

PART B STUDY DESCRIPTION

Title of Protocol	BOTOX effects on seizure severity and susceptibility
Principal Investigator	Rami Burstein

B1. PURPOSE OF PROTOCOL

To test whether BOTOX injections into the scalp raise seizure threshold such that focal seizures are less likely to occur, and less likely to generalize.

Objectives:

1. To test whether scalp BOTOX injections mitigate seizure frequency or seizure severity. This objective will be tested using a prospective clinical observation in patients with focal epilepsy (see definitions below)
2. To test whether quantitative measures of seizures susceptibility (cortical excitability) are altered by scalp BOTOX injections. This objective will be tested using 24-hour ambulatory scalp EEG recording and transcranial magnetic stimulation (TMS) with simultaneous EEG/EMG a noninvasive tool to measure cortical excitability (Tsuboyama et al 2019).

Clarification of terminology:

- Focal seizures are seizures that arise in one area of the brain.
- Focal seizures with impaired awareness are seizures that arise in one area of the brain, and often spread to areas associated with conscious experience (i.e., are associated with alteration of awareness).
- Focal to bilateral tonic clonic seizures are seizures that arise in one brain region and spread to the entire forebrain, bilaterally and manifest as a convulsion.
- Primary generalized seizures are seizure that arise simultaneously in both hemispheres.

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Defining unmet needs in epilepsy

Epilepsy is a common neurologic disorder globally, with a lifetime prevalence of 7.60 per 1000 persons (95% CI 6.17-9.38) with incidence of 61 per 100,000 person-years (95% CI 50.75-74.38), and has one of the highest disability-adjusted life years (DALYs) among neurologic disorders (Fiest et al 2017, Murray et al 2012). Approximately 1/3 of patients with epilepsy have seizures refractory to medications (Ablah et al 2014, Kalilani et al 2018), a proportion that has remained unchanged despite the advent of over 20 new antiepileptic drugs over the last 30 years (Biton et al 2014, Brodie et al 2010, Krauss et al 2012, Loscher 2011, Loscher & Schmidt 2011, O'Connell et al 2017). While ~10% of these patients may find seizure relief with surgery, the remaining ~90% are in need of a novel intervention (Sanchez Fernandez et al 2017, Zarrelli et al 1999) to reduce seizure burden, improve quality of life, and reduce seizure-related morbidity and mortality. Patients with medically refractory epilepsy are also at increased risk of sudden unexplained death in epilepsy (SUDEP), with a high lifetime burden of frequent generalized tonic clonic seizures (GTCs) further elevating SUDEP risk (Verducci et al 2019).

Most relevant to the present proposal are patients with drug-resistant focal seizures with impaired

awareness, and particularly focal seizures with secondary generalization (i.e., focal to bilateral tonic-clonic seizures per 2017 ILAE nomenclature) (Fisher et al 2017, Hesdorffer et al 2012), as they are at particular risk for injury and for sudden unexpected death in epilepsy (SUDEP). Mortality in this cohort can approximate up to 1% per year of life, and quality of life is severely impaired by the unpredictable risk of severe seizures with impaired awareness, which restricts patient capacity to drive or participate in other essential daily activities. We therefore **propose to test a novel therapeutic strategy based on our preclinical data where focal BOTOX injection will be used to limit spread of focal seizures, and thus reduce the risk of injury and improve quality of life in patients with focal seizures with impaired awareness or focal to bilateral tonic-clonic seizures.**

BACKGROUND AND RATIONALE

Seizure, post-ictal headache and the trigeminovascular system

Attempting to unravel the pathophysiology of ictal and post-ictal headache (i.e., headache that follows epileptic seizure), we recently reported (Melo-Carrillo et al 2020) that generalized seizures activate a range of peripheral and central trigeminovascular neurons in the trigeminal ganglion and spinal trigeminal nucleus, respectively. Specifically, we noted that in the trigeminal ganglion, generalized seizure activated 50% of the thinly myelinated A-delta fibers and 54% of the unmyelinated C-fibers whose receptive fields include the intracranial dura (i.e., classified as meningeal nociceptors), and that in the spinal trigeminal nucleus, the generalized seizure activated 68% of the Wide-Dynamic Range (WDR) neurons and 39% of the High-Threshold (HT) neurons whose receptive field include the intracranial dura. Regardless of their class, all activated neurons exhibited a 2-4-fold increase in their firing, which started immediately (1 min) or up to 90 min after seizure initiation and lasted as little as 10 min or as long as 120 min. Based on these findings, we concluded that seizure could induce headache by activating the same sensory/nociceptive pathway that is involved in the initiation and maintenance of migraine.

Given our findings, we suggested that BOTOX - an FDA approved drug for the treatment of chronic migraine - can block the seizure-induced activation of the meningeal nociceptors. To test this hypothesis, we designed experiments in which we tested the effects of seizure on activation of trigeminovascular neurons in animals that received 5 units of BOTOX injections to their scalp and pericranial muscles 7 days earlier.

As is the case in innovative science, the most unexpected and unpredicted results usually lead to the most exciting breakthrough in our understanding of human diseases and ways to treat them.

OnabotulinumtoxinA effects of generalized seizure

While BOTOX injections into the scalp and pericranial muscles (injections paradigm that follows the FDA-approved guideline for BOTOX injection in chronic migraine patients) was effective in blocking the activation of the unmyelinated C-fibers but not thinly myelinated A δ -fibers (nociceptors that send pain signals from the dura to the spinal trigeminal nucleus), it also prevented focal/localized seizures from spreading to remote cortical areas and becoming generalized.

BOTOX is a safe FDA-approved drug for the treatment of multiple neurological (spasm, dystonia, migraine), cosmetic (wrinkles), and autonomic (blepharospasm) conditions. It is used widely in the United States and around the world for many decades. Within all Harvard affiliated Hospitals (including BIDMC), BOTOX is given thousands of times to thousands of patients. Its favorable safety profile and its wide use at BIDMC is a critical component in our quest to test its ability to prevent/reduce seizure spread and generalization among high-risk patients. Regarding safety, there are currently several peer-review manuscripts describing the use of Botox in the treatment of refractory motor seizures (Lee et al 2017), simple partial motor seizures (Mader et al 2012), and how

treatment of chronic migraine with botox also improves epileptic seizures (Zachariah et al 2017). Importantly, no safety issues were raised in these reports. (see further explanation in the Possible Risk section)

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

In a single-center open-label study, patients with pharmaco-resistant focal epilepsy will undergo 8-week seizure monitoring and baseline 24-hour ambulatory EEG and TMS-EEG-EMG. This period will take place between day 1 and day 59 (see flowchart). Each patient will then be injected with BOTOX (145 units) according to the FDA-approved paradigm for the treatment of migraine, plus injections along the sagittal suture. Seizure diary will be maintained for the duration of the study. EEG and TMS-EEG-EMG will be repeated 21 days, when BOTOX effects usually begin, and 8 weeks after injection, when BOTOX effect are usually at their peak. Data will then be analyzed to measure BOTOX antiepileptic capacity.

Screening and Enrollment Period (1 in-person visit):

Participants will initially be screened in person and written consent will be obtained. Screening will include a review of medical, surgical and seizure history and current medication review. They will be provided instruction on maintaining a daily seizure diary for 8 weeks in order to capture their baseline seizure frequency. If frequency is less than an average of 3 seizures/month or if there is a change in their seizure medication, the participant will be excluded at that time. Due to variability in seizure frequency, the baseline seizure monitoring period may be extended up to an additional 4 weeks.

Baseline and Follow-up EEG, MRI, and TMS with EEG Assessments (2 visits at each time point – 6 total visits):

Once the participant is fully screened, they will come to BIDMC to be set up with a 24 hour ambulatory EEG. If the participant has not completed a clinical MRI within the past 3 years then they will also complete a structural magnetic resonance imaging (MRI) scan. A second study visit will include the TMS with EEG testing (details provided below in “Procedures”). If a participant screens out of being TMS eligible, the participant will still be included and this visit will not occur. These assessments will be repeated 21 and 56 days (+/- 5 days) after the Botox injection. Neuro QOL questionnaires will be completed at baseline, 56 weeks after Botox and the final visit.

Daily reporting of seizure related events using the seizuretracker app. (150 days)

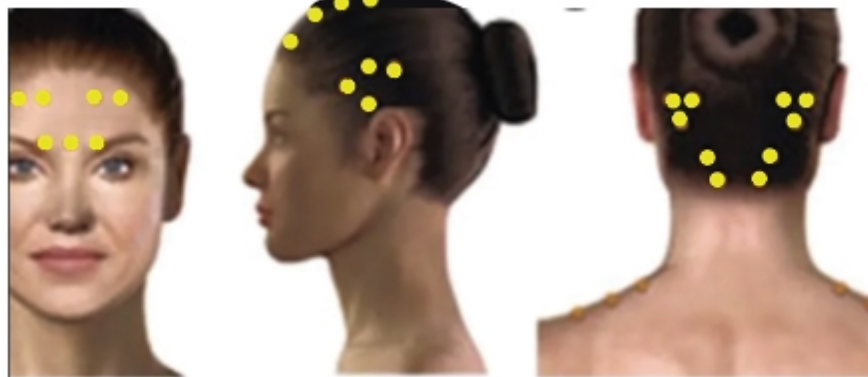
1. Screening potential candidates in-person 2. Presenting study details to participants and their families 3. Recruitment 4. Informed consent 5. Completing the Neuro-QOL questionnaire (baseline values) 6. Education on the requirement to fill correctly the online daily seizure diary	Day 0: (in-person Visit 1)
24 hours ambulatory EEG recording (defined as pre-treatment baseline EEG and EEG-TMS-EMG)	Day 45 (in-person Visit 2) EEG #1
Injecting 145 Units of BOTOX per FDA-approved protocol (and Standard-of-Care) for the treatment of chronic migraine in adolescents.	Day 60: (in-person Visit 3) BOTOX INJECTIONS
24 hours ambulatory EEG recording (defined as early-phase treatment EEG and EEG-TMS-EMG) Completing the Neuro-QOL questionnaire (post-treatment values)	Day 81: (in-person Visit 4) EEG #2
24 hours ambulatory EEG recording (defined as late-phase treatment EEG and EEG-TMS-EMG)	Day 116: (in-person Visit 5) EEG #3
Completing the Neuro-QOL questionnaire (post-treatment values) Study summary with subjects and their families	Day 150: (in-person Visit 6)

PROCEDURES

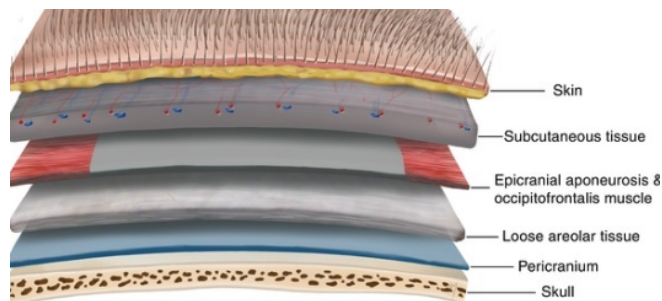
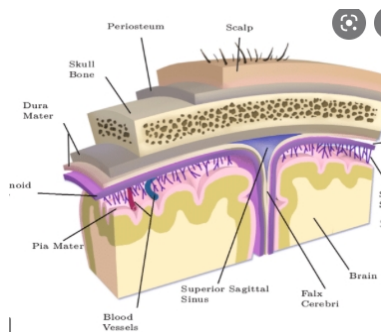
-Botulinum A toxin injection: Will follow the FDA-approved guideline of the treatment of chronic migraine. The following modifications are planned: (a) Total units 145 instead of 155. (b) Number of injection sites 29 instead of 31. (c) the 6 injection sites in the trapezius muscle will be eliminated as they are irrelevant to our attempt to reduce seizure events. Instead, 4 injections will be made subcutaneously along the superior sagittal suture (see figures below), where no muscles exist and thus no muscle weakness is likely. This dose (145 Units) is well below the FDA-approved guideline on safety for adolescents and adults (no more than 10 Units/Kg or a total of 340 Units).

Botox injections will take place in Shapiro 8 on the East campus of BIDMC and in the BIDMC Headache Clinic which is a part of the Arnold Pain center at 1 Brookline Place. Injections will be administered by Dr. Sait Ashina, the Director of the Headache Clinic.

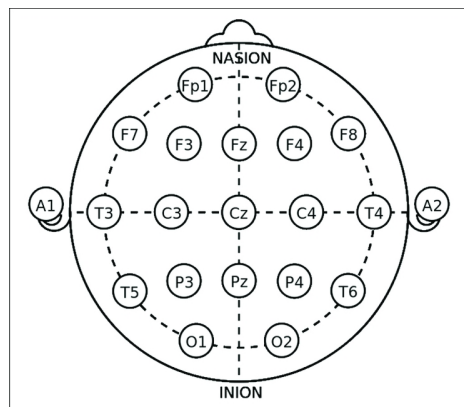
29 injection sites



Gross anatomy of the human calvaria (left) and the key layers of the scalp (right). The 4 injections along the superior sagittal suture will be placed in the subcutaneously.



EEG: 24-hour ambulatory EEG with 10-20 international system of electrode placement will be obtained at three time points: (1) 1-4 weeks prior to BOTOX injections, (2) 21 days/3 weeks (+/- 5 days) after BOTOX injections, (3) 56 days/8-weeks (+/- 5 days) after BOTOX injection.



10-20 International system of electrode placement

From the EEG, the following metrics will be obtained:

- Average interictal spike count based on 5-minute epochs once per hour evenly distributed throughout the recording. For each 1-hour epoch, spike count = number of spikes/300 seconds.
- Spectral analysis and power in conventional frequency bands (delta, theta, alpha, beta and gamma), in the global EEG and in the quadrant containing the seizure focus

MRI Scan

All MRI imaging will be conducted at the Beth Israel Deaconess Center Medical (East campus) on BIDMC's 3T GE MR750 MRI Scanner. Scans will be without contrast and will consist of T1 MPRAGE, GRE, FLAIR, Coronal T2/STIR, DTI and resting state scans. Scan. The time for these scans is approximately 60 minutes

The subject will be brought into the scanner room and instructed to lie down on a foam-padded table that can slide into the scanner. Subjects will be handed the emergency button which they can squeeze at any point during the procedure to inform the investigators if they have a question, are feeling uncomfortable, or are in distress. The subject's head will be carefully positioned, and foam-padded cushions will be placed on either side of their head in order to prevent movement during the scanning session. The subject will receive earplugs to wear during the entire scanning session in order to minimize the noise of the scanning machine. Due to physical limitations of the MRI scanner, participants whose abdomen, shoulder, or hip circumference is greater than 180cm may not be able to get an MRI.

The MRI done in this study is for research purposes only. It will not be read by a radiologist. If there are incidental findings noted on the MRI, the subject will be notified and advised to see their primary care provider for a diagnostic MRI.

Participants who have undergone equivalent MRI procedures within the past 3 years may not need to repeat these measures if such data are available.

TMS:

TMS-derived metrics will be obtained at the same three time points as EEG: (1) 1-4 weeks prior to BOTOX injections, (2) 21 days/3 weeks (+/- 5 days) after BOTOX injections, (3) 56 days/8-weeks (+/- 5 days) after BOTOX injection. TMS is a safe, non-invasive method of focal cortical stimulation used to measure the cortical excitation/inhibition (E:I) ratio. A magnetic field is generated by a powerful extracranial magnet that induces intracranial electrical currents over the focal region of stimulation. When coupled with surface EMG electrodes (TMS-EMG), output resultant from stimulation over the motor cortex can be measured as a motor evoked potential (MEP) from a target muscle (most often the abductor pollicis brevis, APB).

All TMS-EMG-EEG sessions will be identical. Subjects will be set up in a chair with an EEG cap and with EMG electrodes placed on both hands for collection of MEPs during stimulation over the bilateral motor cortices (M1). The EEG cap and electromyography (EMG) electrodes will remain in place throughout the TMS session. The session will include resting-state EEG measurements; determination of motor threshold and input-output curve, cortical silent period, single pulse and paired pulse TMS-EEG in up to 8 brain regions (left and right frontal lobes, left and right motor cortex, left and right parietal lobes, and left and right occipital lobes). Each subject will undergo sham stimulation to control for nonspecific effects, such as the auditory evoked potential. The total time of the session will be approximately 4-5 hours.

- Resting State EEG and artifact recording:
EEG recordings will be obtained with the eyes open for five minutes and then eyes closed for five minutes. Subjects will be asked to briefly move their eyes, clench their jaws, and tense their foreheads so that the EEG artifacts associated with these movements can be recorded and similar artifacts removed from the remaining EEG recordings.
- Assessment of motor hotspot and resting motor threshold:
Resting motor threshold (RMT) will be determined by applying single pulses to M1 and will be defined as the minimum stimulus intensity that produces a motor evoked potential (MEP), measured by EMG, of at least 50 μ V in the hand muscles in at least 5 of 10 trials. Determination of RMT will be used to guide intensity to be used for the visit.
- Single pulse TMS-EEG
Cortical hypersynchrony will be assessed by applying single pulses of TMS to the identified brain regions at an intensity of up to 135%-140% of RMT.
- Paired Pulse TMS
Long-interval intracortical inhibition (LICI - GABA-B mediated inhibition) paired-pulse TMS protocol may be administered as follows: 2 pulses at 120% RMT administered 100-300 ms apart; up to 100 pairs of pulses applied up to once every 4 seconds.

Relevant to our proposal, antiepileptic target engagement is detected by these measures such that successful antiepileptic therapy resulting in seizure freedom corresponds to a decline in cortical excitability and/or increase in cortical inhibition (Badawy et al 2013, Badawy et al 2010).

Seizure Tracking:

All subjects and families will utilize a digital seizure diary (seizuretracker.com), but with the option to use paper diaries instead if they prefer. Proficiency in seizure diary maintenance will be confirmed by study staff during the screening period. Study staff may call the participant to remind them to complete their diary entries and/or to re-educate the participant regarding maintaining the diary. Seizure documentation (frequency, severity, gross description) will be maintained for 8 weeks before and 12 weeks after BOTOX injections.

If participants choose to use the digital seizure diary, they will be asked to share their information with the study team via the Valet system, by printing reports from SeizureTracker or by visually and verbally (via phone call check-ins) sharing the information that they have documented in their diary, just as they would if they choose to keep a paper diary. It is not possible to download data from the Valet system – the study team will write down and/or direct enter into REDCap the details that the participant shares regarding their diary. Of note, is that SeizureTracker is a very common App that patients with epilepsy routinely use and are familiar with. Participants who choose to join seizuretracker to maintain their diary for the study will be advised to not utilize the Alexa feature and will be instructed to carefully review the features that they can opt out of along with the Terms and Conditions for users. There are participants who may already use seizuretracker prior to engaging in the study, therefore, they will already have made their personal choices regarding use of the program. Lastly, participants will have the option of continuing or closing their account at the end of the study.

Study staff will check the seizure diary weekly to make note of frequency as compared to baseline. If a participant has an increase in seizure frequency at or above 100% from baseline over 4 weeks, the study MD will review the seizure tracking and diary, talk with the participant and, per the clinician judgement, may refer the participant to their provider for follow-up. The 4 week time frame is to account for a patient population that has frequent seizures and can experience clusters of seizures and/or can have stressful conditions/triggers that may temporarily increase seizure frequency. In addition, the

study team (including the study MD/epileptologist) will review the seizure frequency/diary of all post-Botox injection participants on a weekly basis to identify if a participant is trending in this direction so that the study MD can make a judgement if there is a clinical concern/need to further review the participant's status at any point.

Neuro-QOL:

Participants will be asked to complete components of the standardized Neuro Quality of Life assessment, a self-report tool used to measure health related quality of life in a wide range of neurologic disorders. Participants are asked to score their responses to prompts on a scale of 1-5. The following components will be used in this study (copies of the scales are attached): Ability to Participate in Social Roles, Anxiety, Depression, Emotional and Behavioral Dyscontrol, Fatigue, Positive Affect and Well-Being, Stigma, Satisfaction with Social Roles and Activities, and Cognitive Function.

Incidental Findings:

It is possible that a seizure could be captured in the 24 hour EEG. If a seizure is detected, this will be reported to the individual and shared with their provider. The EEG recording will be made available to the provider as needed (e.g. if the captured seizure is of clinical relevance to the care of the participant)

B. Statistical Considerations**a. Sample Size Justification:**

Seizure reduction of 30-45% is a common finding in recent pivotal trials that have led to FDA clearance of drugs and neurostimulation devices for the treatment of epilepsy (Ben-Menachem et al 1994, Fisher et al 2010, Glauser et al 2008, Morrell & Group 2011). Based on these studies, an estimated 100-200 participants will be required to identify this degree of seizure reduction. Sample size of a pilot study should be at least 10% of the sample size projected for the larger study (Connelly 2008). Therefore, a sample size of 25 participants will be sufficient to detect seizure reduction of 35% for the present open-label pilot study. This approach was validated in a recent study involving Dr. Shafi (Kaye et al 2021).

b. Data Analysis:**PRIMARY ENDPOINTS:**

- Reduction in incidence of generalized seizures
- Reduction in incidence of focal seizures with impaired awareness

SECONDARY ENDPOINTS:

- Reduction in overall seizure frequency
- Reduction in net cortical excitability metrics
- Improvement in quality-of-life metrics

Seizure frequency will be averaged per time blocks as follows: (1) baseline, 8 weeks before botulinum A toxin injection, (2) 0-4 weeks after BOTOX injections, and (3) 5-12 weeks after BOTOX injection. Means will then be compared by one-way repeated measures ANOVA.

Spike count at 3 weeks and 8 weeks after BOTOX injection will be normalized to baseline recordings per subject -- normalized values at these time points will then be compared by paired t-test.

TMS metrics of rMT, CSP, LICI, and TMS-EEG excitability metrics will each be averaged over at least 20 trials per subject per time block (at baseline, and 3 weeks and 8 weeks after BOTOX injections). Per metric mean values will then be compared by one-way repeated measures ANOVA.

Blended Neuro-QOL scores will be averaged at baseline, and at the 8-12 week after BOTOX injection period, and compared by paired t-test.

C. Subject Selection

Patients with focal drug-resistant epilepsy (see inclusion and exclusion criteria).

Potential study subjects will be provided an informed consent form (ICF) to review. Those who are interested in participating will provide informed consent and then be screened for eligibility (inclusion/exclusion criteria). Individuals screened as potential study subjects must meet all the following inclusion criteria and none of the following exclusion criteria.

Inclusion criteria:

- Age: 18-85 years, inclusive
- Sex: Males and females
- Pharmacologic-resistant focal epilepsy with >3 seizures a month

Exclusion criteria:

- Cranial or scalp surgery within 3 months of recruitment
- Change in antiepileptic medication <2 months before recruitment
- History of status epilepticus within 12 months of recruitment
- History of psychogenic nonepileptic seizures
- History of poor medication compliance
- Any unstable medical condition
- Any psychiatric disorder that could interfere with trial participation
- Substance use disorders within the past six months
- Pregnancy, breastfeeding, or planning a pregnancy during the trial; unable or unwilling to use a reliable form of contraception during the trial - All individuals of childbearing potential will undergo urine pregnancy testing
- TMS exclusion only (If a participant does not meet TMS criteria, they will not be excluded from the study/the TMS assessments will not be completed):
 - Intracranial metal implants (excluding dental fillings) or devices such as pacemaker, medication pump, nerve stimulator, TENS unit, ventriculo-peritoneal shunt unless cleared by the responsible covering TMS MD.
 - Any intracranial lesions or prior brain surgeries other than minor procedures as reviewed and approved by the TMS MD (e.g. history of brain biopsy, depth electrodes, ICP monitoring, intraventricular and subdural drains...)

Exclusion criteria for Botox

- History of botulinum A toxin injection within 3 months of recruitment
- Allergy to botulinum toxin
- Any medical condition that might put participants at increased risk if exposed to onabotulinumtoxinA (e.g. neuromuscular diseases such as myasthenia gravis, Eaton-Lambert)

Syndrome, amyotrophic lateral sclerosis)

- History of hemiplegic and basilar- type migraine
- Fibromyalgia
- Use of opioids as acute pain medication
- Skin problems, infections, profound atrophy, or excessive weakness in the target areas of the injection sites
- Concurrent chronic use or chronic use in the 3 months prior to the screening period of muscle relaxants

B4. POSSIBLE BENEFITS

This is a proof-of-concept study to test the feasibility of Botox for treatment of focal epilepsy. The tests and procedures from this study may help develop a viable treatment option with patients with focal epilepsy refractory to conventional treatments available.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

Risk of Botox:

The following risks have been reported for Botox with same dose and insertion points during the migraine treatment trials:

- double vision
- dizziness
- fatigue
- numbness
- allergic reaction
- flu like symptoms
- local infection
- local bleeding
- transient headache or neck pain,
- minor temporary drop of eyelid or eye brow
- post treatment discomfort, swelling, redness, and bruising

Regarding risk of seizure, we are submitting the following information:

In Allergan analysis of BOTOX double blind studies, they have not seen a signal of increased risk in the BOTOX treated groups with exception to pediatric patients where the reports in children were

predominantly from cerebral palsy patients treated for upper limb spasticity (see Table 22 from the Package Insert).

Importantly, it must be noted that the risk for seizure was found when the dose was **6 Units/Kg** but not with **3 Units/Kg**. For your information, we are proposing to use **1.8 Units/Kg** in our study. That is a huge point that negates the risk of seizure.

Table 22: Adverse Reactions Reported by $\geq 2\%$ of BOTOX 6 Units/kg Treated Patients and More Frequent than in Placebo-Treated Patients in Pediatric Upper Limb Spasticity Double-Blind, Placebo-Controlled Clinical Trial (Study 1)

Adverse Reactions	BOTOX 6 Units/kg (N=77) %	BOTOX 3 Units/kg (N=78) %	Placebo (N=79) %
Infections and infestations			
Upper respiratory tract infection*	17	10	9
General disorders and administration site conditions			
Injection site pain	4	3	1
Gastrointestinal disorders			
Nausea	4	0	0
Constipation	3	0	1
Respiratory, thoracic and mediastinal disorders			
Rhinorrhea	4	0	1
Nasal congestion	3	0	1
Nervous system disorders			
Seizure**	5	1	0

*Includes upper respiratory tract infection and viral upper respiratory tract infection

**Includes seizure and partial seizure

Also, this risk was not seen in the analysis of the lower limb cerebral palsy population, including at the higher doses of 8 Units/Kg (see Table 23 in the PI).

Table 23: Adverse Reactions Reported by $\geq 2\%$ of BOTOX 8 Units/kg Treated Patients and More Frequent than in Placebo-Treated Patients in Pediatric Lower Limb Spasticity Double-Blind, Placebo-Controlled Clinical Trial (Study 2)

Adverse Reactions	BOTOX 8 Units/kg (N=128) %	BOTOX 4 Units/kg (N=126) %	Placebo (N=128) %
General disorders and administration site conditions			
Injection site erythema	2	0	0
Injection site pain	2	2	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	2	0	1
Injury, poisoning and procedural complications			
Ligament sprain	2	1	0
Skin abrasion	2	0	0
Metabolism and nutrition disorders			
Decreased appetite	2	0	0

Allergan medical analysis of this data **did not support a conclusion of a causal relationship between seizures and the use of Botox**. Their conclusion was that none of the reported seizure events was considered treatment-related.

This information should be considered when defining the overall risk level.

Breach of confidentiality:

- as we are collecting PHI, there is a risk of breach of confidentiality.

Risks of TMS:

More Common Side Effects:

- Up to 20%-40% of subjects undergoing TMS experience headaches or neck pain, which are believed to be due to muscle tension. All prior cases of headaches induced by TMS have promptly resolved on their own or with an over-the-counter painkiller (e.g., acetaminophen, ibuprofen, or aspirin). In some cases, TMS may cause tenderness or muscle discomfort at or around the site of stimulation.
- Redness: Participants may have some redness on their head from elastic band that they may wear during the TMS sessions. This redness is temporary.

Rare Side Effects:

- Seizures: TMS may sometimes cause a seizure. This is rare and occurs in 0.4-1.5% of participants with epilepsy. A seizure may be thought of as a convulsion where a person's body shakes. Many seizures are not like this. Some have very mild symptoms. Experiencing a seizure caused by TMS does not mean that participants will have another seizure. Participants who had seizures from TMS have not had any continued seizure related health problems. In individuals with a known history of seizures, the occurrence of a seizure temporally proximate to TMS is uncommon; the overall rate of any seizure associated with single- and paired-pulse TMS in those with known epilepsy less than 2%, and less than 3% in patients tapered off AEDs prior to TMS; almost all seizures were identical to those typically experienced by the individual, making it unclear whether seizures were causally related to the TMS or not (Schrader et al, 2004). Indeed, a paper published from this center reported a seizure during TMS of a patient with epilepsy; the seizure onset zone was from the patient's typical ictal onset region, and distinct from the site of stimulation (Vernet et al, 2012). No instances of status epilepticus have ever been reported in association with TMS. Finally, several studies have actually looked at the use of TMS as a potential therapeutic option in those with medically uncontrolled epilepsy, and several have found that TMS helped to reduce seizures. Our own group has significant experience with conducting TMS studies in patients with a known history of epilepsy.
- TMS produces a loud clicking sound when a current is passed through the stimulation coil. This loud click can result in ringing in the ear and temporary shifts in the ability to determine the pitch and loudness of sounds, if no protection is used. In order to prevent this possible side effect, we will ask participants to wear earplugs or in-ear headphones that block the noise of the TMS. Animal and human studies have shown that earplugs can effectively prevent the risk of hearing disturbance due to TMS. The forms of TMS that we will use in this study have never caused hearing problems.
- Syncope can occur due to anxiety and psychophysical discomfort during testing and treatment with TMS. This is reported less than seizure activity, but the true number may be higher due to under-reporting. Subjects will be monitored for feeling any signs or symptoms of a pending syncopal event (i.e., feeling dizzy or lightheaded). If these symptoms occur, TMS will immediately be stopped and the subject will be assisted.

Risk of Electromyography (EMG):

- The sticky pads used for the test may cause skin irritation

EEG

- There are no known serious risks associated with EEG, nor does the combination of TMS and EEG appear to confer an increased risk of harm. Subjects may rarely experience scalp irritation from the electrode placement, but this is almost universally transient (lasting only a day or two).

MRI

MRI is a painless and safe technique that can be used to investigate brain structure and functioning. Participants will be screened for MRI exclusionary criteria. We will follow all the guidelines and recommendations endorsed by the National Advisory Mental Health Council (NAMHC) Workgroup on MRI Research Practices that was convened on September 14, 2005.

There are no known or foreseeable risks or side effects associated with conventional MRI procedures except to those people who have electrically, magnetically or mechanically activated implants (such as cardiac pacemakers) or to those who have clips on blood vessels in their brain. Participants will therefore be screened very carefully to exclude the possibility that they have any such devices and/or implants and will be excluded from participation in the event that they do. There are no known additional risks associated with functional MRI. Both the conventional and the functional MRI systems have been approved by the FDA and will be operated within the standards reviewed and accepted by the FDA.

A magnetic resonance scan might be uncomfortable if participants are a) prone to claustrophobia (fear of enclosed spaces); b) do not like to lie still for a period of time, or c) do not like banging or beeping sounds. The researcher will explain the procedure and if a potential participant expresses any doubt about a), b), or c), he/she will not be included in the study. In normal operation, some subjects could also experience warmth or heating. This should not be uncomfortable. With any radiofrequency (RF) coil, there is a risk of skin burns if the coil is used improperly. When very high-speed methods are used for imaging, some people experience a mild twitching sensation.

Fast imaging has been done for several years and no serious side effects have been encountered. At scan speeds much higher than those that are capable with our scanner it is possible to induce irregular heartbeats. However, the system operates well below the threshold of potential ill effects in the heart. All participants will be told that they can notify the researcher in charge of the scan if they feel uncomfortable, and ask to be taken out of the scanner at any stage. Participants will wear earplugs to reduce scanner noise and will be able to contact the investigator at any time during the scan via a squeeze ball and intercom system. Due to physical limitations of the MRI scanner, for safety reasons, participants whose abdomen, shoulder, or hip circumference is greater than 180cm may not be able to undergo the MRI. This could make participants feel uncomfortable.

Minimizing risks:

- This protocol will utilize the FDA approved dose of BOTOX and insertion points for treatment of migraine headache.
- We will utilize HIPAA secure databases, REDCap and secure office for data storage.
- Safety precautions are in place for the TMS portion of the study, including stimulation protocols well within guidelines for TMS safety. All TMS sessions will be conducted by staff trained in the safe and efficient administration of TMS, and with an on-call neurologist on-site.

Data Safety Monitoring Plan

The PI will have the responsibility for continually monitoring all aspects of the study, including adverse events, and for their reporting according to the local IRB/Committee on Clinical Investigations (CCI) guidelines and according to the DSMB Charter.

Data and Safety Monitoring Board (DSMB)

The study will be monitored by a DSMB. A group of three independent experts with relevant expertise who

are independent from any professional or financial conflict of interest with this research project and investigators will be designated for the DSMB. This group will be responsible for reviewing study data for data integrity; participant safety; study conduct and progress; and providing directives regarding study continuations, modifications, and terminations. Please refer to Part P and the DSMB charter for further details.

Adverse Event Monitoring

Adverse effects will be collected for the duration of study participation. All adverse events, regardless of attribution to BOTOX, MRI, or TMS/EEG, will be collected and recorded using standard adverse event forms. Participants will be asked, in an open-ended way, about the presence of any such events. TMS-related adverse effects will be collected after every TMS session. Intensity of each adverse event will be graded as mild, moderate or severe. Events will be medically evaluated as appropriate, including testing and referral.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

Dr. Shafi and his team will identify patients with refractory epilepsy under his care who are interested in hearing more about the study. In addition, the research team will email the Epilepsy Attendings to introduce the study and inquire about patients that may be eligible. The study will also be presented to the Epilepsy Division at the Epilepsy Research Meeting, which introduces new studies that are enrolling to inform providers of eligibility criteria. BIDMC patients may also be recruited using a review of clinic schedules or by ICD-10 codes for epilepsy via Clinical Query 2 using the CQ2 Data Download Tool to identify potential participants. Additionally, the InSIGHT (Integration of Standard Information Gathered using Healthcare Technology) Core service at BIDMC may be used in combination with CQ2 to further filter out potential eligible subjects. Medical records will be reviewed of the identified patients to assess for study eligibility. Patients of other neurologists will be contacted once their provider has confirmed that they are appropriate for the study. Potential participants will be contacted by the research team initially via mail. If they are interested in participating, they are provided contact information for a member of the research team. The participant can opt out of being contacted about the study by contacting a member of the research team as described in the letter. If the research team does not receive an opt out message from the subject, a member of the research team will call potential subjects approximately two weeks after the initial mailed letter to follow up. Potential subjects will be contacted a maximum of three times. Clinicians caring for patients with refractory epilepsy will introduce the concept of this study to these outpatients and/or inpatients appointments and ask if they are interested in learning more about participation. If they wish to learn more, an investigator or coordinator will either meet with them onsite, or arrangements will be made for the coordinator to call to arrange for a recruitment appointment.

Consent

Potential research subjects will be consented in a private space either before the screening visit in Dr. Shafi's clinic or on the day of their Screening Visit in the Center for Noninvasive Brain Stimulation. The study will be explained by the primary investigator, or by another one of the qualified investigators and the Study Coordinator. Detailed information relating to the study drug and study procedures, along with information about the risks and benefits of participating in any research study and in this specific study, will be provided to the participant. It is possible that consent will be completed remotely to best accommodate the participant. If the consent process is conducted remotely, it will be completed via an IRB approved method (e.g. REDCap). If electronic consent is obtained via REDCap, a hard copy of the

consent will be printed from REDCap and retained in the subject binder. If electronic consent is obtained via a video-conferencing platform (e.g. Microsoft Teams), a wet signature will be obtained remotely and then the signed ICF will be scanned and sent via email or mailed to study staff. The consenting process will be documented on a consent checklist, subjects will be given a copy of the signed informed consent form, and notes will be recorded about the consent discussion. Only licensed MDs will obtain consent.

Subject Protection

There will be no coercion or undue influence placed on patients. They will be informed of the study and given the freedom to participate or not, and this will not influence any care provided to them.

B7. STUDY LOCATION

Privacy

Conversations with potential study subjects will be done in a private clinic room in the Epilepsy clinic at 330 Brookline Ave or in a private lab the Center for Noninvasive Brain Stimulation. Conversations over the phone will be done in offices within the hospital so that sensitive information cannot be overheard by anyone other than study staff.

Physical Setting

The study will be performed in standard patient rooms in the BIDMC epilepsy clinic, the Center for Noninvasive Brain Stimulation, the Ansin 3 MRI Research Scanner room, and the William Arnold – Carol A. Warfield, MD Pain Center. All locations provide protection against study subjects being witnessed and conversations overheard by anyone other than study staff.

B8. DATA SECURITY

We will store data in a password-protected directory on a secure server behind the BIDMC firewall and/or REDCap. All paper records will be stored in a locked room that will be accessed only by members of the study team. Only the study team will have access to identifiable information.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☐ Yes ☐ No

Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☐ No

Not applicable

B10 Dissemination of Research Results

Subjects will be thanked for their participation at the completion of their study and follow-up procedures. Publications will be printed in publicly available journals.

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