Panelists also debated whether focal delivery offers a sufficient advantage over systemic administration for drugs that partially cross the BBB. This could also reduce the required dose, thereby minimizing toxicity. Some suggested emergency applications, such as delivering concentrated medications to specific regions during status epilepticus. Others proposed combining BBB opening with gene therapy approaches, where viral vectors or suicide gene systems could be activated focally. The discussion highlighted that laser ablation can maintain increased permeability for up to two months at specific isothermal lines around ablated tissue, offering unique delivery windows.

The session concluded with recognition that while FUS technologies show promise for epilepsy treatment, critical questions remain about optimal targets, patient selection, and integration with existing surgical approaches. The technology appears most immediately applicable for deep thalamic targets and may eventually enable personalized functional mapping, though substantial development and validation work will be necessary.

### Patient Experience with FUS

Thatcher Carr, a patient who underwent an experimental FUS procedure as part of a clinical trial, described his experiences. Carr, a former US Marine and Naval Academy cadet, first experienced epilepsy with a sudden seizure during class. After being discharged from the military, Carr underwent extensive treatment, including five different medication combinations, and a surgical resection of a left temporal lobe focus, which reduced his generalized tonic-clonic seizures but did not eliminate his focal preserved and focal impaired consciousness seizures. Despite taking four anti-seizure medications, he continued experiencing seizures ranging from brief speech and cognitive impairment lasting 10 seconds to episodes extending 2 to 5 minutes, with frequency varying from once daily to clusters of up to five seizures per day. Dr. Krishna enrolled Carr in an experimental FUS clinical trial targeting the anterior thalamic nucleus. Carr's goal for the procedure was to reduce the number of medications he was taking. The procedure, which took approximately two hours, successfully ablated 60% to 70% of the anterior nucleus volume while preserving the fornix and mammillothalamic tract. Carr underwent four ablations at 55°C while remaining conscious throughout, with memory function monitored via word-recall tests between sonications. He felt that the procedure was not a "big deal," given his prior medical history, which included MRIs, surgeries, and an EEG. At 30 days post-procedure, Carr reported complete elimination of seizures while remaining on his current medication regimen, expressing gratitude for the opportunity to participate in advancing epilepsy treatment options.

# What is the Dream Machine?

**Moderators:** **Ellen Bubrick**, MD and **Rees Cosgrove**, MD

**Panelists:** **Jon Kubanek**, PhD; **David Moore**, MSc; **Shayan Moosa**, MD and **Henrik Odéen**, PhD

This panel explored the development of optimal FUS devices for treating epilepsy. The conversation centered on whether a single universal machine could address all therapeutic needs or whether specialized devices are required.

The panelists agreed that FUS applications fall into two distinct categories requiring different approaches. HIFU for ablative procedures demands millimeter-level precision, necessitating stereotactic frames and MRI guidance. These one-time treatments justify the invasive setup. In contrast, LIFU for neuromodulation or BBB opening can have larger focal zones and less precise targeting, making stereotactic frames unnecessary and allowing for more comfortable, repeatable treatments. Future devices should allow movement toward peripheral areas and enable larger, customizable volumes that conform to seizure origins.

Several key challenges emerged regarding device design. Currently, commercialized HIFU systems are limited in their ability to access peripheral brain regions, constraining the range of targets that can be ablated. The ability to target peripheral brain regions and skull-base areas remains unattainable. Current systems excel at central targets but struggle with lateral structures like the temporal lobe. Participants discussed lowering frequencies to improve penetration, though this raises safety concerns about cavitation. The panel emphasized the need for real-time feedback mechanisms to confirm target engagement and ensure safety, noting that current thermal monitoring has limitations.

There is uncertainty about the durability of neuromodulation treatments. Effects may last only seconds to minutes acutely, though repeated treatments might produce cumulative or longer lasting neuroplastic changes. This uncertainty complicates decisions about device portability and frequency of use. Participants debated whether patients would comply with daily clinic visits, home-based wearable devices, or implantable systems. Patient representatives expressed willingness to undergo frequent treatments or use a wearable device, though clinicians cautioned that most patients show much lower adherence. There will need to be multiple options to accommodate patient preferences. Participants asked about patient tolerance for various devices and requirements, and Ms. Falk confirmed that she would likely accept a lot of different scenarios, including daily or weekly treatments, to control her epilepsy. However, clinicians indicated that their patient populations would not be willing to tolerate a device that required daily charging, etc., and that developers should consult with patient focus groups during the design process. Several eligible trial participants have declined participation because of the requirement with some devices and protocols to shave a patch of hair. There was a suggestion that the FUS Foundation conduct a patient survey on preferences for FUS for epilepsy, with the data shared publicly.

Multiple speakers emphasized that efficacy must drive device development. Without proven clinical benefit, investment in solving technical challenges cannot be justified. The panel acknowledged that epilepsy encompasses heterogeneous conditions requiring different interventions. Some patients need precise targeting of small deep nuclei, while others benefit from broad neocortical modulation. The ability to safely ablate the amygdala or hippocampus would be helpful. Treatment approaches might include acute seizure interruption, chronic neuromodulation, targeted drug delivery through BBB opening, or permanent ablation. Different tools will likely be needed for other targets.

The discussion also explored using FUS for diagnostics by neuromodulating hypothesized seizure locations to test their effect on seizure frequency, which would require a device capable of rapidly targeting any area of the brain.

The panel explored various deployment scenarios. For frequent neuromodulation, participants discussed wearable devices for home use, implantable subdural transducers like responsive neurostimulation systems, or simplified clinic-based systems operated by nurses or technicians. Each approach presents distinct challenges regarding user compliance, technical complexity, and cost accessibility. Hair preparation was noted as a barrier, with current protocols requiring extensive scalp preparation that may limit accessibility and patient acceptance. Participants indicated that solving such practical issues becomes worthwhile only after establishing clinical efficacy.

Regulatory and reimbursement considerations significantly shaped the discussion. FDA representatives clarified that FUS devices require premarket approval and cannot rely on DBS as a predicate device because of fundamental technological differences. The Breakthrough Device Designation program was highlighted as a mechanism to obtain early input from both regulators and insurers. Reimbursement requirements remain unclear, with questions about what level of efficacy payers would consider sufficient and what documentation would be required to justify cost.

Cost and accessibility concerns concluded the discussion. Current systems that require dedicated MRI time and cost millions of dollars limit availability to elite academic centers. Participants discussed alternative business models, including device rental and multi-use systems that could treat different conditions across neurology, neurosurgery, and oncology departments to improve utilization. Another feature to plan for in the future is to make any device that requires in-office management also usable by technicians or nurses, rather than only physicians. This is particularly important considering the business of physician practices. Many participants indicated that simplicity and ease of use are also crucial to clinician acceptance. The NaviFUS machine's test stimulation feature is valuable for verifying correct targeting. As FUS devices proliferate among patients and less experienced physicians, devices must incorporate safety limits to prevent brain damage, similar to how neurostimulation devices restrict output to safe levels, particularly by preventing unintended cavitation during LIFU procedures. This may require establishing initial safety parameters that, once set for variable conditions, cannot be exceeded during operation.

The consensus held that, rather than a single ‘dream machine,’ the field needs a suite of specialized tools matched to specific clinical applications, with device complexity and invasiveness proportional to the precision required and the treatment frequency needed.

# What Are Ideal Clinical Trial Designs from the Perspective of Physicians?

**Moderators:** **Ellen Bubrick**, MD; **Rees Cosgrove**, MD; and **Laura Lubbers**, PhD

**Panelists:** **John Stern**, MD and **Jerzy Szaflarski**, MD, PhD

This session discussed optimal clinical trial designs for FUS treatments in epilepsy. The discussion centered on identifying tractable clinical scenarios and establishing frameworks for both early feasibility studies and future pivotal trials.

Dr. Rees Cosgrove opened by noting that demonstrating efficacy in epilepsy is considerably more challenging than in essential tremors, where FUS outcomes are more predictable and rapidly identified. The goal was to identify specific epilepsy syndromes and clinical scenarios in which efficacy could be proven beyond a reasonable doubt, using LIFU, HIFU, or BBB techniques. The panel emphasized the importance of establishing proof-of-concept before pursuing larger trials. Once efficacy is demonstrated, broader support and resources become available. However, participants acknowledged that the field is in the early stages of phase 1 or 2 clinical trials, requiring substantial groundwork before pivotal trials.

Key considerations for trial design included determining appropriate targets, whether treating structural lesions like hypothalamic hamartomas or periventricular nodular heterotopia, versus pursuing neuromodulation approaches. The choice between ablative and neuromodulatory techniques will fundamentally shape trial parameters. For neuromodulation specifically, critical unknowns remain regarding treatment frequency, duration, and long-term maintenance requirements.

Outcome measures generated extensive discussion. While seizure control remains the primary endpoint, participants stressed the need for robust monitoring beyond patient diaries. Suggestions included subcutaneous EEG monitoring, wearable devices, and long-term EEG recordings. Additional outcomes such as mood and cognitive effects (e.g., memory) warrant attention, particularly since many epilepsy treatments worsen these domains. One proposed approach involved targeting frequent interictal spikes as a more readily measurable biomarker than sporadic seizures.

FDA representatives provided valuable guidance on regulatory pathways. Early feasibility studies enable device refinement without requiring multicenter randomization or a strict statistical plan. Feasibility studies should demonstrate signals of effectiveness with locked prototypes, while pivotal trials demand predetermined statistical plans, defined outcome measures, and established minimal clinically important differences. It was strongly encouraged to engage with the FDA early through pre-submission meetings rather than waiting until the pivotal trial submission.

Practical trial design considerations included simplicity and replicability. There are differences between scientifically ideal trials that explore neuromodulatory mechanisms and practically ideal trials that enable efficient recruitment. The time-to-end-seizure approach is a more efficient outcome measure, though FDA acceptance remains uncertain outside formal approval processes.

The control group design was debated. Some participants suggested using sham stimulation with coupling pads that block ultrasound transmission while allowing sound transmission. Others proposed targeting inert regions, such as cerebrospinal fluid (CSF) spaces, though concerns arose about potential confounds from CSF flow modulation. Ventricular targeting emerged as a promising sham approach, with neurosurgeons noting the safety of CSF manipulation in clinical practice.

Technical challenges included device standardization across different FUS systems. While frequencies differ between transducers, most low-intensity parameters should be customizable within reasonable ranges. However, significant variability exists in targeting accuracy and energy delivery predictions. The field requires a better understanding of the actual dose delivered to targets.

The presence of implanted electrodes, particularly RNS or DBS systems, generated extensive discussion. While plastic components in electrodes may cause some energy absorption and artifacts, several groups have successfully combined FUS with implanted systems. Participants suggested testing brain phantoms before human studies and using cavitation detectors during treatments. Alternative approaches include targeting connected network nodes rather than electrode locations, allowing electrophysiological readout without directly sonicating electrode sites.

Looking ahead, participants discussed mesial temporal lobe sclerosis as a suitable target for early trials, whether using ablative or neuromodulatory approaches. However, the scientific appeal of LIFU lies in its potential to explore non-invasive neuromodulation effects and network interactions, potentially informing broader epilepsy treatment strategies beyond FUS itself.

The session concluded with an emphasis on iterative design processes that incorporate user feedback, and learning from existing device experiences. Iterative design processes must account for real-world usage scenarios and all relevant stakeholders, including clinicians, patients, and clinical assistants. Human factors testing must authentically simulate the intended use environment, noting that hospital and ambulance settings represent fundamentally different conditions. Comprehensive human factors studies, conducted separately from pivotal trials, should validate device safety through appropriate design iterations, user training protocols, and clear instructional materials. The FDA stressed demonstrating safety through comprehensive biocompatibility testing matched to device invasiveness levels, with benefit requirements scaling proportionally to risk profiles.

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# Roadmap Discussion

**Moderator: Suzanne LeBlang**, MD

## Parameter Optimization and Standardization

The discussion centered on establishing optimal parameters for LIFU neuromodulation in clinical trials for epilepsy. Participants acknowledged significant gaps in understanding how different parameters affect outcomes. The group emphasized the need for preclinical work to identify the best neuromodulation parameters before advancing to clinical trials.

Several participants proposed creating a shared Google spreadsheet for researchers to document their clinical trial parameters, facilitate comparisons, and identify common ground. The concept of establishing common data elements was discussed as crucial for advancing the field. Participants stressed the importance of determining which parameters can be standardized across studies. Key parameters under consideration included pulse-repetition frequency (PRF), duty cycle, and pulse duration. The group discussed the need to document not only which parameters should be reported, but also to identify known relationships between specific parameter changes and physiological effects. Separate tracking would be required with parameters for HIFU and LIFU. There was also a request for a dose metric or measurement system to track and quantify what is being delivered, whether through cavitation or another method.

## Safety Guidelines and Boundaries

Regulators proposed the creation of a comprehensive reporting framework listing all FUS parameters researchers should document, identifying which parameters have known physiological effects when altered (such as changes in duty cycle), and flagging parameters that pose safety concerns, such as cavitation or thermal injury risks, when they exceed or fall below certain thresholds. This systematic approach would help standardize reporting across studies while highlighting critical safety boundaries and distinguishing between parameters whose effects are already understood and those that require further investigation. The ITRUSST consensus guidelines were highlighted as an essential framework for establishing safety boundaries. These recently published guidelines provide recommendations on mechanical and thermal safety limits. The recommended mechanical index limit is 1.9, with temperature rise recommendations below 2°C.

Participants debated whether staying within diagnostic ultrasound safety standards might limit therapeutic efficacy. However, several researchers expressed confidence that durable neuromodulation effects could be achieved while remaining within these safety parameters. The consensus initially leaned toward working within established safety guidelines, with careful monitoring if venturing beyond these boundaries becomes necessary.

## Preclinical Research Needs

The discussion highlighted the need for more comprehensive preclinical studies, particularly in chronic rather than acute epilepsy models. Participants called for more thorough mapping of the parameter space rather than isolated parameter studies. The gap between animal model results and human outcomes was acknowledged as a persistent challenge.

The group showed enthusiasm for exploring naturally occurring epilepsy in dogs as a potential research avenue. Dogs have epilepsy rates between 0.5% and 5%, with beagles showing a particularly high incidence. This approach could provide valuable translational data while treating veterinary patients. A working group at Duke University is already developing protocols for collecting data from veterinary patients with neurological disorders.

### Target Definition and Localization

The group discussed methods for defining seizure targets, including scalp EEG, high-density dipole localizing EEG, magnetoencephalography, and stereo EEG. While connectomics was raised as a potential tool, neuroimaging experts cautioned against relying on it prospectively due to the lack of validated interpretation frameworks, even for established interventions such as temporal lobectomy.

### Future Clinical Directions

Three main therapeutic approaches were discussed: neuromodulation, opening the BBB for drug delivery, and ablation.

For studies on BBB opening, participants expressed a strong interest in combining FUS with targeted drug delivery. The regulatory landscape for combination products was clarified, noting that jurisdiction depends on whether the primary mechanism of action is the drug or the device. Water-soluble therapeutics with high molecular weight, such as monoclonal antibodies, channel blockers, mRNA, and antisense oligonucleotides, were identified as promising candidates. A working group could put together comprehensive ideas and identify targets to move forward into clinical trials.

For clinical trial design, the group favored starting with temporal lobe epilepsy patients already undergoing surgical evaluation. This approach offers lower risk and clearer outcome measures, as patients can avoid surgery if they respond to treatment, while still having surgery as a backup.

A patient working group could help identify a list of feasibility criteria to share with the FUS community. The group also discussed developing standardized patient follow-up questionnaires specifically for epilepsy patients treated with FUS.

### Action Items

1. Establish a parameter optimization working group.
2. Create a comprehensive table documenting all ongoing clinical trials and their specific FUS parameters will be created in accordance with ITRUSST reporting standards.
3. Consider adopting an acoustic dose metric for NM.
4. Discuss what preclinical study would best contribute to improved translational data.
5. Engage in conversation to study naturally occurring epilepsy in dogs.
6. Form a BBB opening and drug delivery working group to design early-phase studies.
7. Create a patient advocacy group to improve design and usability for FUS devices and identify follow-up FUS outcome metrics.
8. Create a blog or perspective paper on non-significant risk determination and host on the FUSF website.
9. Create paper on safety and efficacy of NM.

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# Prereading Material

## Review Paper

**Focused ultrasound for treatment of epilepsy: a systematic review and meta-analysis of preclinical and clinical studies.** Soltani Khaboushan A, Zafari R, Sabahi M, Khorasanizadeh M, Dabbagh Ohadi MA, Flouty O, Ranjan M, Slavin KV. Neurosurg Rev. 2024 Nov 10;47(1):839. doi: 10.1007/s10143-024-03078-5. PMID: 39521750.

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## Clinical Research

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**Pilot study of focused ultrasound for drug-resistant epilepsy.** Lee CC, Chou CC, Hsiao FJ, Chen YH, Lin CF, Chen CJ, Peng SJ, Liu HL, Yu HY. Epilepsia. 2022 Jan;63(1):162-175. doi: 10.1111/epi.17105. Epub 2021 Nov 2. PMID: 34729772; PMCID: PMC9297900.

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## Preclinical Research

**Focused ultrasound suppresses pentylenetetrazol-induced epileptiform activity in rats and alters connectivity measured by functional MRI.** Chu PC, Ruan WH, Huang CS, Juan YJ, Chen JH, Yu HY, Fisher RS, Liu HL. Sci Rep. 2025 Aug 12;15(1):29551. doi: 10.1038/s41598-025-15305-0. PMID: 40797064; PMCID: PMC12343953.

**Repetitive pulsed-wave ultrasound stimulation suppresses neural activity by modulating ambient GABA levels via effects on astrocytes.** Mishima T, Komano K, Tabaru M, Kofuji T, Saito A, Ugawa Y, Terao Y. Front Cell Neurosci. 2024 Mar 27;18:1361242. doi: 10.3389/fncel.2024.1361242. PMID: 38601023; PMCID: PMC11004293.

**Pulsed-Focused Ultrasound Provides Long-Term Suppression of Epileptiform Bursts in the Kainic Acid-Induced Epilepsy Rat Model.** Chu PC, Yu HY, Lee CC, Fisher R, Liu HL. Neurotherapeutics. 2022 Jul;19(4):1368-1380. doi: 10.1007/s13311-022-01250-7. Epub 2022 May 17. PMID: 35581489; PMCID: PMC9587190.

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# Focused Ultrasound (FUS) & Epilepsy — Clinical Studies

| NCT number | Study Title | FUS type | Target population | Status | Sponsor/ Manufacturer/ Device |
|---|---|---|---|---|---|
| NCT02804230 | MR-Guided Focused Ultrasound in the Treatment of Focal Epilepsy (EP001) | Ablation | Focal medication-refractory epilepsy | Unknown status (last update posted 2022-09) | InSightec/ Exablate (MRgFUS) |
| NCT03417297 | Focused Ultrasound Thalamotomy for prevention of secondary generalization in focal onset epilepsy (22-0350) | Ablation | Adults with refractory focal onset epilepsy | Active, not recruiting | UNC Chapel Hill/ InSightec/ Exablate (MRgFUS) |
| NCT07249190 | MRgFUS Anterior Thalamic Nucleus Ablation for drug-resistant epilepsy (301EP) | Ablation | Adults with drug-resistant epilepsy (DRE) | Not yet recruiting | Chinese PLA General Hospital/ InSightec / Exablate (MRgFUS) |
| NCT06292494 | Focused Ultrasound for Drug-resistant Epilepsy (1129052082) | Ablation | Localized DRE | Recruiting | Taipei Veterans General Hospital/ InSightec Exablate (MRgFUS) |
| NCT05032105 | The Impact of Focused Ultrasound Thalamotomy of the Anterior Nucleus for Focal-Onset Epilepsy on Anxiety (2023H0325) | Ablation | DRE and anxiety | Recruiting | Ohio State University/ InSightec / Exablate (MRgFUS) |
| NCT02151175 | Low-intensity Focused Ultrasound stimulation/ suppression visible with fMRI (BX001) | NM | Adults with drug-resistant temporal lobe epilepsy | Enrolling by invitation | BrainSonix (LIFUP) |
| NCT03657056 | Focused Ultrasound Neuromodulation for Treatment of Temporal Lobe Epilepsy (LIFUP) (2018P001352) | NM | Intractable temporal lobe epilepsy | Withdrawn (no subjects enrolled) | Massachusetts General Hospital/ BrainSonix (LIFUP device) |
| NCT03860298 | Safety of Using NaviFUS™ System in Patients with DRE (NF-2018-01) | NM | DRE undergoing stereoelectroence-phalography | Completed/ Recruiting finished (completed 2020-11) | Taipei Veterans General Hospital/ NaviFUS™ (LIFUP) |
| NCT03868293 | Low Intensity Focused Ultrasound Epilepsy Study (2018P000125) | NM | Drug-resistant temporal lobe epilepsy | Recruiting | Brigham and Women's Hospital/ LIFUP-custom |

| NCT number | Study Title | FUS type | Target population | Status | Sponsor/ Manufacturer/ Device |
|---|---|---|---|---|---|
| NCT04999046 | NaviFUS™ System Neuromodulating Treatment for Patients with DRE (NF-2021-01) | NM | DRE | Unknown status (last update posted 2023-09) | Taipei Veterans General Hospital/ NaviFUS™ (LIFUP) |
| NCT05784805 | Acute Effects of Focused Ultrasound Modulation on EEG Behavior in Status Epilepticus Patients (2000034504) | NM | Adults with non-convulsive status epilepticus/ focal motor status epilepticus | Recruiting | Yale New Haven Hospital/LIFUP |
| NCT05947656 | Evaluation of the NaviFUS™ system in DRE (GNIA22-001) | NM | DRE | Recruiting | The Alfred in Melbourne, Australia/ NaviFUS™ (LIFUP) |
| NCT06388707 | Safety, Tolerability, and Preliminary Efficacy of LIFU neuromodulation in drug-resistant epilepsy (NF-2022-01) | NM | Drug-resistant uni/bilateral temporal lobe epilepsy | Recruiting | NaviFUS Corporation / NaviFUS™ (LIFUP) |
| NCT06492720 | Efficacy and Safety of NaviFUS™ System Neuromodulating Treatment in DRE (NF-2023-02) | NM | DRE | Recruiting | Taipei Veterans General Hospital/ NaviFUS Corporation/ NaviFUS™ (LIFUP) |
| NCT07353918 | Low-Intensity Focused Ultrasound for epilepsy patients with implanted RNS (IRB-24-2194) | NM | Epilepsy + RNS implant | Enrolling by invitation | Fralin Biomedical Research Institute (VTC) / LIFU) |

# Abbreviations

| | |
|---|---|
| BBB | Blood-brain barrier |
| DBS | Deep-brain stimulation |
| FUS | Focused ultrasound |
| EMU | Epilepsy Management Unit |
| FDA | Food and Drug Administration |
| HIFU | High-intensity focused ultrasound |
| IDE | Investigational Device Exemption |
| IRB | Institutional Review Board |
| LITT | Laser interstitial thermal therapy |
| PRF | Pulse-repetition frequency |
| TMS | Transcranial magnetic stimulation |
| TRPC | Transient receptor potential canonical |

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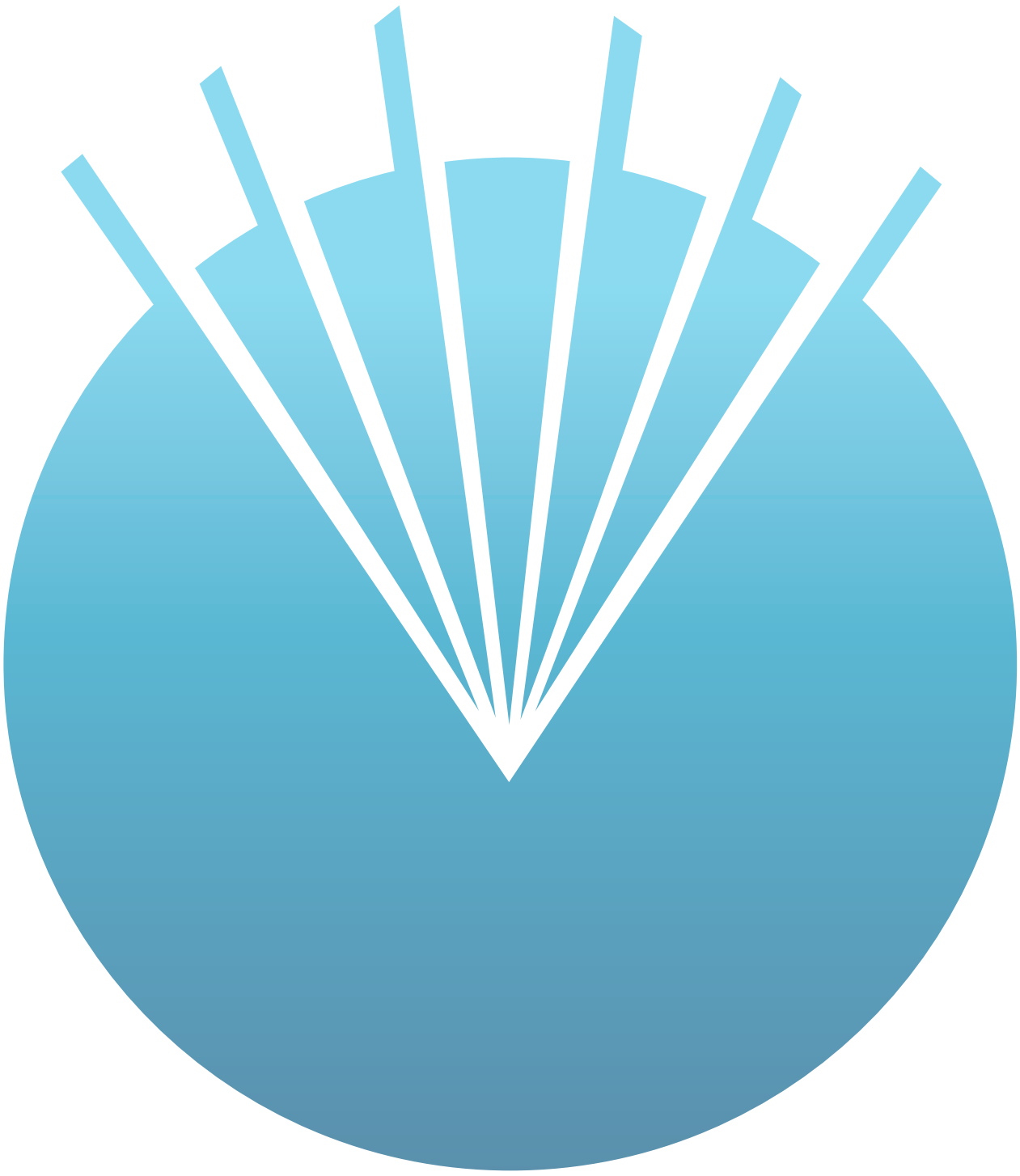

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