Study Title: Focal Electrically-Administered Seizure Therapy (FEAST): Studies at two enrolling sites to further test and refine the treatment

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FDA INVESTIGATIONAL DEVICE EXEMPTION APPLICATION

DEVICE: MECTA Spectrum 5000Q FEAST Device

Study Title: Focal Electrically-Administered Seizure Therapy (FEAST): Studies at two enrolling sites to further test and refine the treatment

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Table of Contents

Focal Electrically-Administered Seizure Therapy (FEAST): Studies at two enrolling sites to further test and refine the treatment

I. INTRODUCTORY STATEMENT

This open label investigation further evaluates the safety, efficacy and potential mechanisms of action of a new form of electroconvulsive therapy (ECT). Both the efficacy and adverse cognitive effects of ECT are highly contingent on the intracerebral current paths and current density of the ECT stimulus (1993, Sackeim et al., 2000b, Sackeim, 2004a, McCall et al., 2000, Sackeim et al., 2008). However, the impedance of the skull and individual differences in skull anatomy severely limit the spatial targeting of stimulation, and create marked individual differences in intracerebral current density (Weaver et al., 1976, Sackeim et al., 1994, Deng et al., 2009, Peterchev et al., 2010). To address these problems, we have been exploring various means of overcoming this limitation. One approach is to induce the seizure using magnetic fields [magnetic seizure therapy (MST)] (Sackeim, 1994b, Lisanby et al., 2001b, Lisanby et al., 2003a, Lisanby et al., 2001c, Luber et al., 2013, Kayser et al., 2013, Hoy et al., 2013, Fitzgerald et al., 2013). MST uses high power repetitive magnetic stimulation to induce sufficient current flow in brain to elicit self-sustaining seizures. MST must overcome technological barriers as the energy transfer from current in a coil to that induced in brain is inefficient, and it is not clear that a form of MST will be developed that is sufficiently powerful to match the efficacy of ECT.

An alternate approach is to modify the electrical stimulus to induce focal seizures. The most common methods of ECT administration in the US use a bidirectional, constant current, brief or ultrabrief pulse, with large (approximately 3 sq. in. surface area) and identically sized and shaped electrodes. In contrast, in this protocol we have coupled unidirectional current flow with an electrode geometry involving a small and large electrode that differ by more than 5:1 in surface area.

Unidirectional currents were widely used in ECT during the 1940's and 1950's and continue to be used in European and American devices today (Alexander, 1955, Epstein and Wender, 1956, Friedman, 1949, Friedman, 1942, Hovorka et al., 1960, Impastato et al., 1951, Pacella, 1952, Rappa and Tanowitz, 1959). Indeed, a unidirectional current option is incorporated in the US marketed Thymatron System IV (Somatics Corp.). Transcranial electrical stimulation can be made focal by

stimulating with an anode-cathode arrangement (unidirectional stimulation), with the electrodes differing in surface area (Amassian et al., 1990, Stewart et al., 1990, Cracco et al., 1989, Amassian et al., 1989a, Amassian et al., 1989b). We have shown in nonhuman primates the capacity to produce focal frontal seizure induction under conditions when a unidirectional current flows from a small anterior anode (placed on the forehead over the nasion) to a large posterior cathode just anterior to the motor strip (Spellman et al., 2009). Furthermore, many of these seizures in primates did not result in motor convulsions. We tested this new stimulation method in 4 nonhuman primates, who on several occasions had seizure threshold titrated with current either flowing from the small anterior electrode to the large posterior electrode or the reverse (Spellman et al., 2009). In 7 of 7 tests, EEG seizures were evoked at low stimulus intensity and most did not result in motor convulsion. The seizure threshold in the instances of an electrographic seizure without motor convulsion was at the first step in the titration schedule, with only 3 mC being administered. For each animal, seizure threshold with typical ECT parameters is substantially higher. These findings were remarkable and demonstrated that this method can produce focal frontal seizures, which we have hypothesized as key to therapeutic mechanisms (Sackeim et al., 1983; Sackeim, 1999, (Nobler et al., 1994, Sackeim et al., 1996). Furthermore, it appears that seizure threshold may be reduced with this approach (Sackeim, 2004a).

We have recently completed preliminary open-label studies with FEAST, first at Columbia University, and then at the Medical University of South Carolina in Charleston (Nahas et al., 2013b). We have published the outcomes of the first 17 patients studied. One patient withdrew from the study after a single titration session. After the course of FEAST (median 10 sessions), there was a 46.1 $\pm$ 35.5% improvement in Hamilton Rating Scale for Depression (HRSD24) scores compared to baseline (33.1 $\pm$ 6.8, 16.8 $\pm$ 10.9; $P < 0.0001$). Eight of 16 patients met response criteria ($\geq$50% decrease in HRSD24) and 5/16 met remission criteria (HRSD24$\leq$10). Patients achieved full re-orientation (4 of 5 items correct) in 5.5 $\pm$ 6.4 min (median time = 3.6 min), timed from when their eyes first opened after treatment. We have now studied 18 more patients (see results below), and we are completing the study in the original IDE with another two more patients still to enroll.

This work allowed us to refine the treatment. For example, we selectively modified the electrode geometry to decrease interelectrode resistance. Additionally we

modified the titration schedule, now only administering a standard 800 ma ultrabrief pulse, and thus no longer titrating in the current domain.

II. Study Objectives

This study will provide preliminary evaluation of the following:

1. Further characterization of the efficacy of FEAST and the safety of the treatment.
    a. The primary efficacy measure will be the 24-item Hamilton Rating Scale for Depression. The changes in these scores from before to immediately following the treatment course will be compared in patients treated with the FEAST methodology and matched to nonrandomized patients at our facilities who were treated with conventional ECT methods (ultrabrief right unilateral [RUL] ECT).
    b. Acute and subacute cognitive side effects following FEAST will be assessed with a brief neuropsychological battery. The primary acute measures will be the time to return of orientation following seizure induction. The primary subacute measures will be assessment of retrograde amnesia for autobiographical information. The neuropsychological measures will be compared in the patients treated with the FEAST methodology (under this IDE) and matched (but nonrandomized) patients who are treated with conventional ECT methods (also covered under this IDE).
    c. Safety will also be determined by examining the number and frequency of serious adverse advents and adverse events.
2. Characterization of the focal nature of the seizure onset with FEAST and RUL ECT. We will use two main methods to address the issue of focality.
    a. Resting state fMRI before and after a course of FEAST (or conventional RUL ECT). We will address whether FEAST causes changes in hyper connected prefrontal cortical subcortical networks, and whether such an effect is more restricted to prefrontal cortex with FEAST relative to conventional RUL ECT.
    b. Peri-ictal EEG acquired immediately before, during and immediately after the FEAST seizure. We will acquire this in all patients at all treatment sessions. Again, for comparison, we will use identical EEG acquisition methods in patients treated with conventional RUL ECT.

Section IV.B.17 describes the statistical plan for addressing these objectives.

III. Report of Prior Investigations

A. Experience of the Investigators

The original applicant, Dr. Sackeim, remains a key co-investigator on this proposal that is now transferred from NYSPI, Columbia University to the Institute of Psychiatry at MUSC. Dr. Sackeim been engaged since 1979 in research using ECT devices produced by the MECTA Corporation. The applicant has over 250 publications in the area of ECT and over 425 total publications. Representative efficacy and safety findings from the major studies over this period are reported in the following:

- Lisanby, S.H., Maddox, J.H., Prudic, J., Devanand, D.P., & Sackeim, H.A. (2000). The effects of electroconvulsive therapy on memory of autobiographical and public events. *Archives of General Psychiatry, 57*, 581-590.
- McElhiney, M.C., Moody, B.J., Steif, B.L., Prudic, J., Devanand, D.P., Nobler, M.S., & Sackeim, H.A. (1995). Autobiographical memory and mood: Effects of electroconvulsive therapy. *Neuropsychology, 9*, 501-517.
- Sackeim HA (2004): The convulsant and anticonvulsant properties of electroconvulsive therapy: towards a focal form of brain stimulation. *Clinical Neuroscience Review* 4:39-57.
- Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ, McElhiney MC, Coleman EA, Settembrino JM (1993): Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *N Engle J Med* 328:839-46.
- Sackeim HA, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, Fitzsimons L, Moody BJ, Clark J (2000): A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry* 57:425-34.
- Sackeim, H.A. (1986). Acute cognitive side effects of ECT. *Psychopharm Bull, 22*, 482-484.
- Sackeim, H.A., Decina, P., Kanzler, M., Kerr, B., & Malitz, S. (1987a). Effects of electrode placement on the efficacy of titrated, low-dose ECT. *American Journal of Psychiatry, 144*, 1449-1455.

- Sackeim, H.A., Portnoy, S., Neeley, P., Steif, B.L., Decina, P., & Malitz, S. (1986). Cognitive consequences of low-dosage electroconvulsive therapy. *Annals of the New York Academy of Sciences, 462*, 326-340.
- Sobin, C., Sackeim, H.A., Prudic, J., Devanand, D.P., Moody, B.J., & McElhiney, M.C. (1995). Predictors of retrograde amnesia following ECT. *American Journal of Psychiatry, 152*, 995-1001.

These publications support the efficacy of ECT and the MECTA Corporation devices in particular. The most recent publications (Sackeim et al., 2000, Sackeim et al. 2008) used the MECTA Spectrum 5000Q, which is the device modified for this protocol. Earlier publications reported studies using the MECTA Model D and the MECTA SR-1. However, across these studies, fundamental characteristics of the electrical stimulus were kept constant throughout, including use of a bidirectional, constant current, brief pulse stimulus, with amplitude of 800 mA. This work has consistently yielded short-term remission rates on the order of 60-80% for the most effective forms of ECT. This work has also demonstrated that efficacy and cognitive side effects are determined by the current paths of the ECT stimulus (electrode placement) and current density, especially when assessed in terms of dosage relative to threshold.

Contributions made by the original applicant and his collaborators to advancing the practice and understand of ECT include:

(a) Invention of stimulus dose titration (Sackeim et al., 1987d), widely considered the most precise and optimal method for determining electrical dosing in ECT (American Psychiatric Association, 2001);

(b) Establishing the safety of repeated subconvulsive stimulation as used in the titration technique (Prudic et al., 1994);

(c) Establishing the correlates of seizure threshold, including gender, age, and electrode positioning effects and relations to dynamic impedance and EEG seizure manifestations (Sackeim et al., 1987d, Sackeim et al., 1987c, Sackeim et al., 1991);

(d) Describing the physical properties of the ECT electrical stimulus and introducing the use of charge as the preferred summary dosage unit (Sackeim, 1994b, Sackeim et al., 1994, Weiner et al., 1987);

(e) Demonstrating in a set of randomized, double-blind trials that both the efficacy and cognitive effects of ECT are sensitive to electrical dosage, often in relation electrode placement, thereby overturning fundamental views about ECT's mechanisms of action and offering new methods to optimize treatment administration (Sackeim et al., 1987b, Sackeim et al., 1993, Sackeim et al., 2000b, Sackeim, 2004a);

(f) Demonstrating that ultrabrief stimuli are considerably more efficient that the traditional brief pulse stimulus used in ECT and result in marked cognitive savings relative to standard ECT techniques (Sackeim, 2004a);

(g) Describing the effects of ECT on brain electrical (EEG) activity and on regional Cerebral Blood flow and Cerebral Metabolic rate and demonstrating that specific alterations in anatomically distinct areas are associated with the therapeutic and amnestic effects of the treatment (Nobler et al., 1993, Nobler et al., 1994, Sackeim et al., 1996, Nobler et al., 1999, Nobler et al., 2000b, Luber et al., 2000, Nobler et al., 2000a, Perera et al., 2004, Sackeim and Mukherjee, 1986, Sackeim et al., 2000a);

(h) Development of new cognitive procedures and characterization of ECT's acute, short-term and long-term cognitive effects (McElhiney et al., 1995, Sobin et al., 1995b, McElhiney et al., 1997, Steif et al., 1986, Prudic et al., 1999, Sackeim et al., 1986, Devanand et al., 1991, Sackeim, 1992, Sackeim et al., 1993, Lisanby et al., 2000, Sackeim, 2000, Sackeim et al., 2007, Sackeim, 2014b);

(i) Developing the methods now widely used to assess medication resistance (Antidepressant Treatment History Form) and determining its predictive value with respect to ECT immediate clinical outcome and relapse following remission (Sackeim et al., 1990a, Sackeim et al., 1990b, Prudic et al., 1990, Prudic et al., 1996, Sackeim et al., 2000b, Sackeim et al., 2001a);

(j) Characterization of relapse rates in naturalistic studies both in research and community samples and investigation of optimal continuation pharmacotherapy following ECT, using placebo-controlled, randomized, double-blind designs (Sackeim et al., 1990b, Sackeim et al., 2000b, Sackeim et al., 2001a, Prudic et al., 2004a, Prudic et al., 2013);

(k) Introducing and evaluating novel theories regarding the mechanisms of ECT's antidepressant and adverse cognitive effects (Sackeim et al., 1983b, Devanand et al., 1995b, Sackeim, 1999, Nobler et al., 2001, Sackeim, 2004a);

(l) Providing the first modern placebo-controlled evidence of the impact of antidepressant pharmacotherapy on the efficacy of ECT in major depression (Sackeim et al., 2009)

(n) Introducing new methods of treatment administration with the aim of reducing ECT's adverse cognitive effects, including the use of dose titration, the use of ultra-brief electrical stimulation, reliance on high dosage right unilateral (RUL) ECT instead of BL ECT, use of a magnetic stimulus to elicit seizures (Magnetic Seizure Therapy, MST), and the topic of this IDE, the use of focal electrically-administered seizure therapy (FEAST) (Lisanby et al., 2003c, Lisanby et al., 2003b, Lisanby et al., 2003a, Sackeim, 1994b, Lisanby et al., 2001c, Lisanby et al., 2001b, Sackeim, 2004a, Sackeim et al., 2008, Sackeim et al., 1993, Sackeim et al., 2000b, Nahas et al., 2013a).

The MUSC team including Dr. Mark George and Dr. Baron Short, also has substantial experience in brain stimulation therapies and clinical research on treatment-resistant depression. Dr. Short is the Brain Stimulation Service director. Dr Mark George is a world-expert in brain stimulation research and the Editor-in-Chief of the journal, *Brain Stimulation*. He is credited with early development of both transcranial magnetic stimulation (George, 2002, George et al., 2010, George et al., 1999, George et al., 1997, O'Reardon et al., 2007) and vagus nerve stimulation (George et al., 2002, George et al., 2005a, George et al., 2005b, Rush et al., 2005) for treatment-resistant depression.

The GRU team consists of Dr. Vaughn McCall and Dr. Peter Rosenquist. Both are highly experienced clinicians in the field of ECT, with an aggregate of >20,000 ECT sessions. Both have participated in the design and execution of influential multi-center studies examining the acute efficacy of ECT and the prevention of relapse following ECGT termination (Sackeim et al., 2009, Prudic et al., 2013). Dr. McCall has led the field of ECT in examining the effects of the treatment on functional outcomes, specifically quality of life (McCall et al., 2006, McCall et al., 2001, McCall et al., 2013, McCall et al., 2011a, Rosenquist et al., 2006). He and Dr. Rosenquist have also made seminal contributions to identification of optimal forms of ECT (McCall et al., 1995, McCall et al., 2002, McCall et al., 2000, McCall et al., 1993), and the characteristics and significance of the ictal EEG (Krystal et al., 1996a, Krystal et al., 1996b, Krystal et al., 1993, McCall et al., 1996a, McCall et al., 1996b, McCall et al., 1998, Rosenquist et al., 1998). Dr. McCall is the editor-in-chief of the *Journal of ECT*.

This extensive experience of the teams in carrying out seminal work that has shaped this field lends confidence that this study will be carried out in a highly professional manner, both protecting the welfare of patient participants and yielding information that may be critical in devising and testing a new treatment, FEAST, that will have a superior risk/benefit ratio relative to traditional ECT.

B. Efficacy of ECT

B.1 Short-term Clinical Outcome

ECT is widely considered the most effective, short-term treatment for major depression. Its effectiveness in this disorder has been the subject of many reviews (American Psychiatric Association, 2001, Crowe, 1984, Sackeim et al., 1995, Abrams, 2002, Royal College of Psychiatrists, 1995, Sackeim, 1989, Salzman et al., 2002) and formal meta-analyses (Janicak et al., 1985, Parker et al., 1992, NICE, 2003, Kho et al., 2003, Pagnin et al., 2004). Each of these evaluations concluded that ECT exerts substantial short-term therapeutic effects in the treatment of major depression, with the conclusion also commonly reached that no other treatment has demonstrated short-term therapeutic effects that exceed those of ECT.

Especially important are the putative effects of ECT on mortality. Large samples are necessary to detect any effect on mortality rates, and this issue has mainly been examined in naturalistic studies, often using retrospective comparisons [see Prudic and Sackeim (1999) for a critical review]. Post (1972) suggested that, prior to the introduction of ECT, elderly patients with depression often manifested a chronic course or died of intercurrent medical illnesses in psychiatric institutions. A number of studies contrasted the clinical outcomes of depressed patients who received inadequate or no biological treatment to those of patients who received ECT. While none of this work used prospective, random assignment designs, most studies indicated that ECT resulted in decreased chronicity and morbidity, and decreased rates of mortality (Avery and Winokur, 1976, Babigian and Guttmacher, 1984, Black et al., 1989, Philibert et al., 1995, Wesner and Winokur, 1989). In much of this work, the advantages of ECT were particularly pronounced in elderly patients. For example, in a recent retrospective comparison of elderly depressed patients treated with ECT or pharmacotherapy, Philibert et al. (1995) found that rates of mortality and significant depressive symptomatology were higher in the pharmacotherapy group at long-term follow-up. Prudic and Sackeim (1999) noted that all but one study (Black et al., 1989) found a reduction in long-term mortality rates in patients treated with ECT. There is little

evidence that ECT has long-term impact on suicide (Milstein et al., 1986, Sharma, 1999). Rather, the putative benefit appears to be reduced morality due to natural causes (e.g., cardiovascular illness), and the mechanisms mediating such an effect are unknown.

With the introduction of the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), a series of random assignment trials were conducted in depressed patients. ECT was used as the "gold-standard" by which to benchmark the efficacy of these new medications. Three of these early studies involved random assignment and blinded ratings, and each found a significant therapeutic advantage for ECT over TCAs and placebo (Greenblatt et al., 1962, Greenblatt et al., 1964, Medical Research Council, 1965, Gangadhar et al., 1982). Other studies also reported ECT to be as or more effective than TCAs (Bruce et al., 1960, Kristiansen, 1961, Norris and Clancy, 1961, Robin and Harris, 1962, Stanley and Fleming, 1962, Fahy et al., 1963, Hutchinson and Smedberg, 1963, Wilson et al., 1963, McDonald et al., 1966, Davidson et al., 1978) or MAOIs (King, 1959, Kiloh et al., 1960, Stanley and Fleming, 1962, Hutchinson and Smedberg, 1963, Davidson et al., 1978). In a meta-analysis of this work, Janicak et al. (1985) reported an average response rate to ECT that was 20% higher than that of TCAs and 45% higher than MAOIs.

It should be noted that standards for adequate pharmacological treatment have changed over the decades (Quitkin, 1985, Sackeim et al., 1990a, Sackeim, 2001), and that, by current criteria, few of these early comparative trials used aggressive pharmacotherapy in terms of dosage and/or duration (Rifkin, 1988). In addition, these studies usually focused on depressed patients who were receiving their first biological treatment during the index episode. In a small study, Dinan and Barry (1989) randomized patients who did not respond to monotherapy with a TCA to treatment with ECT or the combination of a TCA and lithium carbonate. The ECT and the pharmacotherapy groups had equivalent efficacy, but the TCA/lithium combination may have had an advantage in terms of speed of response.

Only one study has contrasted the efficacy of ECT with one of the newer selective serotonin reuptake inhibitors. Folkerts et al. (1997) studied 39 patients with major depression and with at least two adequate failed antidepressant trials (mean = 4.9 trials). These patients were randomized to either paroxetine (n=18) or right unilateral (RUL) ECT (n=21). At the end of treatment, there was a reduction in the HAMD score of 59% for the ECT group and of 29% for the paroxetine group ($P<0.001$). In the ECT group, 71% of subjects met response criteria (at least a 50% decrease in total HAMD

score). The authors concluded that ECT was superior to paroxetine in medication-resistant major depression, both in terms of degree and speed of response. However, no other study has used a randomized design to compare the efficacy of ECT with newer antidepressant medications, including other SSRIs or medications such as buproprion, duloxetine, mirtazapine, nefazodone, venlafaxine, or the combination of an antidepressant and an atypical antipsychotic. However, no trial of any type has ever found an antidepressant medication regimen to be more effective than ECT.

Among patients who are receiving ECT as a first-line treatment, or who have received inadequate pharmacotherapy during the index episode due to intolerance, response rates continue to be reported in the range of 80-90% (Sackeim et al., 1990b, Prudic et al., 1990, Prudic et al., 1996, Sackeim et al., 2000b, O'Connor et al., 2001, Petrides et al., 2001, Kellner et al., 2010). Among patients who have not responded to one or more adequate antidepressant trials, the response rate is still substantial, in the range of 50-60% (Sackeim et al., 2000b, Sackeim et al., 1990a, Prudic et al., 1990, Prudic et al., 1996). A recent meta-analysis confirmed that clinical outcome is significantly poorer in medication-resistant patients compared to patients who did not receive an adequate medication trial in the current episode prior to ECT (Heijnen et al., 2010)

The time to achieve full symptomatic improvement with antidepressant medications is typically estimated as 4 to 6 weeks (Quitkin et al., 1984, Quitkin et al., 1996). This delay until response may be longer in older patients (Salzman et al., 2002). In contrast, the average ECT course for major depression consists of 8-9 treatments (Sackeim et al., 1993; Prudic et al., 1996). Thus, when ECT is administered at a schedule of three treatments per week, the usual schedule in the US, full symptomatic improvement typically occurs more rapidly than with pharmacological treatment (Sackeim et al., 1995, Nobler et al., 1997b).

ECT is a highly structured treatment, involving a complex, repeatedly administered procedure that is accompanied by high expectations of therapeutic success, and involves an extensive consent process and period of patient education. Such conditions may augment placebo effects. Given this concern, a set of double-blind, random assignment trials were conducted in England during the late 1970's and 1980's that contrasted 'real' ECT with 'sham' ECT — the repeated administration of anesthesia alone. With one exception (Lambourn and Gill, 1978), real ECT was found consistently to be more efficacious than sham treatment (Freeman et al. 1978; Johnstone et al. 1980; West 1981; Brandon et al. 1984; Gregory et al. 1985; see Sackeim 1989 for a

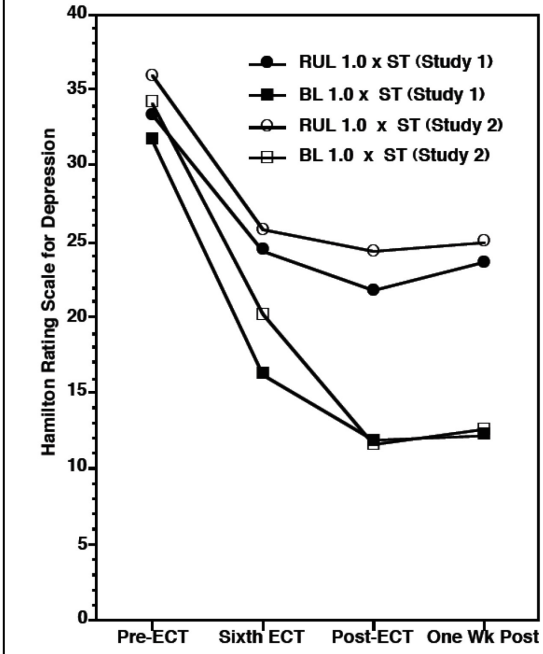


Figure 1. Serial HRSD scores for groups treated with either low dosage (1 x ST) RUL or BL ECT in Sackeim et al. (1987a) [Study 1] and Sackeim et al. (1993b) [Study 2]. Note the strong replication of the effects

review). Lambourn and Gill (1978) had used a form of real ECT, involving low stimulus intensity and right unilateral electrode placement, that is now known to be ineffective (Sackeim et al., 1987b, Sackeim et al., 1993, Sackeim et al., 2000b).

Overall, the real vs. sham ECT studies demonstrated that the passage of an electrical stimulus and/or the elicitation of a generalized seizure were necessary for ECT to exert antidepressant effects. Following the randomized acute treatment period, the patients who participated in these studies were free to receive other forms of acute or continuation treatment, including ECT. Consequently, information regarding the duration of symptomatic improvement with real versus sham treatment could not be obtained in this research.

Finally, there have been a host of studies in the treatment of major depression that have contrasted variations in ECT technique, manipulating factors such as stimulus waveform, electrode placement, and stimulus dosage. An important practical observation that emerged was that the efficacy of ECT is equivalent regardless of the use of sine wave or brief pulse stimulation, but that sine wave stimulation results in more severe cognitive impairments (Carney et al., 1976-, Weiner et al., 1986, Scott et al., 1992, Prudic et al., 2004a, Sackeim et al., 2007). More critical in establishing the efficacy of ECT was the series of demonstrations that the clinical outcome with ECT is dependent on electrode placement and stimulus dosage (Sackeim et al., 1987b, Sackeim et al., 1987c, Sackeim et al., 1993, Sackeim et al., 2000b, Sackeim, 2004a, McCall et al., 2000, Sackeim et al., 2008). These factors can dramatically impact on the efficacy of the treatment, with widely varying response and remission rates. For example, the low dosage right unilateral ECT condition in the study by Sackeim et al. (1993b) resulted in 17% final response rate compared to about 70% for the other 3 conditions. As illustrated in Figure 1, this effect was highly replicable. In this figure, the changes in HRSD scores over time are presented for the low dose RUL and

bilateral (BL) ECT conditions in the 1987a and 1993b studies by Sackeim et al. The values per condition are virtually identical across the studies. Augmenting the dosage of RUL ECT substantially enhances efficacy (McCall et al., 2000). Furthermore, it has recently been shown that the efficacy of BL ECT can also be comprised by coupling ultrabrief (0.3 ms) stimulation with a dose only 2.5 times above seizure threshold (Sackeim et al., 2008).

This work went beyond sham-controlled studies and provided powerful demonstrations of the intrinsic efficacy of ECT. In this set of studies, patients were randomized to alternative ECT conditions under strict double-masked conditions. The forms of ECT that differed markedly in outcome all involved general anesthesia, electrical stimulation of the brain, and production of a generalized seizure, using conservative criteria for seizure adequacy. This work established by technical factors in ECT administration — the form or intensity of stimulation and anatomic positioning of electrodes — strongly influence efficacy.

Finally, another source of evidence is often overlooked. Patients form their own impressions regarding the treatments that have helped them the most or least. These subjective evaluations, while likely influenced by a variety of factors, are especially critical since they may impact on willingness to receive treatments in the future. Parker et al. (Parker et al., 1999) had 27 Australasian psychiatrists interview 341 non-psychotic depressed patients who rated the extent to which previous antidepressant treatments had been effective. ECT (both bilateral and unilateral) was judged as highly effective by both melancholic and non-melancholic patients. Antipsychotic medication similarly rated highly (but was judged as more effective by the non-melancholic than melancholic patients). TCAs and irreversible MAOIs were rated as more effective by the whole sample than several newer antidepressant classes (including SSRIs, venlafaxine, mianserin and moclobemide), whether effectiveness was examined dimensionally or categorically. Comparison of the overall tricyclic and SSRI classes indicated that any superior tricyclic effectiveness was specific to the melancholic patients. In short, using this methodology, some drug classes showed specificity to the presence or absence of melancholia. In contrast, regardless of this distinction, patients rated ECT as most effective. In general, patient self-evaluation of the effects of ECT on depressive symptoms closely mirrors that of trained observers (Berman et al., 2008, Sayer et al., 1993)

B.2 Persistence of Benefit and Relapse

ECT is the only treatment in psychiatry that is usually stopped once it is found effective. This presents a dilemma in that it is known that without continuation treatment virtually all patients will relapse after achieving remission with ECT. For example, in the only modern placebo-controlled trial of continuation pharmacotherapy following ECT, Sackeim et al. (2001a) reported that 84% of patients randomized to placebo relapsed within 6 months of remitting with ECT.

The literature on the persistence of benefit following ECT and the efficacy of alternative somatic continuations treatments (physical and pharmacological) in preventing postECT relapse were reviewed by Sackeim (1994a) and Bourgon (2000). A variety of studies have provided controlled or naturalistic data on relapse (Sackeim et al., 1993, Shapira et al., 1995, Lauritzen et al., 1996, Flint, 1997, Flint and Rifat, 1997, Stoudemire, 1997, Lauritzen et al., 1997, Stoudemire et al., 1998, Sackeim et al., 2000b, Doraiswamy and Scates, 2001, Grunhaus et al., 2001, Fox, 2001, Dannon et al., 2002, Flint and Gagnon, 2002, Andrade and Kurinji, 2002, Russell et al., 2003, Prudic et al., 2004a, Birkenhager et al., 2004, Little et al., 2004, Sackeim et al., 1990b, Lemstra et al., 1996, Brakemeier et al., 2014, Prudic et al., 2013, Kellner et al., 2006, Nordenskjold et al., 2011, Navarro et al., 2008, Youssef and McCall, 2014).

It appears that in community practice, relapse rates are substantial following remission with ECT. Prudic et al. (2004) followed 347 patients with a depressive mood disorder who received ECT at 7 hospitals in the NYC metropolitan area. In this cohort, up to 70% of patients classified as remitters following ECT relapsed during the 6-month follow-up period. While relapse was common, typically patients who relapsed did not return to the same level of symptomatology as at the start of ECT, showing some residual gains. While relapse rates vary considerably from study-to-study, it is a fair estimate that 50-70% of patients treated in an unstructured manner in community settings while show substantial deterioration in the first six months following ECT. A similar, thought slightly less dire, conclusion was derived from a recent meta-analysis of studies of relapse following ECT (Jelovac et al., 2013).

There appear to be two main factors that impact on the likelihood of relapse in the postECT period: the medication-resistant status of the patient and the form of continuation treatment used. Following the originally observation by Sackeim et al. (1990b), there have been several replications of the phenomenon that patients who have demonstrated clear cut medication resistance in the depressive episode prior to

receiving ECT are at heightened risk for postECT relapse (Sackeim et al., 1993, Sackeim et al., 2000b, Sackeim et al., 2001a, Shapira et al., 1995, Lauritzen et al., 1996). That medication resistance would have clinical significance as a relapse predictor is not surprising on two grounds. First, medication resistance appears to be a potent predictor of both difficulty in achieving response or remission regardless of the subsequent intervention [e.g., ECT: (Prudic et al., 1990, Prudic et al., 1996, Sackeim et al., 2000b, Heijnen et al., 2008) and VNS: (Sackeim et al., 2001b)]. Second, it has not been uncommon to use as continuation therapy the very same medication strategies that were ineffective in the acute treatment of the depressive episode (Benbow, 1992-1993, Sackeim, 1994a). There is no evidence that medications that were ineffective in treating the acute episode are useful as continuation treatments following ECT (Sackeim et al., 1990b).

There is evidence that the form of continuation treatment used can impact on relapse. In a placebo-controlled, randomized, double-blind trial, we reported relapse rates over 6 months postECT of 84%, 60% and 39% for placebo, monotherapy with nortriptyline, and combined nortriptyline-lithium treatment, respectively (Sackeim et al., 2001a). Similarly, in a naturalistic series followed for one year following ECT-induced remission, patients treated with combined TCA-lithium treatment had half the relapse (Sackeim et al., 2000b). Another approach is to use ECT itself as a form of continuation treatment, and, indeed, for some patients, this may be the only effective from of relapse prevention (Decina et al., 1987). However, there is very little information on optimal schedules of continuation ECT and cumulative effects on cognition. A recent, NIH-supported supported study randomized patients to nortriptyline-lithium following ECT and an aggressive from of continuation ECT. No difference was detected in relapse rates, despite large samples(Kellner et al., 2006). Thus, at present, this form of pharmacotherapy is likely optimal, and recent research has shown that the same benefit obtains with a regimen that may be better tolerated, i.e., venlafaxine-lithium (Prudic et al., 2013). There is also initial evidence that the combination of an antidepressant and a form of psychotherapy (CBT) may protect against relapse (Brakemeier et al., 2014). This issue represents a critical limitation of ECT since even with what might be considered optimal continuation treatment relapse rates are high, about 40-50% over the first 6 months following ECT-induced remission.

B.3 Predictors of Outcome and Indications for Use

There are several demographic and clinical features that show a statistical relationship to ECT short-term outcome [see (Nobler and Sackeim, 1996) for a review]. However,

none of these relationships show sufficient sensitivity and specificity to guide patient selection (American Psychiatric Association, 2001).

As indicated, patients with demonstrated medication-resistance tend to have a poorer outcome with ECT than those who come to the treatment without having failed an adequate medication trial (Sackeim et al., 1990a, Prudic et al., 1990, Prudic et al., 1996, Sackeim et al., 2000b) [see (van den Broek et al., 2004) for a negative study and (Heijnen et al., 2010) for a meta-analysis]. However, it is likely that the rates of response/remission seen with ECT in medication-resistant patients (e.g., 50-60%) exceed that of any other treatment alternative. Consequently, the leading indication for the use of ECT is, in fact, medication resistance (Prudic et al., 2004a, American Psychiatric Association, 2001).

Alternatively, a large percentage of patients are treated with ECT who have not received an "adequate" medication trial during the current episode. There are several reasons for this. First, a substantial percentage of patients treated with ECT have psychotic features, i.e., psychotic or delusional depression. Adequate pharmacotherapy in this subgroup requires combined treatment with an antidepressant and an antipsychotic medication (Spiker et al., 1985, Nelson and Bowers, 1978, Glassman and Roose, 1981, Sackeim, 2001). Prior to the widespread use of atypical antipsychotics, it was unusual for delusional patients to receive sufficient dosage for these combined trials to be considered adequate. For example, using the ATHF criteria for this condition, Mulsant et al. (1997) reported that only 4% of patients with psychotic depression treated at three different hospitals had an adequate medication trial prior to ECT. While this rate has gone up substantially in recent years due to better tolerability of some atypical antipsychotics, this rate was still only 25% in the psychotically-depressed patients represented in our recent study of ECT in community settings (Prudic et al., 2004a).

Besides issues of tolerability, there are other reasons for primary use of ECT (in the absence of prior medication failure in the current episode). These issues include a history of poor medication response and good ECT response in prior episodes, urgency for rapid remission due to psychiatric (suicidality) or medical (inanition) reasons, and patient preference. The American Psychiatric Association Task Force on ECT (APA, 2001) detailed the circumstances when ECT should be considered as a primary (first-line) treatment and when it should be reserved for patients with established medication resistance. These considerations will guide patient selection in this protocol and the rationale for use of FEAST will be documented.

A factor strongly related to medication resistance is episode duration. Patients with more chronic episodes (longer duration) tend to have poorer outcome with ECT (Nobler and Sackeim, 1996). When both medication resistance and episode duration are considered simultaneously they make independent statistical contributions to outcome prediction. Age also has shown consistent relations [see (Sackeim, 2004b) for a review]. Surprisingly, the majority of studies have found a positive association between advancing age and ECT outcome, one of the few instances in medicine where older patients have superior outcome. Due to problems of medication tolerance with advanced age and the toll of severe episodes of depression, ECT is particularly likely to be recommended in older individuals (Olfson et al., 1998, Thompson et al., 1994).

Patients with psychotic depression tend to have superior outcome with ECT than nonpsychotic patients (Petrides et al., 2001, Birkenhager et al., 2003), but this distinction is likely reflects the low level of medication resistance seen in psychotic depression (Prudic et al., 1990, Prudic et al., 1996). Otherwise, none of the phenomenological features of major depression show a consistent relationship, even at the statistical level, with ECT outcome. For example, severity of depressive symptoms, the presence of double-depression, or the presence (or absence) of melancholia do not have predictive value (Nobler and Sackeim, 1996, Prudic et al., 1993, Sackeim and Rush, 1995, Fink et al., 2007). There is some evidence that patients with borderline personality disorder may have poorer outcomes, especially in the long-term (DeBattista and Mueller, 2001, Feske et al., 2004, Flint and Hill-Johnes, 2008, Kramer, 1982, Ostergaard et al., 2014), but these effects are too weak to consider the presence of this disorder exclusionary. There are no biological tests that reliably predict ECT outcome (Scott, 1989, Nobler and Sackeim, 1996).

C. Adverse Effects of ECT

C.1 Mortality

Rates of mortality attributable to ECT are difficult to determine due to methodological issues intrinsic to studies of medical mortality, such as uncertainty as to cause of death, the time frame for linking death to ECT, and variability in reporting requirements. The mortality rate associated with ECT is thought to be about the same as that associated with minor surgery (McCabe, 1985, Badrinath et al., 1995, Warner et al., 1993, Jan et al., 2005, Schwandner et al., 2005, Yip et al., 2004) or childbirth (Salanave et al., 1999). Published estimates from large and diverse patient series over several decades report up to 4 deaths per 100,000

treatments (Heshe and Roeder, 1976, Fink, 1979, Babigian and Guttmacher, 1984, Crowe, 1984, Kramer, 1985, Abrams, 1997, Reid et al., 1998, Nuttall et al., 2004, Shiwach et al., 2001, Prudic and Sackeim, 1999, Ostergaard et al., 2014). Despite the frequent use of ECT in patients with significant medical complications (Zielinski et al., 1993) and in the elderly (Sackeim, 1998, Sackeim, 2004b), the mortality rate appears to have decreased in recent years.

A reasonable current estimate is that the rate of ECT-related mortality is 1 per 10,000 patients or 1 per 80,000 treatments (American Psychiatric Association, 2001). This rate may be higher in patients with severe medical conditions. The rate of significant morbidity and mortality is believed to be lower with ECT than with some types of antidepressant medication (e.g., TCAs) (Glassman et al., 1993, Roose et al., 1998a, Zielinski et al., 1993). There is also evidence from longitudinal follow-up studies that mortality rates following hospitalization are lower among depressed patients who received ECT than among patients who received other treatment modalities or no treatment (Avery and Winokur, 1976, Philibert et al., 1995), although there is also a negative report (Black et al., 1989).

Our FEAST research originated at Columbia University. Dr. Lothar Kalinowsky introduced ECT to the US at the Department of Biological Psychiatry, New York State Psychiatric Institute in September 1940. There has been no known death linked to ECT over this 75-year period at NYSPI. During a significant part of this time, NYSPI had a specialized unit for patients with serious cardiac illness and major depression. This unit, directed by Drs. Glassman and Roose, identified the cardiac effects of TCAs and SSRIs (Glassman et al., 1993, Roose et al., 1994, Roose et al., 1998b, Roose et al., 1981), and large numbers of medication intolerant and resistant patients with significant cardiac disease were referred to ECT with few complications (Zielinski et al., 1993).

C.2 Serious Medical Complications

When mortality occurs with ECT, it typically happens immediately following the seizure or during the postictal recovery period. Cardiovascular and pulmonary complications are the leading cause of death and of significant morbidity (Pitts, 1982, Burke et al., 1987, Welch and Drop, 1989, Zielinski et al., 1993, Rice et al., 1994, Rayburn, 1997, Nuttall et al., 2004). Despite the short-lived increases in cerebral blood flow and intracranial pressure, cerebrovascular complications are notably rare (Hsiao et al., 1987). Given that cardiac arrhythmias are common in the immediate

postictal period, the majority of which are benign and resolve spontaneously, it is important that ECG be monitored during and immediately following the procedure and that significant arrhythmias resolve before patients are taken to the recovery area. Furthermore, vital signs (pulse, systolic and diastolic pressure) should be stable before the patient leaves the recovery area. Patients with pre-existing cardiac illness are at greater risk for post-ECT cardiac complications (Prudic et al., 1987, Zielinski et al., 1993, Rice et al., 1994). Indeed, there is evidence that the type of pre-existing cardiac disease predicts the type of complication that may be encountered following ECT. For example, ventricular arrhythmias are more common in patients with pre-existing ventricular abnormalities than in patients with ischemic heart disease (Zielinski et al., 1993). There are hosts of treatments available to manage emergent cardiac complications and for prophylaxis (American Psychiatric Association, 2001, Saito, 2005, Saito et al., 2000).

Two other possible sources of morbidity are prolonged seizures (seizures lasting longer than 3 minutes) and status epilepticus (continuous seizure activity lasting longer than 30 minutes or longer or two or more seizures occurring without return of consciousness between seizure activity) (Engel, 1989, Epilepticus, 1993). While there are no firm data on the frequency of these events in patients receiving ECT, it is clear that they are very rare occurrences. Failure to terminate seizures within a period of 3 to 5 minutes may increase postictal confusion and amnesia. Inadequate oxygenation during prolonged seizures increases the risk of hypoxia and cerebral dysfunction, as well as cardiovascular complications. In animal studies, seizure activity that is sustained for periods exceeding 30-60 minutes is associated with an increased risk of structural brain damage and cardiovascular and cardiopulmonary complications, regardless of steps taken to maintain appropriate levels of blood gases (Meldrum et al., 1974, Meldrum, 1986, Post et al., 1984, Nevander et al., 1985, Siesjö et al., 1986, Ingvar, 1986, Devanand et al., 1994, Dwork et al., 2004).

Prolonged seizures and status epilepticus may be more likely in patients with pre-existing neurological disorders and those receiving medications or having medical conditions that lower seizure threshold or interfere with seizure termination. These include theophylline, even at therapeutic levels (Peters et al., 1984, Devanand et al., 1988a, Fink and Sackeim, 1998), pre-existing electrolyte imbalance (Finlayson et al., 1989), and the repeated induction of seizures within the same treatment session (i.e., multiple monitored ECT) (Strain and Bidder, 1971, Maletzky, 1981). The American Psychiatric Association Task Force on ECT (2001) discouraged the practice of

multiple monitored ECT, which involved eliciting as many as 6 seizures in the same session. With this practice, seizure duration increases with repeat seizures, probably reflecting dissipation of the inhibitory mechanisms responsible for seizure termination (Sackeim et al., 1983b, Sackeim et al., 1987c, Sackeim, 1999, Sackeim, 2004a), and increasing the potential for prolonged seizures or status epilepticus.

Nonconvulsive status epilepticus may also occur during the postictal or interictal period, with an abrupt onset of delirium, unresponsiveness, and/or agitation as distinguishing clinical features (Grogan et al., 1995, Parker et al., 2001). Cessation of EEG abnormalities and improved cognitive function following short-acting anticonvulsant treatment (e.g., intravenous lorazepam or diazepam) may prove diagnostic, and this condition may worsen with use of high potency antipsychotics (American Psychiatric Association, 2001).

The concern has been raised that the rate of seizure disorder is increased following the course of ECT (Assael et al., 1967, Devinsky and Duchowny, 1983). However, follow-up studies indicate that new onset of a seizure disorder following receipt of ECT is very rare and probably do not differ from population base rates (Blackwood et al., 1980, Small et al., 1981). Indeed, due to its pronounced anticonvulsant properties, ECT has been used with some frequency as a last resort treatment for patients with intractable seizure disorder (e.g., idiopathic generalized seizures) (Sackeim et al., 1983b, Griesemer et al., 1997) and patients in status epilepticus (Lisanby et al., 2001a, Kellner and Fink, 2009, Kamel et al., 2009).

Prolonged postictal apnea is a rare event that occurs primarily in patients who have slow metabolism of succinylcholine (Packman et al., 1978). Maintaining adequate oxygenation is critical in such instances, which invariably resolve spontaneously within 10 to 60 minutes. To establish etiology, it is helpful to obtain a dibucaine number assay or a pseudocholinesterase level before the next treatment. At subsequent treatments, either a very low dose of succinylcholine may be used or a non-depolarizing muscle relaxant, such as atracurium, may be substituted (Hickey et al., 1987, Hickey, 1987, Hicks, 1987, Stack et al., 1988, Kramer and Afrasiabi, 1991, Lui et al., 1993-, Corominas et al., 1989).

Another rare complication is the experience of being partially consciousness while paralyzed. This phenomenon is frightening and results from an insufficient dose of the anesthetic agent or an insufficient interval between administration of the

anesthetic and muscle relaxant. For this reason, it is preferable to establish onset of the anesthetic effect before administering the muscle relaxant. It is noteworthy that with the use of improved forms of ECT that result in rapid return of consciousness and orientation following seizure termination, such as administration of RUL ECT with an ultrabrief pulse width (<0.5 ms), the risk of such an event has increased, as patients awaken much more rapidly than in the past with clear consciousness. It is clear from our observations that FEAST shares the property of rapid reorientation. Anesthetic management will be carefully monitored, and especially if convulsive manifestations are absent or weak, reduced doses of succinylcholine will be used or an additional bolus of anesthetic may be administered to ensure unconsciousness throughout the period of respiratory paralysis. While such an event does not place the patient at medical risk, as they are being continuously ventilated, the psychological state is aversive, warranting consideration of such an event as a serious medical complication.

To a significant extent, medical adverse events can be anticipated. Patients with significant pre-existing cardiac illness, compromised pulmonary status, history of CNS insult, or other compromising medical conditions, and those with a prior history of serious complications following general anesthesia or ECT are especially likely to be at increased risk (American Psychiatric Association, 2001, Zielinski et al., 1993). The steps taken in this protocol to minimize risks are discussed in Section IV.C.

C.3 Systemic Side Effects

Headache is a common side effect of ECT, and is observed in as many as 45% of patients during and shortly following the postictal recovery period (Devanand et al., 1995a, Freeman and Kendel, 1980, Gomez, 1975, Sackeim et al., 1987e, Tubi et al., 1993, Weiner et al., 1994, Dinwiddie et al., 2009). However, the precise incidence of post-ECT headache is difficult to determine due to methodological issues. These include the high baseline (pre-ECT) occurrence in patients with depression, the potential effects of concurrent medication or medication withdrawal, and differences in headache assessment across studies. Post-ECT headache appears to be especially common in younger patients (Devanand et al., 1995a). It is not known whether pre-existing headache syndromes (e.g., migraine) increase the risk of post-ECT headache, but it is clear that ECT may exacerbate a previous headache condition (Weiner et al., 1994). The occurrence of post-ECT headache has not been found related to stimulus electrode placement (Fleminger et al., 1970, Sackeim et al., 1987e, Tubi et al., 1993, Devanand et al., 1995a), stimulus dosage (Devanand et al.,

1995a), or therapeutic response (Sackeim et al., 1987e, Devanand et al., 1995a). In most patients, the post-ECT headache is mild (Freeman and Kendel, 1980, Sackeim et al., 1987e), although some patients report severe pain associated with nausea and vomiting. Typically the headache is frontal in location with a throbbing character.

The etiology of post-ECT headache is uncertain. Its throbbing character suggests a similarity to vascular headache, and ECT may be associated with a temporary change in headache quality from muscle-contraction type to vascular type (Weiner et al., 1994, Weinstein, 1993). ECT upregulates 5-HT_2 receptors and 5-HT_2 receptor sensitization has been associated with development of vascular headache. Other suggested mechanisms include electrically-induced temporalis muscle spasm or the acute increase in blood pressure and cerebral blood flow (American Psychiatric Association, 2001, Abrams, 2002). It is also possible that nitrates used to control blood pressure during ECT contribute to post-ECT headache (Cleophas et al., 1996, Tassorelli et al., 1999).

Treatment of post-ECT headache is symptomatic. Typically, aspirin, acetaminophen, or non-steroidal anti-inflammatory drugs (NSAIDs) are highly effective, particularly if given promptly after the onset of pain (Hawken et al., 2001, Markowitz et al., 2001, Leung et al., 2003, Roth, 2004, Drew et al., 2005, Stead and Josephs, 2005). Sumatriptan, a serotonin $5HT_{1D}$ receptor agonist, has also been effective at doses of 6 mg subcutaneously (DeBattista and Mueller, 1995), 25-100 mg orally (Fantz et al., 1998) or 20 mg intranasally (Markowitz et al., 2001, White et al., 2006). Most patients also benefit from bed rest in a quiet, darkened environment.

Post-ECT headache may occur after any ECT treatment in a course, irrespective of its occurrence at any prior treatment. Patients who experience frequent post-ECT headache may benefit from prophylactic treatment, such as aspirin, acetaminophen, or NSAIDs (e.g., IV ketorolac) immediately after seizure induction, or immediately prior to the ECT treatment. In a patient with severe, resistant post-ECT headache, subcutaneous sumatriptan 6 mg given several minutes prior to ECT was found to provide effective prophylaxis (DeBattista and Mueller, 1995).

Some patients report general muscle soreness following ECT. These complaints are most common after the first treatment, and often are not reported subsequently. Muscle soreness due to strong fasciculations following administration of a depolarizing muscle relaxant (succinylcholine) can be reduced at subsequent

treatments by blocking the fasciculations with a nondepolarizing agent, such as a small dose of curare. Alternatively, muscle soreness due to excessively vigorous convulsive movements can be managed by increasing the dose of the muscle relaxant. In either case, muscle soreness can be treated symptomatically with analgesic agents, such as aspirin, acetaminophen, or NSAIDs.

The ECT stimulus results in direct stimulation of the pterygoid, masseter, and temporalis muscles. This action produces a clamping action of the jaw that is not attenuated by the muscle relaxant (Minneman, 1995). Firm pressure, ensuring closure of the teeth around the bite-block, may minimize jaw pain. Such pain can be treated with aspirin, acetaminophen, or NSAIDs.

This clamping action of the jaw as a direct result of the electrical stimulus is responsible for the occasional dental complications. The greatest force is exerted on the molars and, with rare exception, a bite block that is constructed to absorb this force over these teeth should be inserted prior to electrical stimulation. In most cases, dentures should be removed prior to the start of treatment and before the insertion of the bite block. A dental consultation is advisable in patients with poor dentition and especially teeth vulnerable to fracture or loss (Morris et al., 2002, Faber, 1983, McCall et al., 1992, Weiner and McCall, 1992).

Estimates of the prevalence of nausea following ECT vary from 1.4-23% of patients (Gomez, 1975, Sackeim et al., 1987e), but, as with headache, methodological issues make determination of the rate problematic. Nausea can occur secondary to headache or its treatment with narcotics. It may also occur as a side effect of anesthesia, withdrawal or institution of psychotropic medications, or through other mechanisms. When nausea accompanies headache, the primary treatment should focus on the relief of headache. Otherwise, post-ECT nausea is typically well controlled with dopamine-blocking agents, such as phenothiazine derivatives (e.g., prochlorperazine and others), butyrophenones (haloperidol, droperidol), trimethabenzamide, or metoclopramide (Cook et al., 2000). All of these agents have the potential to cause hypotension and motoric side effects, and may lower seizure threshold. If nausea does not respond to these treatments or if side effects are problematic, the serotonin $5HT_3$ receptor antagonists, ondansetron or dolasetron, may be useful alternatives. If nausea routinely follows the use of a particular anesthetic, an alternative anesthetic agent may be considered.

C.4 Psychiatric Complications

At one or more treatments, a minority of patients, perhaps on the order of 5%, develop a postictal delirium or excitement (Devanand et al., 1989, Sackeim et al., 1983a). This state is characterized by motor agitation, disorientation, and poor response to commands. For some patients, postictal delirium may occur at one or two treatments and never recur, or it may be manifested at all treatments. Recovery may take from 5 to 45 minutes, and patients are usually amnestic for the episode. Postictal delirium may result in physical injury if the patient thrashes against hard objects or injury to staff attempting to protect the patient. In addition, patients may dislodge the intravenous line, complicating management. Depending upon severity, postictal delirium may be managed supportively or pharmacologically. Pharmacological prophylaxis should be considered for patients who repeatedly manifest postictal delirium and usually involve administration of a rapidly acting benzodiazepine (midazolam, lorazepam) or administration of the anesthetic used in ECT (often at half the original dose). It has also been suggested that increasing the dose of succinylcholine can prevent postictal delirium (Swartz, 1990).There is no indication that methods of ECT administration (e.g., electrode placement, dosage, etc.) differ in likelihood of postictal delirium and this state is also commonly seen with emergence from general anesthesia outside the context of ECT.

All known antidepressant pharmacological treatments have the potential of producing a switch into hypomania or mania in patients presenting with depression or a mixed state. Such a switch may also occur with ECT (Devanand et al., 1988b, Andrade et al., 1988, Andrade et al., 1990, Angst et al., 1992, Devanand et al., 1992, Saatcioglu and Guduk, 2009). However, this phenomenon appears to be rare with ECT (Devanand et al., 1992), perhaps because ECT is one of the few treatments that is effective in both the treatment of depression and mania (Mukherjee et al., 1994, Mohan et al., 2009). When it is manifested, it almost invariably occurs in patients with bipolar disorder. In some patients, the severity of manic symptoms may worsen with further ECT treatments. In such cases, it is important to distinguish treatment emergent manic symptoms from delirium with euphoria (organic euphoria) (Devanand et al., 1988b). There are a number of phenomenological similarities between the two conditions. However, in delirium with euphoria, patients are typically confused and have pronounced memory disturbance. The confusion or disorientation should be continuously present and evident from the period immediately following the treatment. In contrast, hypomanic or manic symptomatology may occur in the context of a clear sensorium. In addition, states of delirium with euphoria are often characterized by a giddiness in mood or "carefree"

disposition, whereas the classical features of hypomania, racing thoughts, hypersexuality, irritability, etc., may be absent. In delirium with euphoria, resolution of the condition may be facilitated by increasing the time between treatments, decreasing the stimulus intensity, changing from bilateral to unilateral electrode placement, and switching to an ultrabrief pulse width.

Various approaches can be used in the context of emergent hypomania or mania. Some practitioners continue with ECT with the view that the treatment will address both residual depressive symptoms and the emergent hypomania. Others may follow the same strategy but add a mood stabilizer (other than lithium). Still others may stop ECT and observe the patient. Often with this strategy the hypomanic or manic symptoms resolve spontaneously and depressive symptoms may or may not return (American Psychiatric Association, 2001).

There is no evidence that ECT worsens depressive symptoms or results in an increase in suicidality or aggressivity in even a small number of patients. For example, in the recent large prospective study of ECT in community settings, Prudic et al. (2004) found that non-remitters to ECT (defined as HRSD > 10 after termination of the acute course) showed on average a 33% improvement in HRSD scores that was maintained over a period of 6 months. Critically, of the 347 patients evaluated before and after ECT, only 3 (0.9%) individuals had an increase in HRSD scores > 4 points, and one of these patients received only 2 ECT treatments and another only 4 treatments. Thus, worsening of depressive symptoms is extremely unlikely. While there is no evidence that ECT exerts long-term benefit in reducing suicide rates (Prudic and Sackeim, 1999), suicidality is one of the symptoms to show the most robust and earliest improvement (Prudic et al., 1989-, Kellner et al., 2005).

C.5 Objective Cognitive Side Effects

The cognitive side effects of ECT and its potential for relapse are the major factors limiting its use. The neuropsychological accompaniments and sequelae of ECT have been the subject of intense investigation since the 1940's (Janis, 1948, Janis and Astrachan, 1951, Zubin, 1948, Zubin and Barrera, 1941, Daniel and Crovitz, 1986, Daniel and Crovitz, 1983b, Daniel and Crovitz, 1983a, Daniel et al., 1985, Daniel et al., 1983, Daniel and Crovitz, 1982, Calev et al., 1991a, Calev et al., 1989, Calev et al., 1991b, Zervas et al., 1993, Lerer et al., 1995, Calev, 1994, Calev et al., 1995, Shapira et al., 1998, Frith et al., 1987, Frith et al., 1983, Lancaster et al., 1958, Kriss et al., 1978, Pratt et al., 1971, Warrington and Pratt, 1973, Cronholm and Ottoson, 1963, Mindus et al., 1975,

Cronholm and Ottosson, 1963b, Cronholm and Molander, 1957, Cronholm and Ottosson, 1963a, Cronholm and Ottosson, 1961, d'Elia, 1981, d'Elia et al., 1977, d'Elia et al., 1976, d'Elia and Raotma, 1977, d'Elia, 1976, d'Elia, 1970, Fromholt et al., 1973, Strömgren et al., 1976, Shimamura and Squire, 1987, Squire, 1986b, Weiner et al., 1986, Squire et al., 1984, Squire and Slater, 1983, Spanis and Squire, 1981, Cohen and Squire, 1981, Squire et al., 1981a, Squire et al., 1981b, Squire and Chace, 1975, Squire et al., 1976a, Squire and Cohen, 1979, Squire and Miller, 1974, Squire et al., 1976b, Squire and Slater, 1978, Squire et al., 1976c, Squire et al., 1978, Squire et al., 1979).

A particular focus of the ECT research at NYSPI has been better characterizing these cognitive adverse effects, determining their severity and persistence, and identifying the patient characteristics that predict vulnerability, and developing treatment techniques that can lead to their reduction, if not complete amelioration (Sackeim et al., 2000a, Sackeim, 1992, Sackeim et al., 1987c, Steif et al., 1986, Sackeim, 1986a, Sackeim et al., 1986, Sackeim et al., 1983c, Devanand et al., 1991, Sackeim et al., 1992a, Sackeim et al., 1991, Sackeim et al., 1992b, Prudic et al., 1994, McElhiney et al., 1995, Perera et al., 2004, Sackeim, 2004a, Moscrip et al., 2005, Sobin et al., 1995b, Coleman et al., 1996, Prudic et al., 1999, Sackeim, 2000, Sackeim et al., 1993, Lisanby et al., 2000, McCall et al., 2000, Sackeim et al., 2000b, Sackeim et al., 2007, Sackeim et al., 2008, Berman et al., 2008, Sackeim et al., 2009, Sackeim, 2014b, Sackeim, 2014c).

There are four central features to the cognitive side effects of ECT (Sackeim, 1992). First, both *the nature and severity of cognitive alterations change rapidly with time since the last treatment*. The most severe cognitive side effects and the broadest range of impairment are observed in the immediate postictal period. Following seizure induction, patients experience a variable period of disorientation, with impairments in attention, language, praxis, and memory (Sackeim, 1986a). Indeed, the most profound deficits are seen as soon as patients can be evaluated with the return of spontaneous respiration and the capacity to respond to oral command. At this time, as with recovery from spontaneous seizures (Trimble and Thompson, 1986), soft neurological signs may be evident and there may be gross disturbance in attention and language abilities, in concert with clouded consciousness (Kriss et al., 1978, Kriss et al., 1980, Pratt and Warrington, 1972, Warrington and Pratt, 1973). Within minutes, neurological signs remit and there is dramatic improvement in orientation. Indeed, it is common in the immediate postictal period to observe patients progressively "return to the present," stating that they are far younger than their true age, speaking perhaps only their first language, and steadily "aging" over

a period of minutes, as if a deep, temporally graded retrograde amnesia was rapidly lifting (Daniel and Crovitz, 1982, Daniel et al., 1987, Sobin et al., 1995b).

This pattern pertains generally to the cognitive sequelae of ECT, which differ in their rates of recovery (e.g., anterograde vs. retrograde amnesia) (Squire and Miller, 1974, Squire and Chace, 1975, Squire, 1975, Squire et al., 1981b, Sackeim, 1992). Consequently, the magnitude of deficits observed during the course of ECT will be a function, in part, of the time of assessment relative to the last treatment, the number of treatments received, and the temporal dynamics of the cognitive function, as well as individual difference factors (Daniel and Crovitz, 1983b, Daniel and Crovitz, 1983a, Lerer et al., 1995, Squire and Zola-Morgan, 1985). In general, when treatments are applied that result in more profound cognitive deficits, such as sine wave stimulation and/or the use of the bilateral electrode placement, recovery may be incomplete by the next treatment. In such a circumstance, a pattern of progressive deterioration can be documented, with neuropsychological functioning deteriorating over the treatment course (Daniel and Crovitz, 1982, Daniel and Crovitz, 1983b, Daniel and Crovitz, 1983a). In the most extreme cases, the period of disorientation will become longer following each treatment and a continuous delirium can be produced (Summers et al., 1979, Miller et al., 1986). In contrast, when "softer" forms of ECT are applied the opposite can occur. For example, the period of disorientation in the postictal period is progressively briefer when low dosage, RUL ECT is applied (Sackeim et al., 1986). The reasons given for this counterintuitive phenomenon are that the combination of low dosage and RUL electrode placement minimizes untoward effects on orientation recovery and, critically, under these conditions, seizure duration has a significant association with time to orientation recovery (Sackeim et al., 1987c). Seizures are progressively shorter in duration over the course of ECT, reflecting one of ECT's anticonvulsant properties (Sackeim, 1999). This same progressive improvement in speed of orientation recovery has been especially marked with the use of RUL ECT and ultra-brief pulse width stimulation, even though dosage was substantially suprathreshold in order to preserve efficacy (Sackeim, 2004a, Sackeim et al., 2008).

The second general feature is that *the methods used in ECT administration profoundly impact on the nature and magnitude of cognitive deficits*. For example, to use the example described above, ECT treatment technique is a major determinant of the percentage of patients that develop delirium, characterized by continuous disorientation (Miller et al., 1986, Daniel and Crovitz, 1986, Sackeim et al., 1986, Sackeim et al., 1993, Sackeim et al., 2000b, Sackeim, 2004a). In general,

bilateral electrode placement, sine wave stimulation, high electrical dosage relative to seizure threshold, use of a wide pulse width, closely spaced treatments, larger numbers of treatments, and high dosage of barbiturate anesthetic agents are each independently associated with more intense cognitive side effects compared to right unilateral electrode placement, brief pulse waveform, lower electrical intensity, use of an ultrabrief pulse width, more widely spaced treatments, fewer treatments, and lower dosage of barbiturate anesthesia (Miller et al., 1985, Sackeim et al., 1986, Sackeim et al., 1993, Sackeim et al., 2000b, Sackeim, 2004a, Weiner et al., 1986, Lerer et al., 1995, Shapira et al., 2000, McElhiney et al., 1995, Sackeim et al., 1992a, Lancaster et al., 1958, Squire and Zouzounis, 1986, Sackeim et al., 2007, Sackeim et al., 2008, Sackeim et al., 2009, Sackeim, 2014b). Optimization of these parameters minimizes short-term cognitive side effects and likely reduces the magnitude of long-term changes (Sobin et al., 1995b, Sackeim, 2014b, Sackeim et al., 2007).

Scores of controlled, small sample studies have documented the effects of treatment parameters on the short-term cognitive effects of ECT [see (Sackeim, 1992) for a review]. In contrast, the follow-up period has rarely been longer than 2 months and the sample sizes have most often been too small to detect persistent deficits. Indeed, there has been only one modern large scale, prospective study of the nature and long-term persistence of ECT's cognitive effects. Prudic et al. (Prudic et al., 2004a) followed 347 patients treated with ECT at 7 different hospitals in the NYC metropolitan area. The sample was administered a neuropsychological battery at preECT baseline, following the acute ECT treatment course (mean=4 days postECT), and, again, 6 months later. The 7 hospitals differed in a host of cognitive outcome measures at the postECT time point and in Mini-Mental State Exam scores (a measure of global cognitive status) and retrograde amnesia scores (for autobiographical information) at the six-month time point (Sackeim et al., 2007). At both time points the differences among the hospitals in cognitive outcomes was fully attributable to differences in treatment technique. In particular, the use of sine wave stimulation resulted in a marked deficit on reaction time tasks, with this deficit persistent at 6 months for 2 of 3 measures. The use of bilateral ECT was associated with greater retrograde amnesia at both time points (relative to right unilateral ECT), and this effect was linearly related to the number of bilateral ECT treatments. These findings indicated that the effects of electrode placement and stimulus waveform could be detected six months following the termination of ECT. In general, especially with respect to retrograde amnesia, deficits observed this long after ECT termination are

not expected to reverse. Thus, this study provided the first definitive evidence of persistent cognitive impairment resulting as a function of variation in ECT technique.

In a recently completed study at NYSPI, patients were randomized to RUL ECT at 6 times initial seizure threshold or BL ECT at 2.5 times initials seizure threshold. In addition, the groups were also randomized to use of a traditional wide pulse width (1.5 ms) or use of an ultra-brief pulse width (0.3 ms) (Sackeim, 2004a, Sackeim et al., 2008). There were marked advantages for the ultra-brief pulse width in acute, short-term and long-term cognitive outcomes. For example, a normal comparison group, comprised of individuals with negative psychiatric and neurological histories, matched to the patient sample in age, gender, education, and verbal IQ, was administered the same neuropsychological battery at the same time interval as given to patients. The Columbia University Autobiographical Memory Interview (AMI) is extremely sensitive to the amnestic effects of ECT in producing forgetting for past autobiographical events (McElhiney et al., 1995, Sackeim et al., 1993, Sobin et al., 1995b, Lisanby and Sackeim, 2000, Sackeim et al., 2000b). Patients treated with RUL ultrabrief ECT did not differ from the normal comparison group in amnesia scores when tested a few days (mean=4 days) following the ECT course. This outcome was striking. In contrast, the BL ultra-brief group had a significant deficit, but was superior to the RUL wide pulse width group, who in turn were superior to the BL wide pulse width group. At the short-term time point, the deficit in the BL wide pulse width group was equivalent to a reduction (relative to controls and RUL ultra-brief ECT) of approximately 1.5 SD. This pattern was also maintained at reassessment 6 months following the end of ECT. Thus, these new findings suggest that some forms of ECT result in persistent impairment, especially in the area of retrograde amnesia, but that some innovations in ECT technique may minimize such deficits. The use of ultra-brief stimulation and the right unilateral electrode placement appears to retain efficacy and yet lead to the least degree of impairment. The ultimate goal of the research proposed in this application is to determine whether an additional modification, the use of FEAST to produce greater focality of stimulation, is of further benefit in protecting patient from adverse cognitive effects.

The third general feature is that *patients vary considerably in the extent and severity of cognitive side effects following ECT*. There has been limited investigation of the factors that contribute to these individual differences. Among depressed patients without known neurological disease or insult, there is evidence that the extent of pre-ECT global cognitive impairment, i.e., Mini-Mental State Exam (MMSE) scores,

predicts the magnitude of retrograde amnesia for autobiographical information at long-term follow-up. In these patients, ECT typically results in improved global cognitive status, as a function of symptomatic response. Nonetheless, these same patients may have greater persistent amnesia for personal memories (Sobin et al., 1995b). Similarly, there is evidence that the duration of disorientation immediately following the ECT treatment is an independent predictor of the magnitude of retrograde amnesia for autobiographical information. Patients who require prolonged periods to recover orientation may be at greater risk for more profound and persistent retrograde amnesia (Sobin et al., 1995b). Patients with pre-existing neurological disease or insult (e.g., Alzheimer's disease, Parkinson's disease, stroke) may also be at increased risk for ECT-induced delirium and memory deficits (Figiel et al., 1991, Mulsant et al., 1991-). Magnetic resonance imaging (MRI) findings of basal ganglia lesions and severe white matter hyperintensities have also been linked to the development of an ECT-induced delirium (Figiel et al., 1990). Some medications may exacerbate ECT-induced cognitive side effects. These include lithium carbonate (Small et al., 1980, Weiner et al., 1980), and medications with marked anticholinergic properties, particularly in elderly patients.

It has long been thought that age is a risk factor for greater adverse cognitive effects, although the evidence for this has been relatively weak (Zervas et al., 1993, Stoudemire et al., 1991, Mulsant et al., 1991-) [see Sackeim (2004b) for a review]. In the study of ECT in community settings (Prudic et al., 2004a, Sackeim et al., 2007), there were two individual difference factors that were strongly related to short- and long-term cognitive outcomes. Older patients generally showed greater deficits and those with higher premorbid IQ [assessed with the National Adult Reading Test; (Crawford et al., 1991)] had smaller deficits. These findings confirmed the suggestion that that there is great vulnerability to adverse cognitive effects with advanced age, and raise the possibility that higher premorbid IQ has protective effects, perhaps through a cognitive reserve mechanism, as seen in neurological disorders (Stern, 2002, Legendre et al., 2003).

The fourth central feature is that *ECT results in highly characteristic cognitive changes*. Across psychiatric disorders and prior to receiving ECT, many patients have deficits in attention and concentration that limit their capacity to learn new information (immediate memory) (Byrne, 1977, Pogue-Geile and Oltmanns, 1980, Cornblatt et al., 1984, Sackeim and Steif, 1988, Zakzanis et al., 1998, Majer et al., 2004). For example, patients with severe psychopathology often have deficient recall of

information that was just presented to them (immediate memory). In depressed patients, these deficits are most marked for unstructured material that requires effortful processing in order to impose organization (Weingartner et al., 1981, Weingartner et al., 1983, Weingartner and Silberman, 1984, Roy-Byrne et al., 1986, Burt et al., 1995, Burt et al., 2000). However, such patients are less likely to have deficits in retaining the new information that they do learn (delayed memory) (Cronholm and Ottosson, 1961, Sternberg and Jarvik, 1976, Steif et al., 1986). During the ECT course, deficits in attention and concentration may be accentuated (Sackeim et al., 1992b, Sackeim, 1992, Calev et al., 1995). In contrast, with symptomatic response following ECT, these deficits usually resolve. Consequently, measures of immediate memory are either unchanged or improved within a few days of ECT termination (Cronholm and Ottosson, 1961, Steif et al., 1986, Weiner et al., 1986, Rossi et al., 1990, Sackeim et al., 1993, Sackeim et al., 2000b, Sackeim et al., 2007).

Since attention and concentration are essential to many aspects of cognitive function, it is not surprising that shortly following completion of the ECT course improvement may be observed in a wide variety of neuropsychological domains, including global cognitive status (Sackeim et al., 1993, Sobin et al., 1995b) and measures of general intelligence (IQ) (Huston and Strother, 1948, Stieper et al., 1951, Squire and Chace, 1975, Malloy et al., 1982, Sackeim et al., 1992a) [see (Semkovska and McLoughlin, 2010) for a recent meta-analysis]. There is no evidence that ECT results in lasting impairments of executive function (e.g., the capacity to shift mental sets), abstract reasoning, creativity, semantic memory, implicit memory, or skill acquisition or retention (Weeks et al., 1980, Frith et al., 1983, Squire et al., 1984, Taylor and Abrams, 1985, Abrams and Taylor, 1985, Jones et al., 1988). Indeed, the fundamental distinction between declarative and nondeclarative memory systems, as formulated by Squire, was based partly on evidence that ECT patients showed deficits in the retention of information consciously recalled or propositional in nature, while retention of procedural learning (mirror reading), classical conditioning, word priming, etc. was unimpaired even shortly following treatments (Squire, 1986a).

Against this background of unchanged or improved neuropsychological performance, ECT selectively results in anterograde and retrograde amnesia (for declarative information). The anterograde amnesia is characterized by rapid forgetting of newly learned information (Cronholm and Ottosson, 1961, Squire, 1986b, Steif et al., 1986, Weiner et al., 1986, Frith et al., 1987, McElhiney et al., 1995, Sackeim, 2000, Lisanby et

al., 2000). As noted, compared to preECT baseline, patients tested a few days following ECT may recall more items from a list that was just presented. However, recall after a delay will often be impaired (Korin et al., 1956, Cronholm and Molander, 1964, Squire and Miller, 1974, Squire and Chace, 1975, d'Elia et al., 1976, Robertson and Inglis, 1978, Steif et al., 1986, Weiner et al., 1986, Calev et al., 1989, Sackeim et al., 1993, Sackeim et al., 2000b, Sackeim et al., 2007). The extent and persistence of this rapid forgetting of newly learned information varies among patients and should be considered when making recommendations regarding the post-ECT convalescence period. Until there is substantial resolution of the anterograde amnesia, returning to work, making important financial or personal decisions, or driving may need to be restricted.

Following the termination of ECT, the anterograde amnesia rapidly resolves. Indeed, no study has documented anterograde amnestic effects of ECT more than a few weeks following the ECT course (Strain et al., 1968, Bidder et al., 1970, Heshe et al., 1978, Jackson, 1978, Fraser and Glass, 1980, Weeks et al., 1980, Gangadhar et al., 1982, Frith et al., 1983, Weiner et al., 1986, Sackeim et al., 1993, Sackeim et al., 2000b) [see (Semkovska and McLoughlin, 2010) for a recent review]. It is unlikely that ECT has any long-term effect on the capacity to learn and retain new information.

Following ECT, patients also display retrograde amnesia. Deficits in recalling both personal (autobiographical) and public (impersonal) information are usually evident, and are typically greatest for events that occurred temporally closest to the treatment (Janis, 1950, Cronholm and Molander, 1961, Strain et al., 1968, Squire and Chace, 1975, Squire, 1975, Squire et al., 1976a, Squire et al., 1976c, Squire et al., 1981b, Weeks et al., 1980, Sackeim et al., 1986, Sackeim et al., 1993, McElhiney et al., 1995, Sackeim et al., 2000b, Sackeim et al., 2007, Sackeim, 2014b). The magnitude of the retrograde amnesia is greatest immediately following the treatment. A few days following the ECT course, memory for events in the remote past is usually intact, but there may be difficulty in recalling events that transpired several months to years prior to ECT. The retrograde amnesia over this time span is rarely complete. Rather, patients have gaps or spottiness in their memories of personal and public events (Donahue, 2000). Recent evidence suggests that the retrograde amnesia is typically greater for public information (knowledge of events in the world) as compared to personal information (autobiographic details of the patient's life) (Lisanby et al., 2000). The emotional valence

of autobiographical events, i.e., memories of pleasant or distressful events, is not related to their likelihood of being forgotten (McElhiney et al., 1995).

As time from ECT increases, there is usually a substantial reduction in the extent of retrograde amnesia. Older memories are more likely to be recovered earlier, if at all. However, the time course for this reduction in retrograde amnesia is often considerably more gradual than that for the resolution of anterograde amnesia. In many patients, the recovery from retrograde amnesia will be incomplete. While several authorities have contended that all the cognitive side effects of ECT are transient, there is now compelling evidence that ECT can result in some degree of persistent or permanent memory loss in some patients (Squire et al., 1981b, Weiner et al., 1986, McElhiney et al., 1995, Sobin et al., 1995b, Chahine et al., 2014, Sackeim et al., 2008, Anderson et al., 2009). In this respect, the most important evidence comes form the recently completed study of ECT practices in community settings, where the degree of retrograde amnesia six months after ECT was found to be a function of ECT electrode placement and number of treatments (Prudic et al., 2004b, Sackeim et al., 2007). Indeed, there is evidence that patients'' self-evaluation of the global long-term effect of ECT on their memory is associated with the extent of the objective autobiographical retrograde amnesia (Berman et al., 2008, Brakemeier et al., 2011b). Owing to a combination of anterograde and retrograde effects, many patients may manifest persistent loss of memory for some events that transpired in the interval starting several months before and extending to several weeks following the ECT course. There are individual differences, however, and, uncommonly, some patients may experience persistent amnesia extending several years prior to ECT (Donahue, 2000). Profound and persistent retrograde amnesia may be more likely in patients with pre-existing neurological impairment and patients who receive large numbers of treatments, using methods that accentuate acute cognitive side effects (e.g., sine wave stimulation, bilateral electrode placement). It is hoped that techniques, such as FEAST, will reduce the possibility of such negative outcomes.

D. Rationale for FEAST

Understanding of the safety of ECT has undergone substantial change. It is now apparent that the amnestic effects of the treatment are not always transient, and many patients will have some degree of permanent retrograde amnesia (Sackeim, 2000, Sackeim, 2014b). While for most individuals the extent of amnesia will be limited, patients treated with bilateral ECT, and especially when coupled with inefficient forms of

stimulation or excessive dosage, may experience more pronounced and persistent amnesia. In contrast, we have shown that right unilateral ECT, when administered with an ultrabrief stimulus, maintains efficacy but has marked advantages in cognitive side effects (Sackeim, 2004a, Sackeim et al., 2008). Indeed, with a highly sensitive measure of retrograde amnesia, patients receiving this modality did not differ from healthy comparison subjects in the amount of memory loss over the period corresponding to the ECT course. Thus, factors such as electrode positioning (BL vs. RUL), stimulus waveform (sine vs. brief pulse vs. ultra-brief pulse) and stimulus dosage relative to threshold have a substantial and enduring effect on the safety of the procedure. We hypothesize that further increasing the efficiency of the ECT stimulus, by use of unidirectional stimulation, will result in further reductions in cognitive side effects. Furthermore, increasing the focality of stimulation, and avoiding neural circuitry responsible for ECT's amnestic properties, will provide additional protection.

FEAST, as described in this application, differs from conventional ECT in two ways: electrical waveform and electrode geometry. There is no reason to believe that either of these factors, alone or in combination increases risk. Our experience to date, with 35 depressed patients (7 Columbia, 28 MUSC) having received a course of FEAST has confirmed this expectation.

D.1 Unidirectional Stimulation

The unidirectional waveform of FEAST is identical to the bidirectional stimulus of the marketed MECTA Spectrum 5000Q except that half the pulses are rectified. There is considerable experience with unidirectional stimuli in the US and abroad. For example, all the ECTRON ECT devices, manufactured in the UK (Mark 4, Series 2, Series 3, Series 5, Series 5A, Series 5B, and Series 6) deliver unidirectional stimuli, with the Mark 4 offering a choice of unidirectional or bidirectional stimulation (Lock, 1995). The Series 6 is presently marketed in the UK. A similar choice is available with the Neurotronic Therapy System MKII ECT device, also presently marketed in the UK by Sycopel Scientific Ltd. (Lock, 1995). The Siemens Konvulsator, which was manufactured in Germany and in widespread use especially in Scandinavian countries, used unidirectional partial (chopped) sine wave stimulation. In the US, from 1940's through 1970's a variety of ECT devices delivered unidirectional stimulation, the most well documented being the Reiter devices (e.g., Reiter CW47) produced by Friedman and Wilcox (Epstein and Wender, 1956, Friedman, 1942, Friedman, 1949, Friedman, 1952, Friedman, 1953, Friedman and Wilcox, 1942, Proctor and Goodwin, 1943, Wilcox, 1947). Indeed, Impastato, Pacella and others used unidirectional

stimulation with the Reiter CW47 and symmetric, round 3 cm diameter electrodes to deliberately produce focal seizures, much like the goal of this application. They demonstrated that focal seizures could be produced by, for instance, eliciting convulsive activity unilaterally in a limb (Blaurock et al., 1950, Impastato et al., 1953, Bergman et al., 1953, Pacella and Impastato, 1954). The ElCot MF-1000, marketed in the US by ElCot, Inc. in the late 1980's and 1990's had the option of delivering either unidirectional or bidirectional brief pulses. The currently marketed Thymatron System IV, by Somatics Inc., includes a unidirectional brief pulse stimulation option.

Thus, there has been more than 60 years of experience with unidirectional stimulation in ECT, including devices marketed in the US. It had been frequently claimed that unidirectional stimulation results in lower seizure threshold and, thus, more efficient stimulation than bidirectional stimulation (Alexander, 1950, Alexander, 1955, Andrade et al., 2002, Epstein and Wender, 1956, Friedman, 1942, Friedman, 1949, Friedman, 1952, Friedman, 1953, Friedman and Wilcox, 1942, Liberson and Wilcox, 1945, Hovorka et al., 1960, Hyrman et al., 1985, Impastato et al., 1951, Pacella, 1952, Proctor and Goodwin, 1943, Rappa and Tanowitz, 1959, Wilcox, 1947, Spellman et al., 2009). While this claim has not been validated by randomized comparison, on neurophysiological grounds it would be anticipated that summation would be facilitated by unidirectional relative to bidirectional stimulation, resulting in greater efficiency. Further, it is established that anodal vs. cathodal stimulation can differ several fold in the threshold charge values that produce depolarization, with bidirectional stimulation at the upper end of this range (Roth, 1994, Iles, 2005, Rattay, 1998, Rattay, 1988, Follett and Mann, 1986). Thus, because of greater efficiency resulting in a net reduction in the charge administered, this component of FEAST should confer advantages with respect to cognitive side effects.

For example, there was a dramatic reduction in the cognitive effects of ECT with the move from sine wave to brief pulse stimulation (Weiner, 1986). Similarly, recent data indicate that ultrabrief pulse stimulation results in improved safety relative to standard brief pulse stimulation (Sackeim, 2004a, Sackeim et al., 2008, Loo et al., 2012). Of special note, we have also reported that the acute cognitive side effects of magnetic seizure therapy (MST) are superior to that of state-of-the art ECT (Lisanby, 2002, Lisanby et al., 2003a), although the efficacy of barely suprathreshold MST was inferior. The goal with FEAST is to retain the cognitive advantages of MST, through the efficiency and focality of stimulation, while retaining the efficacy of traditional ECT.

D.2 FEAST Electrodes

Electrode shape and positioning determine the direction of current flow and the degree of focality (current paths) induced by FEAST. The use of a small anterior anode might have increased the risks if it resulted in excessive impedance (inability to deliver the stimulus) or elevated ST through excessively narrow current path. The configuration we used with primates represented an extreme test. The anterior electrode was very small and the inter-electrode distance was short due to the small size of the head (approximately 2-3"). Nonetheless, impedance was not a problem and in all cases dynamic impedance values were in the range obtained with conventional ECS in these same animals (approximately 300 ohms) and seizure threshold values were very low (Spellman et al., 2009).

The implementation of FEAST in this proposal is conservative. The anterior electrode is now1.25″ in diameter (increased from 0.75″). Round stainless steel electrodes with smaller dimensions (0.75″) were used for decades for both the anode and cathode with the Reiter unidirectional ultrabrief pulse ECT stimulator, which had no limit on the charge that could be administered (train duration was maintained indefinitely until the stimulus delivery button was released) (Furst and Reiter, Liberson and Wilcox, 1945, Summerskill et al., 1952, Pacella, 1952, Friedman, 1952, Miller et al., 1953, Pacella and Impastato, 1954). There was no evidence of an increase in burns with this device. Similarly, for decades, the standard in Europe and elsewhere has been a 1″ electrode diameter, and this has not presented problems with respect to excessive impedance or burns.

Nonetheless, in our first approved IDE we reduced the voltage cutoff of the device from 400 V to 240 V. This was done to limit maximal current density in the case of excessive impedance. As a result, impedances in excess of 300 ohms resulted in inability to deliver an electrical stimulus as they would exceed the 240 V cutoff (at 800 mA constant current). The early experience with FEAST under these conditions (Nahas et al., 2013a) demonstrated that we had been wrong in our expectation of low impedance. Impedances were sufficiently high that passage of the electrical stimulus was frequently blocked. This was unacceptable as patients were under time-limited general anesthesia and required treatment. As detailed in our account of this work, we progressively increased the size of the circular anode (from 0.75″ to 1.0″ to 1.25″) as allowed by the IDE. At the 1.25″ diameter, we had no problems at all with impedance, and these values were in the range usually obtained with traditional ECT. Consequently, in our next iteration of the IDE we requested an increase in the voltage

cutoff to the value used in the commercial Spectrum 5000Q (400 V). Since the report by Nahas et al. (2013), we have administered FEAST to an additional 18 patients at MUSC. There have been no instances at any treatment session of burns or indeed of excessive impedance interfering with stimulus delivery. In Section V.D, we provide current, charge, and power density values for the proposed stimulation parameters and electrode geometries.

With respect to optimization of treatment, the key issues are the choice of sites for electrode positioning and the dosing strategy. In using the 1.25" diameter anterior electrode (as opposed to a smaller anode), the degree of focality is reduced and this should protect efficacy. We do not have sufficient knowledge of the functional neuroanatomy to justify greater focality (Nobler et al., 1994, Nobler et al., 2001, Seminowicz et al., 2004). Rather, at this stage, the more limited goals are to restrict seizure onset and expression largely to regions in the right prefrontal cortex (PFC), with virtually no stimulation in left PFC or left or right medial temporal lobe (MTL). In positioning the anode in the area of the Fp2 site in the 10/20 International EEG System, current density will peak broadly through the right anterior PFC. Furthermore, we have taken two steps to ensure that FEAST is not under-dosed. EEG seizures without convulsion are very rare with conventional ECT (Boylan et al., 2001), but may be more frequent with FEAST. Research groups differ in whether or not motor manifestations are required in defining the seizure threshold (ST). In this protocol, we will note the intensity level that results in an "EEG only" seizure, but require that EEG seizure manifestations be clear-cut and last at least 15 s to define the ST value used for subsequent dosing. Second, at any point after the fifth treatment, a clinical evaluation team can recommend a dosage increment, up to 9 x ST. Thus, in this first examination of FEAST, to protect efficacy we have deliberately erred on the side of sacrificing the degree of focality, while also allowing some flexibility in dosing. With stimulation at these levels, it is very unlikely that FEAST will be markedly ineffective, unlike low dosage RUL ECT (Sackeim et al., 1987b, Sackeim et al., 1993). Rather, to determine whether there is any effect on efficacy, a substantial number of patients will have to be treated in a masked, randomized protocol (which is planned following this study). Our published data (Nahas et al., 2013a) has demonstrated that FEAST has marked antidepressant effects. However, in the absence of a masked, randomized comparison with traditional ECT, equivalence in efficacy is unknown. This study focuses on the mechanistic issue and attempts to demonstrate that seizures induced by FEAST show robust electroencephalographic activity in frontal electrodes, but reduced activity in

temporal EEG leads. The lesser involvement of medial temporal structures with the seizures induced by FEAST should result, in turn, in lesser amnestic effects, especially for autobiographical information (Sackeim et al., 2000a). To accomplish this we propose to compare matched groups of patients who have elected to receive FEAST to non-randomized patients received regular treatment with ultrabrief right unilateral (UB RUL) ECT. Since FEAST delivers an ultra-brief stimulus and an identical titration schedule is used in both groups, the only difference in the stimulation given between the groups will be the features unique to FEAST, i.e., the use of unidirectional stimulation and geometry and positioning of the electrodes. As we will carefully evaluate efficacy, this comparison will provide preliminary (but not definitive) data on whether efficacy is equivalent for FEAST relative to traditional ECT.

In summary, we are confident that FEAST does not increase the risks of ECT. It is simply a form of ECT that is more focal and likely more efficient in seizure induction. We have optimized FEAST's potential for being efficacious by limiting its degree of focality and ensuring that markedly suprathreshold electrical dosage can be administered. By using 1.25″ diameter electrodes rather than the earlier 3/4″ electrodes, we have demonstrated acceptable impedances and have had no instances of skin burns.

D.3 Titrating in the Current Domain

Another innovation was originally examined in this study. This modification was the use of current or pulse amplitude as the basis for titrating electrical dosage to the patient's seizure threshold. As explained below, we no longer use procedures for titrating in the current domain as part of this study. Our original rationale for this approach and the reasons we no longer include it in the procedures are explained below.

The empirical titration procedure was introduced to ECT in the 1980's by the NYSPI group (Malitz et al., 1982, Sackeim et al., 1987d), and has become adopted world-wide. The American Psychiatric Association Task Force Report on ECT noted that the method of limits procedure used in titration is the most precise means available to determine dosage (American Psychiatric Association, 2001). Farah and McCall (1993) more than a two decades ago conducted a survey of ECT practitioners and found that the majority reported routine use of titration. The titration procedure involves deliberate administration of subconvulsive stimuli until the convulsive threshold is reached. Prudic et al. (1994) demonstrated that subconvulsive stimuli that preceded convulsive stimulation

had no impact on the cognitive effects of ECT compared to single convulsive stimulation, supporting the safety of the titration procedure.

Until now, it has been impossible to titrate the electrical stimulus in any parameter dimension other than pulse frequency or train duration. There are marked individual differences in ST, and the range is estimated to be at least 50-fold (keeping waveform constant) (Sackeim et al., 1991). Thus, any approach to titration must manipulate dosage over a substantial range. Of the two standard ECT devices in the US, the Thymatron System IV delivers a fixed 900 mA constant current, with no possibility for adjusting pulse amplitude. The standard MECTA Spectrum 5000Q, however, offers a selectable range of 500-800 mA, partially allowing for titrating with current. Indeed, our first IDE application for FEAST was approved with a modification of the MECTA Spectrum 5000Q broadening the range of the constant current to 100–800 mA.

Why did we propose to change the titration procedure and use current as the principal means of dosage adjustment when quantifying seizure threshold? The marked individual differences in ST largely reflect differences in the extent of shunting of current away from brain (Sackeim et al., 1994(Peterchev et al., 2010)). Only a small and variable proportion of the administered current enters brain (Hayes, 1950, Smitt and Wegener, 1944, Weaver et al., 1976, Deng et al., 2009). For example, differences in skull geometry and thickness between men and women contribute to the large gender difference in ECT ST, whereby women require a lower electrical dose than men (Sackeim et al., 1987d, Sackeim et al., 1994). Thus, people differ in the amplitude of the current in brain (charge density per phase) when a standard pulse is administered transcranially. Titrating in the current domain is expected to equate individuals more closely in intracerebral dosage than packing more pulses into the same time frame (increasing frequency) or making the stimulus train longer (increasing duration). In other words, by compensating for differences in the degree of shunting away from brain, the amplitude adjustment should result in greater intracerebral uniformity in dosing. Indeed, the titration paradigm we used in the initial pilot research used the same frequency (60 Hz), pulse width (0.3 ms), and train duration (1 sec) across the first 4 steps of the titration schedule while varying pulse amplitude to titrate dosage.

The increased homogeneity in intracerebral current density as a result of this approach to titration should (1) allow for more rigorous comparison of the effects of treatment and patient variables, by reducing extraneous individual differences and (2) improve

safety. The amplitude of the pulse is a key factor in neuronal depolarization and it would be expected that excessive amplitude results in adverse cognitive side effects, just as we have already shown that excessive pulse width increases adverse side effects. For example, the tolerability of vagus nerve stimulation (VNS) is principally determined by pulse amplitude, which is the primary parameter adjusted with this intervention (Sackeim et al., 2001b). This is also true of many applications of deep brain stimulation (DBS). The present practice of ECT results in uncontrolled difference among individuals in intracerebral current density. Individuals with the least degree of shunting away from brain will have the highest intracerebral pulse amplitudes. Therefore, this original modification should have resulted in improved experimental designs and superior safety.

We continue to believe that titration in the current domain will represent an advance in the practice of ECT. However, for two reasons, we abandoned this approach, and reverted to a traditional titration schedule. First, it is unknown what the optimal intracerebral current level should be to have the most efficient electrical stimulus. While we were conducting the FEAST pilot studies, research has appeared suggesting that the most efficient electrical stimulus has a current level (pulse amplitude) that is higher than that used in any US ECT device (Swartz et al., 2012, Swartz, 2011). For example, using a within-subject design in which patients underwent empirical titration at both the first and second treatment, Swartz et al. (2012) contrasted seizure threshold values when using a standard 900 mA current or an experimental 1150 mA. Substantially less charge was needed to induce a seizure with the higher current value, suggesting that higher current may be more efficient. While this finding is preliminary, it highlights the fact that the optimal level around which one should titrate in the current domain is unknown. In other words, using current values of 200, 400, or 600 mA as starting values for titrating in the current domain may be inappropriate if the optimal level for efficient stimulation is much higher.

The second reason for abandoning in this IDE the notion of titrating in the current domain rests on the principle that current values determine the intracerebral depth (focality) of stimulation (Lee et al., 2010, Peterchev et al., 2010). Low pulse amplitude results in stimulation that is more superficial. We considered that coupling FEAST with low current would result in excessive focality and consequently reduced efficacy. Thus, in our pilot work, we suspended the use of titration in the current domain and the titration and subsequent dosing schedules used in the proposed research employ a fixed pulse amplitude of 800 mA. This fixed current is exactly the same as that used in

the vast majority of clinical applications and research studies using the MECTA devices over the past 35 years.

D.4 Other Procedures

The diagnostic, clinical evaluation, electrophysiological, and neuropsychological procedures described in this protocol have all been used in numerous previous controlled ECT research studies conducted by the applicant and his colleagues at NYSPI, MUSC and GRU. Large data sets are available to be used as references for contrasting the data collected in this study with the highly controlled studies previously conducted at the New York State Psychiatric Institute (Sackeim et al., 1987, 1993, 2000; Sackeim, 2004), a comprehensive study of ECT in community settings (Prudic et al., 2004a), and national prospective trials of ECT outcome and relapse prevention (Sackeim et al., 2001a, Sackeim et al., 2008, Sackeim et al., 2009, Prudic et al., 2013).

D.4 Non-human Primate Experience

Two standard MECTA Spectrum 5000Qs were modified by the MECTA Corporation so that bi- or unidirectional stimulation is selectable as a menu option. We specified that unidirectional stimulation be identical to standard bidirectional stimulation other than the rectification of half the pulses. Using the stimulus acquisition system at NYSPI, we verified the output of these devices across the entire parameter range (Freq: 20-120 Hz; PW: 0.2-2 ms; Duration: 0.1 to 8 s; Current: 0.5-0.8A; charge: 1-576 mC). This involved independent sampling of voltage and current at a rate of 100k samples/s or greater, using procedures previously described (Sackeim et al., 1994).

FEAST electrodes were fabricated at NYSPI, using a disposable Thymapad adhesive electrode cut to the shape of an isosceles triangle with a surface area of ~1.2 cm^2. Since neither the rhesus or bonnet monkey has a forehead, after site preparation, this small electrode was applied in an L-shape so that the point of the triangle was over nasion, and the base extended over the most anterior portion of skull by ~4.2 mm. The posterior electrode used in the three rhesus monkeys was a rectangular stainless steel bar, with a surface area of 25.4 cm^2 (2.86 x 8.89 cm). This large electrode was tangentially centered at vertex, with the short side parallel to the sagittal plane and the long side extending across the right hemisphere. The ECS published methods (Dwork et al., 2004) used ketamine for transport, and atropine, methohexital, and succinylcholine for anesthesia. The FEAST and EEG electrode sites were cleansed with alcohol and then abraded. A conductant gel was liberally placed on the posterior

electrode that was bent to conform to skull curvature. EEG leads, referenced to ipsilateral mastoids, were placed over homologous left and right frontal regions (F7 and F8). ECG, heart rate, respiratory rate, end-tidal CO_2, O_2 saturation, and blood pressure were monitored throughout. The "cuff technique" (Fink and Johnson, 1982) blocked the distribution of succinylcholine in an occluded arm, permitting observation of unmodified motor seizure expression.

At NYSPI, 3 male, adult rhesus monkeys (3.9-5.1 kg) were studied, each on 3 occasions at least one week apart. Using an ABA or BAA design, ST was assessed with the elicitation of a motor seizure as the endpoint of re-stimulation. On two occasions each monkey was titrated with the anode on the small anterior electrode (nasion), and the cathode on the large posterior electrode (largely over supplementary motor area). On one occasion the direction of current was reversed. Staff involved in data collection were masked as to whether the anode was anterior or posterior on a given day. The titration schedule began with a very low charge (3 mC: 0.8A amplitude, 0.3 ms PW, at 20 Hz for 0.4 s duration). Each titration step increased charge by doubling train duration.

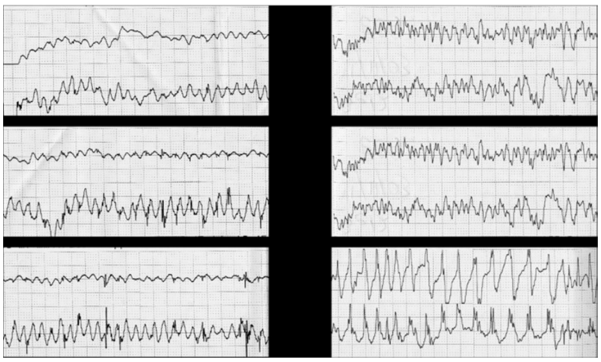
At the outset we had two major concerns about FEAST. Impedance is a function, in part, of electrode surface area, and with the small anterior electrode there was the worry that impedance would be excessive and either the device would limit voltage (400 V) and not deliver the specified current or, worse, it would deliver excessive voltage, with potential for burns. The MECTA 5000Q continuously reports "static impedance" and records this value just prior to stimulation. It also reports the dynamic impedance during stimulation. At each of the 19 stimulations in the 3 monkeys, static impedance was in the acceptable range (790-2,070 Ω; Mn = 1,192.2 Ω; SD=482). The Spectrum 5000Q will "pass" up to a static impedance of 5,000. Dynamic impedance during the 19 stimulations averaged 299 Ω (SD=22.87), with a narrow range (269-333 Ω). This value is in line with what we have obtained with standard BL ECS in primates. While the impedance value is somewhat higher than that typically obtained in human ECT with standard 2" circular electrodes (220 Ω is the nominal value assumed), the assumed value in Europe is 300 Ω, where 1" circular electrodes are common. Dynamic impedance did not differ with direction of current (P=0.23). These observations allayed the first concern we had about FEAST. Despite use of a small anterior electrode, dynamic impedance was within the acceptable range (< 500 Ω for a .8 A pulse) and constant current could be assured. Because the cranium of the adult rhesus

monkey is quite small, the surface area of the electrodes must be considerably smaller than what we have used in the human.

The extent to which current is shunted through the scalp is partly a function of interelectrode distance. In the rhesus monkey, the distance between the FEAST electrodes is much smaller than in the human. Further, the necessity of having the base of the disposable electrode on the same plane as the posterior electrode only increased shunting. Thus, the second concern was that it would be more difficult to evoke seizures with FEAST in the primate than the human, and that high stimulus intensity would be needed. Instead, we found that the ST with FEAST was among the lowest we ever encountered and that with anodal stimulation there was clear-cut evidence for greater focality in seizure expression than ever seen with routine ECT or ECS.

On 6 of 6 occasions at NYSPI with the anode at nasion, EEG seizures were evoked at the first or second step of titration (3-7 mC), most without motor expression and all markedly asymmetric in EEG expression. The seizures without motor convulsion were characterized by sharp spike activity, although unilateral slow wave activity was also present in some cases. These asymmetric EEG seizures had duration of between 8-35 s. On all 6 occasions titration continued and a motor convulsion occurred at a subsequent stimulus. These seizures were also markedly asymmetric in motor and EEG manifestations. Figure 2 presents a typical FEAST seizure with motor expression during the titration procedure. For comparison purposes a standard BL ECS (WIDE PW and 5 X ST) is also presented. The FEAST seizure occurred with stimulation at the minimum level for eliciting motor expression. The ECS seizure was with a dosage 2.5 times this ST, the convention used in a protocol comparing BL ECS to MST (Lisanby et al., 2003c, Moscrip et al., 2005, Dwork et al., 2004, Dwork et al., 2009). It is evident that on the side of stimulation (right) robust and classic spike-and-wave activity was manifested with FEAST. Each of the three NYSPI monkeys had one session in which the direction of stimulation was reversed (posterior to anterior). All 3 animals had motor seizures at the second step of titration (7 mC) that appeared to be more symmetric in motor and EEG expression. Finally, a fourth large male bonnet monkey (12 kg) was titrated with FEAST at the SUNY Downstate primate facility. The same procedures were followed except that the posterior electrode was made from a 20 gauge soft copper-grounding clamp (1.9 x 6.35 cm; 12.07 cm^2). This smaller dimension allowed placement of the electrode anterior to the motor strip and the shorter length should further limit stimulation to temporal areas. The first two

Figure 2. EEG Seizure Expression with FEAST and ECS



stimulations resulted in asymmetric EEG seizure activity without motor expression; an asymmetric motor and EEG seizure was obtained at the third stimulation.

A potential theoretical concern might be that FEAST could concentrate current so intensely as to result in damage to neuronal tissue (Yuen et al., 1981, Agnew et al., 1983, Agnew and McCreery, 1987, McCreery et al., 1990). This concern was obviated by intracranial voltage measurements taken in 3 nonhuman primates, contrasting FEAST with standard bilateral electroconvulsive shock (Spellman et al., 2009). Using chronic, multicontact, indwelling electrodes (recording from 24 locations in brain), the highest recorded values with FEAST were within the range of those seen with BL ECS. All observations indicated that the BL ECS led to a more diffuse spread of current than FEAST. FEAST consistently showed a more marked anterior-posterior gradient than BL ECS, supporting its focality and an absence of excessively high current density.

These data indicate that FEAST is capable of inducing focal seizure activity with stimulus parameters in the range or less intense than that used for traditional ECS. We have hypothesized that the comparable or lower dosing needs of FEAST and the elicitation of focal seizures should confer a superior safety profile for FEAST relative to traditional ECT.

D.6 Human experience

The original FDA IDE approved testing FEAST at NYSPI/Columbia University. The amendments in summer 2010 approved the testing of additional subjects at the Medical University of South Carolina. *Thus, feasibility of FEAST human* work in depressed adults began at NYSPI/Columbia University and further optimization of the stimulation protocol continued at the Medical University of South Carolina. The general protocol was identical at both sites and approved by the respective Institutional Review Boards and under an Investigational Device Exemption from United States Food and Drug Administration. The findings in these first 17 patients were detailed by Nahas et al. (2013).

Using the Structured Clinical Interview for Axis I DSM-IV Disorders, Patient Edition (with Psychotic Screen, Structured Clinical Interview for DSM Disorders), patients met DSM-IV criteria for a major depressive episode (unipolar or bipolar). They scored 21 or greater on the Hamilton Rating Scale for Depression (HRSD, 24-item), and treatment with ECT was indicated. Patients were excluded if they had a history of schizophrenia, schizoaffective disorder, non–mood disorder psychosis, neurological illness, alcohol or drug abuse within 6 months, ECT within 6 months, or severe medical illness.

In this open-label feasibility trial, patients' use of psychotropic medications was discontinued before starting FEAST, other than lorazepam given as needed (up to 3 mg/d). There was no stipulated minimum or maximum number of treatments for patients to be classified as provisional responders; the aim was to achieve maximal improvement. Treatment continued until patients were asymptomatic or had plataeued in improvement over at least two treatments. As a precaution expressly for this preliminary trial, patients who showed less than 40% improvement following 4 treatments (later amended to 6 at MUSC) were withdrawn from the study and offered traditional ECT (UB RUL ECT). Methohexital (0.75-1.0 mg/kg) and succinylcholine (0.75-1.0 mg/kg) were used as anesthetic medications with pre-administration of atropine (0.4-0.6 mg) or glycopyrrolate (0.2-0.4 mg).

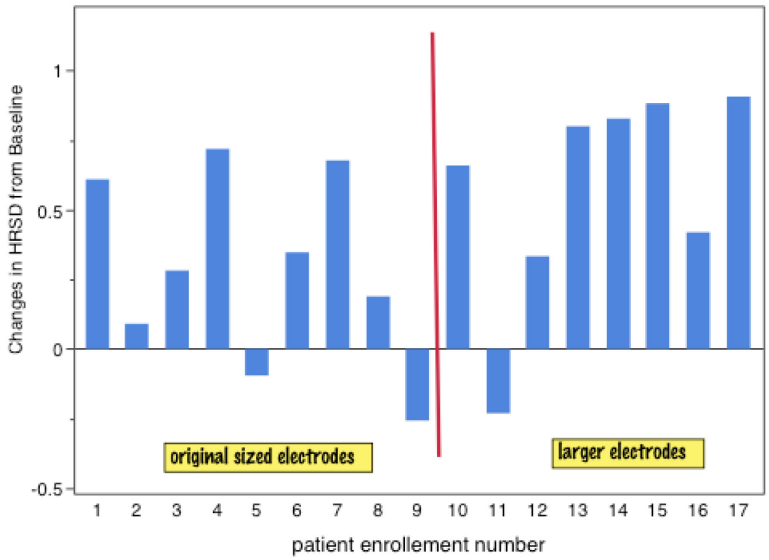
FEAST was administered with a modified MECTA spECTrum 5000Q device (MECTA Corp, Tualatin, Oregon). It relies on a relatively small (reduced surface area) frontal and large posterior electrode to induce focal seizures. Smaller electrodes however can lead to increased dynamic impedance, and failed treatment delivery if the ECT device voltage limit is exceeded or could produce superficial skin burn. When this clinical study was first proposed with a ¾ inch diameter anode electrode, the expectation was that the resulting dynamic impedances would remain in the 200-300 Ω range, but that the likelihood of skin burns could increase due to reduced electrode surface area. To mitigate this risk, the spECTrum voltage shut down limit was reduced from 400 Volts to 240 Volts, thus reducing the allowed dynamic impedance upper limit (at 800 mA) from 500 to 300 Ω. Thus stimulating electrodes consisted of a small (0.75 inch) anterior round stainless steel electrode and a larger posterior oblong stainless steel electrode (1 x 2.5 in) that attaches in a standard manner to the MECTA remote-treat stimulus cables. The smaller electrode was placed anteriorly, with the lower boundary just above the center of the right

eyebrow. The larger posterior electrode was concave in shape to better couple to the scalp. The posterior electrode was placed tangential to the midline and extended across the right supplementary motor cortex. The medial position of this electrode was adjacent to the line connecting the nasion and inion and with the posterior boundary 1.0 inch anterior to the vertex, with the lateral portion extending over the right hemisphere.

As the study began it became apparent that this 300 Ohm limit on dynamic impedance was too restrictive (there were frequent aborted stimuli due to the voltage limit being exceeded). To solve this practical issue in stimulus delivery, the anode electrode size was increased, first to 1 inch and then to 1.25 inches (MUSC). The posterior electrode size was also increased to 2 x 3 inches.

FEAST treatments were given in the morning, 3 times per week. The criterion for an adequate seizure was $\geq$ 20 s motor duration. Subconvulsive stimuli, which occurred only during titration sessions, were followed 20 s later by restimulation. At the first treatment, the empirical titration procedure was used to estimate seizure threshold (ST) (Sackeim et al., 1987c, Sackeim et al., 1987d, Sackeim et al., 1991). Dosing at subsequent treatments was substantially above seizure threshold (6xST) as it is now commonly adopted for UB RUL ECT (Sackeim et al., 2008, Loo et al., 2008). Given insufficient clinical progress, this dosage was increased in some instances to up to approximately 9xST prior to terminating use of FEAST.

The titration schedule we used combined 5 parameters, with a range of charge from 5.4 to 43.2 mC. (See Appendix II for the titration table and dosing schedule for the proposed study.) If a patient did not have an adequate seizure at the highest titration setting (43.2 mC) they exited the protocol and received conventional ECT. However all patients had adequate FEAST induced seizures by this titration step and none exited prior to receiving FEAST. Thus, the highest dosage that was used in this pilot study was 384.0 mC, 66.7% the maximal output of a standard US Spectrum 5000Q (576 mC).



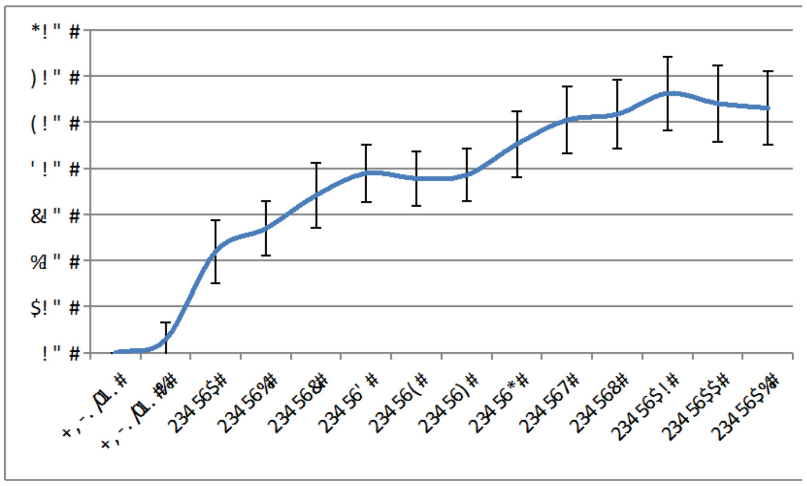
Note how, with improvements in technique, the percent improvement and number of FEAST remitters has increased with time (left, first patient, right, recent). Early patients had lower currents and smaller electrodes.

Seventeen unmedicated depressed adults (7, NYSPI: 10, MUSC) participated. There were 5 men and 3 bipolar affective disorder patients with an average age of 53±16 years. The length of the current depressive episode and lifetime depressive illness were 225.7±257.3 weeks and 20.1±11.2 years, respectively. The average number of FEAST treatment sessions per patient was 8.8, the median was 10, with a range 4-14.

There was a notable 42.1±38.3% improvement after FEAST compared to baseline in $HRSD_{24}$ (32.7±6.8, 17.7±11.2; p=0.0004) and IDS-SR (55±6.5, 28.1±16, p=0.003) scores. At the end of the course, 8 of 17 (47.1%)) patients met response criteria and 5 of 17 (29.4%) met remission criteria. The extent of improvement and likelihood of remission appeared to increase, perhaps because of increases in the size of the anode electrode and use of a fixed pulse amplitude of 800 mA (as opposed to titrating in the current domain). Only 1 of the first 9 patients achieving remission, compared to 4 of the last 8. Two patients presented with severe suicidal ideation but had their Suicidal Scale Inventory scores drop from 26 and 31 at baseline, to 7 and 0 at end of treatment.

The average duration of seizures as recorded on EEG was 57±47 seconds. This value is comparable to that observed with routine ECT.

Cognitive markers: Time to return of full orientation in the postictal period is highly sensitive to ECT technique and is predictive of long-term amnestic effects (Sobin et al., 1995b). Patients achieved full re-orientation in 16.9±7.5 minutes from stimulus delivery or 7.3±9.6 minutes (median=3.6) from when their eyes first opened in the postictal period. This average value for orientation recovery compares favorably with traditonal ECT, even the use of ultrabrief RUL stimulation (Sackeim et al., 2008) .One subject exposed to both FEAST and UB RUL had a substantially shorter time to orientation recovery with FEAST (14.7±6.8 min versus 21.6±6.5).

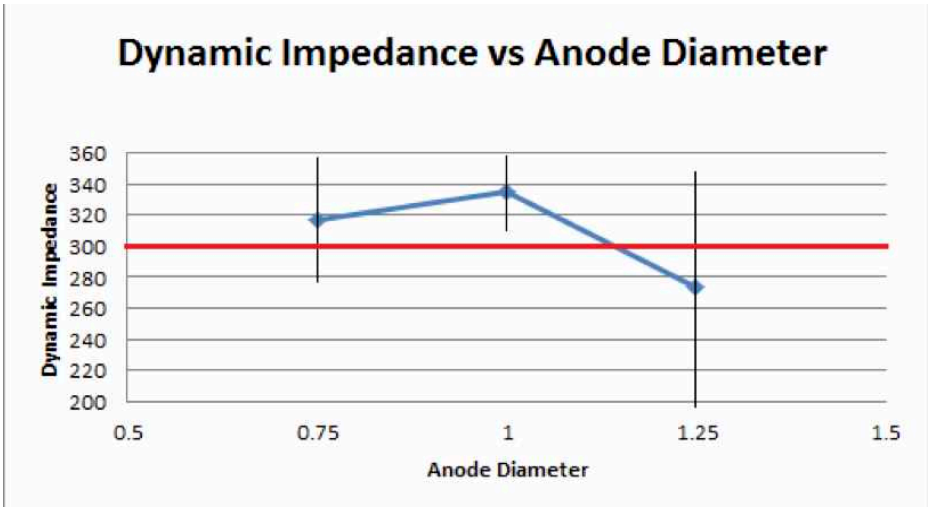


Average positive change from baseline (LOCF) in IDS-SR score with more FEAST sessions (n=10 patients from MUSC). Mean values ±SEM.

Importantly, other measures of cognition showed no change after a full course of FEAST. MMSE scores at baseline and end of treatment were 28.4±1.2 and 29.1±1.3 (p=0.33), respectively. Similarly, AMI-SF scores were 53±4.9 and 51.5±5.1 (p=0.6); RBANS were 90.3±4.2 and 86.2±14.2 (p=0.56).

Adverse Events: There were 2 first-degree burns at the anterior site of stimulation with the smaller 0.75" electrode. One patient exhibited a drop in RBANS score immediately after treatment but recovered by 2 months follow-up and was substantially improved by 4 months.

FEAST technical development for improved feasibility and safety: With successive increases in electrode sizes and thus surface area, the average dynamic impedance dropped from an average of 350 to 250 ohms and the heat flux through the skin decreased by a factor of 2.77 times.



Dynamic impedance function of electrode size. Note that at 800mA stimulus intensity, impedance values greater than 300 Ω lead to failed delivery as voltage exceeds the machine upper limit of 240 V.

The following discussion presents the rationale and supporting data for the changes in electrode size (to 1.25 ") and the increase in voltage cutoff (to 400 V) that were approved in the last IDE submission on FEAST.

In the original IDE proposal (2005), arguments were based primarily upon Power Density concerns. We now believe that this approach was incorrect, and that Energy Density is the correct measure for evaluating safety. The use of Power Density relies upon the fundamental assumption that the skin can conduct heat away in time frames of a few seconds, whereas Energy Density assumes much longer time frames are involved. Research data for fire fighters strongly supports the latter view, that conduction of heat by the skin is a slow process, involving tens of seconds up to minutes. The following analysis will include both Power and Energy Density values for comparison.

Another issue that was not addressed in the original IDE is that of dissimilar electrodes. MECTA's product line utilizes two, 2" diameter electrodes, so the energy absorption is split evenly between the two, thus doubling the effective area and reducing the power densities at the skin. FEAST uses differently sized electrodes, a smaller circular electrode on the forehead and a larger rectangular electrode posteriorly located, above the temple. Analysis shows that rather than the power or energy densities splitting evenly, the densities are substantially higher at the smaller

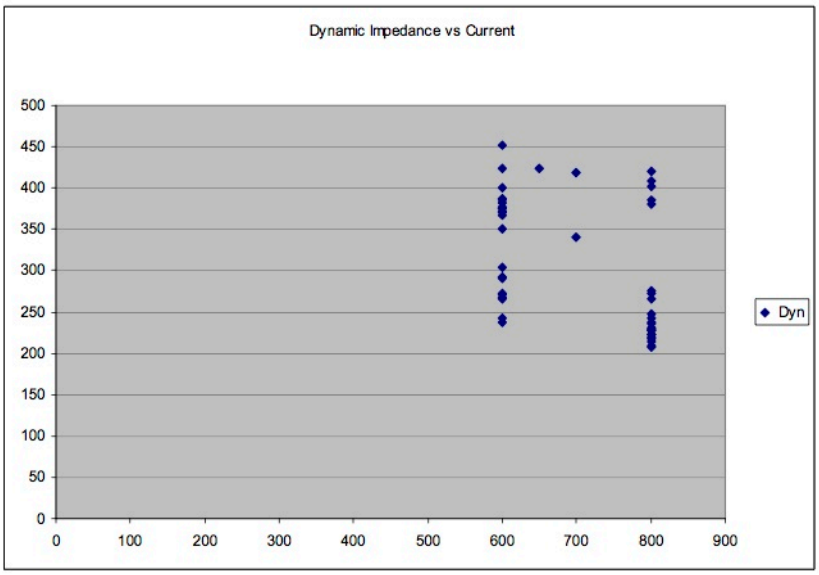
electrode. Thus, density calculations need to consider this, and assume the maximums will occur at the smaller anterior (anode) electrode. The effective area may be calculated as:

$A_{effective} = A_{small}(1+A_{small}/A_{large})$

When the small and large electrodes are equal in area, the effective area is the sum of the two areas (twice either one). Otherwise, the effective area approaches that of the smaller electrode as the ratio of areas gets smaller.

A significant problem in the FEAST study was the inability to treat at 800 mA due to high patient dynamic impedance (above the 300 ohm limit imposed by the 240 V cutoff.) Hence, it was desirable to raise this voltage limit. Graph 1 shows the measured dynamic impedances for the 1.25 inch diameter electrodes. The values above 300 ohms for 800 mA were all attempted treatments that failed. In order to treat at all, the current was dropped back to 600 mA where the effective impedance limit is 400 ohms (240 volts divided by 600 mA.) Nearly every treatment at that level was successful, but there were concerns that efficacy may be reduced at lower pulse amplitude. Indeed, virtually all modern ECT has used 800 or 900 mA pulse amplitudes, so the routine use of lower current values introduced additional uncertainty.

Thus, it was important that the voltage limit be increased to allow dynamic impedances of 500 ohms or less, equivalent to a standard commercial ECT device. This translates to a voltage limit of 400 V.



Graph 1: Dynamic Impedance for 1.25 inch Diameter Electrodes

Table 1 presents electrical parameter sets for the domestic and international commercial Spectrum devices and those proposed in the original IDE and its subsequent iterations. The last set of parameters (Third FEAST IDE) were those last approved and have been used in the last 18 patients at MUSC. When comparing values to the original approved IDE, submitted by Dr. Sackeim in 2005, the Power Densities for the parameters used in the currently approved study and now unchanged in this proposal are lower than in the original IDE submission due to inclusion of the second electrode area and the effective area calculations. In essence, the likelihood of high impedance and/or skin burns has been reduced.

The data submitted with the original FEAST IDE data showed approximately the same power density as obtain with the International spECTrums. However, under our updated calculations, it is evident that these values were twice as high (6.87 vs. 2.84), while the energy density was nearly 5 times higher (54.96 vs. 11.37). This accounts for the skin burn, which had a slightly higher power density than the International device (3.43 vs. 2.84), but a much larger energy density (27.48 vs. 11.37). Further, two safe FEAST deliveries are shown in the Table, each with power densities a little below and energy densities above the international machine maximums.

Table 1

	Max PW ms	Max Freq Hz	Max Dur Sec	Max Cur mA	Max Volts	Anode Radius cm	Cathode Area sq cm	Effective Electrode Area sq cm	Power Density W/sq cm	Total Charge mC	Total Energy J@220 Ohms	Max Dynamic Impedance Allowed	Energy @ max Impedance	Energ Density cm
2011 Domestic spECTrum 100 J	2.00	60	3	800	400	2.54	20.27	40.5367	1.89	576.0	101.38	500	230.40	5.68
2011 International spECTrum 200 J	1.50	120	4	800	400	2.54	20.27	40.5367	2.84	1152.0	202.75	500	460.80	11.37
Original FEAST IDE	1.00	60	8	800	240	0.95	16.13	3.3539	6.87	768.0	135.17	300	184.32	54.96
Second FEAST IDE	0.30	120	8	800	280	1.59	38.71	9.5367	1.69	460.8	81.10	350	129.02	13.53
Third FEAST IDE	0.50	90	8	800	400	1.59	38.71	9.5367	3.02	576.0	101.38	500	230.40	24.16
FEAST Deliveries with no burns														
2 deliveries	0.30	60	7	800	240	0.95	16.13	3.3539	2.06	201.6	35.48	300	48.38	14.43
FEAST Delivery with burn														
1 delivery	0.50	60	8	800	240	0.95	16.13	3.3539	3.43	384.0	67.58	300	92.16	27.48

The formulae used in the preceding table are as follows:

Effective Electrode Area (Aeff) = Anode area (1 + Anode area / Cathode area)
Power density = 2 x I x V x P x F / Aeff
Total Charge = 2 x I x P x F x T
Total Energy at 220 ohms = 2 x I x I x 220 x P x F x T
Max Dynamic Impedance = V / I
Energy at Max Impedance = 2 x I x I x Max Impedance x P x F x T
Energy Density = Energy at max impedance / Aeff

Where I is current, V is max volts, P is pulse width, F is frequency, and T is duration. The 2 in various formulae accounts for 2 pulses per cycle.

The table above also shows Third FEAST IDE Parameters. These were the parameters approved for the current IDE and proposed again for the new study. These include a 400 V limit thus allowing 500 ohm dynamic impedances. They use 1.25 inch diameter anterior electrodes and 2 inch by 3 inch posterior electrode. The

resulting Power Densities are comparable to MECTA's international units (2.69-3.02 vs. 2.84) and less than half the originally approved FEAST device capabilities (2.69-3.02 vs. 6.87). The energy densities are about twice the international units and 10 to 15% below the one FEAST burn stimulus. These parameters will allow treatment of all patients at 800 mA,.

In summary, we propose to continue the following changes, which were modified from the original IDE and have been in use at MUSC for the past two years:

1. Increase the front electrode diameter to 1.25 inches (2.77 times increase in area)

2. Decrease the maximum energy delivery at maximum allowed impedance from 184 Joules to 154 Joules (16% drop in maximum energy)

3. Increase the voltage limit from 240 Volts to 400 Volts to allow 500 Ohms dynamic impedances at 800 mA (1.67 times increase in dynamic impedance.) When compared to approved domestic machines, the proposed changes would adhere to the 100 Joule limit, but would utilize smaller electrodes, thus increasing the burn risk some. However, experience with these smaller electrodes, and with our 200 Joule international machines, indicates that the burn risk should remain small. This has been confirmed in the 18 patients treated with these parameters (see below).

Experience in Ongoing Study of FEAST

The data presented above derive from the first 17 patients treated with forms of FEAST (7 from NYSPI and 10 at MUSC) under the originally approved IDE. These have been published in Nahas et al, 2013. (Nahas et al., 2013b) The ongoing FEAST study was conducted under an IDE with Dr. George at MUSC as the sponsor. In this ongoing study, 18 of a maximum of 20 patients have been enrolled and treated. Analysis of the data from these additional patients is ongoing, but essential observations are reported below.

The 18 patients who have completed the protocol received an average 9.8 treatments (range 3-14), or a total of 168 FEAST administrations. There have been no instances of skin burn. Indeed, in this second cohort there have been no instances of excessive dynamic impedance and consequent inability to deliver the electrical stimulus. There had been 2 burns and frequent instances of inability to

deliver treatment in the first cohort. Thus, the change in the electrode geometry and device electrical parameters proposed in the ongoing study appear to be major improvements and enhance the reliability and safety of the procedure.

One patient was discovered in the 3rd week of treatment to have been misdiagnosed and was diagnoses with lupus cerebritis. We have excluded her from the analysis. After stopping ECT, she received a course of steroids for her lupus and her depression improved remarkably. The remaining 17 patients had average baseline $HRSD_{24}$ scores of 36.7 and postFEAST scores of 16.7, representing an average 59.4% reduction. Of these 18 patients, 13/17 (76%) met response criteria ($\geq$ 50% score reduction) and 9 (53%) met remission criteria (postFEAST $HRSD_{24}$ score $\leq$ 10). Thus, it appeared that the improved efficacy seen in the patients treated at the end of the first cohort was maintained and even amplified in the second cohort. Response and remission rates with ECT vary considerably among institutions. It is not possible to determine whether the observed rates are equivalent to what would be obtained at the same facility in patients receiving traditional ECT. Consequently, the next study in this series will include a non-randomized, non-masked comparison to patients receiving UB RUL ECT. The primary goal of the next study is to contrast the groups in focality of seizure onset EEG measures, and the lack of randomization and masking should have little impact on these measures. While this is more of a concern for the efficacy measures, the comparison of clinical outcomes in the next study, conducted at two centers, should still be informative.

The average time to reorientation was determined for the second cohort. Averaging across all treatments per patient, it took 11.4 minutes to recover full orientation (timed since seizure termination). This value again suggests that FEAST is especially cognitively sparing. Comparison of the cognitive effects of FEAST and UB RUL ECT is of keen interest in this field.

IV. INVESTIGATIONAL PLAN

A. Purpose

The protocol presented in this new IDE will be performed at two clinical sites (MUSC and GRU). At each site 20 patients will be recruited to receive treatment with FEAST, or a total of 40 FEAST patients across the sites. A contemporaneous group of 20 patients will be identified at each site who are receiving standard clinical treament with UB RUL ECT. These pateints will be matched to the FEAST sample (within site)

in the distribution of gender and diagnosis (unipolar vs. bipolar), and the mean, variance and shape of the distributions of age and baseline modified mini-Mental State score (mMMS) (Stern et al., 1987). This RUL cohort is also included under this IDE. [We considered but ultimately abandoned having a formal, blind randomization of patients to FEAST or RUL. While we ultimately hope to perform such a study, the data with FEAST are quite limited at present. There thus may not be true clinical equipoise. Similarly, although the FEAST side effects appear benign, there have still been less than 50 patients total ever treated with FEAST. We thus have settled on a non-randomized but loosely matched comparison group. This group is important for the analysis of the EEG and MRI data, and can also be used for rough comparison of efficacy and cognitive side effects. It is our hope that following this trial, there might be sufficient evidence of efficacy to enable a formal randomized definitive trial.

We will be applying to the NIH for funding to support the conduct of this protocol. This IDE will serve to gather important pilot data and will serve as the IDE for the NIH study, if it is funded.

In an open label study, the investigators intend to test the feasibility, safety and efficacy of a new form of electroconvulsive therapy (ECT), referred to as focal electrically-administered seizure therapy (FEAST). A modified MECTA Spectrum 5000Q device will be used. This device will be capable of delivering unidirectional, ultrabrief stimulation with a montage involving a small circular electrode (anode, 1.25″ diameter) and a larger rectangular electrode (cathode, 2″ x 3"). The primary objective in using unidirectional stimulation with this electrode geometry is to increase the precision of anatomical targeting. FEAST should enhance the capacity to concentrate current density in regions implicated in therapeutic processes and minimize exposure of areas in which stimulation results in adverse cognitive effects. As an expression of this objective, FEAST is expected to result in therapeutic seizures with focal onset and limited generalization. This hypothesis will be tested by comparing the FEAST and UB RUL ECT samples in focality of seizure onset as assessed by EEG ictal measures. A four-lead EEG montage will be employed at every treatment with the expectation that FEAST treatments result in reduced seizure expression in left and right temporal leads compared to traditional UB RUL ECT. In addition, fMRI measures of resting connectivity will be collected before and immediately following the ECT course (24-96 hours post-treatment). It is

hypothesized that FEAST results in greater focality inconnectivity alterations, with primarily a right frontal locus of effects.

A second hypothesis is that FEAST will represent a more efficient form of seizure induction. The FEAST patients in this protocol should have a lower seizure threshold (expressed in the minimal charge to elicit a seizure) compared to the contemporaneous matched reference group.

A third hypothesis is that FEAST should be of similar therapeutic potency with a superior side effect profile when compared to standard UB RUL ECT, the form of traditional ECT with the most benign adverse effect profile and robust efficacy (Loo et al., 2012).

The study is expected to be completed 3 years after the approval of this IDE.

B. Protocol

B.1 Patient Selection

Across the sites 60 patients will be enrolled to achieve 40 FEAST patients who will fully complete this study at the MUSC Institute of Psychiatry, Brain Stimulation Service (BSS) in Charleston, SC, and at GRU in Augusta, GA and Aiken, SC. At both MUSC and GRU, roughly matched 30 patients (each) will also be recruited from those scheduled to receive UB RUL ECT to obtain a cohort of 40 RUL comparison patients. The FEAST and UB RUL ECT groups must meet identical inclusion/exclusion criteria and will undergo identical evaluation procedures. The only difference between the groups will be that one receives FEAST and other UB RUL ECT. The treatment received by the UB RUL ECT group will not be affected by participating in this protocol. This is an open label, non-randomized, non-masked study. Separate consent forms will be used in each group. We are thus asking FDA permission to study 60 patients with FEAST. An additional 60 patients will be studied who receive conventional ECT. Even though they are getting conventional ECT, they are covered by this FDA IDE as their data will be used for comparison purposes with FEAST.

Patients will be selected from those referred for ECT for the treatment of major depressive episode. To verify diagnosis, the SCID-P will be admiinsitered to derive DSM-V diagnosis (unipolar or bipolar major depressive episode) and relevant subtypes and specifiers (American Psychiatric Association, 2013).

Inclusion and exclusion criteria are presented in Table 2. Briefly, patients will be between the ages of 18 and 90 years and will provide informed consent. Exclusions include: history of schizophrenia, schizoaffective disorder or any non-mood disorder psychosis, rapid cycling bipolar disorder, central nervous system illness other than conditions associated with psychotropic exposure, alcohol or substance abuse or dependence in the past 3 months, pregnancy, epilepsy, inability to have stable medications, and ECT within the past six months.

There is no evidence that gender or minority status is related to response to ECT or by extension to FEAST (Nobler and Sackeim, 1996). Patient recruitment will reflect the referral patterns to MUSC and GRU. Given the gender difference in the prevalence of major depressive episode it is expected that approximately two-thirds of the sample will be female. It is expected that the sample composition will be approximately 85% Caucasian, 14% African-American, 1% Hispanic or other ethnic group in line with the historical referral basis for the MUSC ECT service and the GRU ECT services.

B.2 Inclusion Exclusion/Criteria

Table 2 presents the inclusion/exclusion criteria for the next FEAST study. These criteria have been consistent since the original FEAST IDE with the following exceptions. First, all psychiatric diagnoses now are based on DSM-V instead of Research Diagnostic Criteria (RDC) (Spitzer et al., 1978) or DSM-IV. The second change is more substantive. In the previous iterations of this IDE, we required that patients be medication free during the FEAST course, other than lorazepam (up to 3 mg/d). Maintaining this medication-free status was deemed untenable. There is now randomized, blinded, placebo-control evidence from a large multi-center study that the efficacy of traditional ECT is enhanced by the co-administration of antidepressant medication (Sackeim et al., 2009). Thus, medication-free status presents an ethical dilemma as it may diminish the likelihood of clinical benefit. Second, in clinical practice ECT patients commonly receive concomitant psychotropics. Continuing to require medication-free status in the FEAST group would introduce a fundamental confound in comparison with the UB RUL ECT group. The approach we now take excludes exposure to medications that may interfere with ECT efficacy (anticonvulsants, higher doses of anxiolytics) or present a safety risk (e.g., lithium), while permitting medications that may augment clinical efficacy (antidepressants, atypical antipsychotics). Medication status will be carefully tracked and explicitly compared in the two groups.

Table 2. Inclusion and exclusion criteria for study participation

Inclusion Criteria

Age between 18 and 90 years (inclusive)	
Diagnosis of major depressive episode	SCID to derive DSM-V
Pretreatment HRSD score ≥ 21	Hamilton Rating Scale for Depression (24-item)
ECT indicated	Physician evaluation
Willing and capable of providing informed consent	Physician evaluation

Exclusion Criteria

History of schizophrenia, schizoaffective disorder, other functional psychosis, or rapid cycling bipolar disorder	SCID to derive DSM-V; rapid cycling defined as ≥ four episodes in past year
History of central nervous system illness or insult other than conditions associated with psychotropic exposure (e.g., tardive dyskinesia)	Physician evaluation; medical history
Alcohol or substance abuse or dependence in the past year (DSM-V)	Physician evaluation
Secondary diagnosis of a delirium, dementia, or amnestic disorder (DSM-V), pregnancy, or epilepsy	Physician evaluation
Requires especially rapid antidepressant response due to suicidality, psychosis, inanition, psychosocial obligations, etc.	Physician evaluation
No anticonvulsant mood stabilizers (e.g., Depakote, Tegretol, Lamictal); No lithium; No psychostimulants (e.g., Ritalin, Adderall); Allowed medications during FEAST/ECT: Antidepressants, including buproprion Atypical antipsychotics; Hypnotics for sleep; Anxiolytics (limited to up to 3 mg equivalents/day lorazepam)	Treatment history and physician evaluation

ECT in the past six months	Physician evaluation; medical history

Patients with a history of schizophrenia, schizoaffective disorder, or any other (non-mood disorder) psychotic condition, or substance abuse within the past year are excluded. At screening, patients will be administered the Hamilton Rating Scale for Depression (24-item version) (Hamilton, 1967) and must have a score of at least 21. Patients who meet these conditions and the other inclusion/exclusion criteria in Table 2 will be considered for participation. Informed consent will be obtained from all study participants. Capacity to provide consent will be independently documented by a member of the patient's treatment team not involved in the research (likely at MUSC), or have the patient successfully complete a document that shows that they have the capacity to consent to participate (likely at GRU).

The inclusion criteria includes a physician evaluation that ECT is indicated. Medication resistance constitutes but one indication for the use of ECT. The CRF that documents this determination is based on the American Psychiatric Association Task Force Report on ECT (2001) statement of the conditions that justify the primary or secondary use of ECT. The considerations that are weighed in determining whether ECT is indicated include the following:

a. Previous positive response to ECT as ascertained by history.

b. Failure to benefit from adequate pharmacological treatment in the present episode.

c. Presentation of severe symptomatology (e.g., debilitating psychiatric or medical conditions) requiring a prompt antidepressant response.

d. Complicating medical conditions (e.g., heart disease) that could be worsened by the use of psychotropic medications.

e. Complicating adverse reactions to psychotropic medications (e.g., delirium, urinary retention) that contraindicate or limit their use.

The conditions that resulted in recommendation of ECT for each particular patient is documented by the study physician.

B.3 Medical Work-up

At screening, a medical history will be obtained. In patients who have consented to protocol participation, a physical and neurological examination, and EKG will be performed, and blood work-up (Chem20, thyroid function, CBC) and urinalysis will be

obtained. In women of childbearing potential, a pregnancy blood test will be obtained. All patients are evaluated by an internist.

B.4 Treatment History

Life-time exposure to psychiatric treatments is charted, including the medication and ECT trials, and the type, frequency, and duration of psychotherapy. Using the ATHF (Sackeim et al., 1990b, Prudic et al., 1990, Prudic et al., 1996, Mulsant et al., 1997, Sackeim, 2001) the duration, oral dosage, blood levels, compliance, and clinical outcome of each medication trial during the index episode are assessed. These ratings based on information derived from interviews with patients, family members, and treating physicians, and from pharmacy and medical records.

B.5 Pretreatment Procedures

A psychotropic (antidepressants, anxiolytics, mood stabilizers, sedatives, barbiturates, etc.) stabilization period of at least 5 days will be completed prior to the start of FEAST = as it is standard practice in clinical ECT delivery. We allow the as needed administration of lorazepam (up to 3mg/d PRN). Lorazepam is used as a rescue medication for patients in whom insomnia and/or anxiety are intolerable. Baseline evaluation procedures will be conducted after completion of the psychotropic stabilization period.

Table 3 lists the research procedures completed at baseline, prior to the start of FEAST or UB RUL ECT.

TABLE 3. PRETREATMENT ASSESSMENT BATTERY

Clinical Status and Characteristics

1. Structured Clinical Interview for DSM-V (SCID-P)
2. Past and Current Medication and ECT History (Antidepressant Treatment History Form) (Sackeim, 2001, Sackeim et al., 1990b)
3. Clinical Global Impression: Severity & Improvement (CGI:S, CGI:I) (Guy, 1976)
4. Global Assessment Scale (GAS) (Endicott and Spitzer, 1978)
5. Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1967)
6. Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979)
7. Inventory for Depressive Symptoms (IDS-SR) (Rush et al., 1985)
8. Medical Outcomes Study - SF36 (MOS-SF36) (Wells et al., 1992, McHorney et al., 1993)
9. Demographics (age, education, race, martial status) and handedness

Baseline Measures in Cognitive Battery

Global Cognitive Function

1. Modified Mini-Mental State Exam (mMMS) (Stern et al., 1987, Mayeux et al., 1981)

Retrograde Memory

1. Columbia University Autobiographical Memory Interview – Short Form (AMI) (McElhiney et al., 2001, McElhiney et al., 1995, Sobin et al., 1995b, Sackeim et al., 1993, Sackeim et al., 2000b, Sackeim, 2014b)

Anterograde Memory

I. Buschke Selective Reminding Test (BSRT)

Patient Attitudes

1. ECT Attitude Interview (Berman et al., 2008, Brakemeier et al., 2011b)

The measures of Clinical Status and Characteristics in Table 3 are essentially unchanged since the original IDE. The cognitive battery is considerably reduced. This was done since the primary goal of this study is the comparison of the groups in EEG manifestations of seizure, with comparisons of efficacy and side effects secondary. Second, none of the dropped measures showed significant change with FEAST administration in our prior analyses, and the literature on traditional ECT has only shown persistent deficits for retrograde memory for autobiographical events (Sackeim, 2014b). The measures that were retained serve a particular purpose: (1) the mMMS at baseline is used for sample characterization and matching of the two groups. A significant difference between the groups would denote an effect pertaining to global cognitive status. This is not expected. (2) Orientation recovery will be assessed at each treatment (but obviously not at preFEAST baseline). This measure has been extremely sensitive to differences in ECT treatment modalities (sine wave vs. brief pulse; ultrabrief vs. brief pulse, BL ECT vs. RUL ECT, etc.) and has been found to predict long-term deficits in autobiographical memory (Sobin et al., 1995b). We expect the FEAST group to manifest faster recovery of orientation than the UB RUL ECT group, even though the latter has manifested remarkably rapid recovery compared to other ECT modalities (Sackeim et al., 2008). (3) The most critical measure is the CUAMI-SF. This measure has repeatedly shown differences between modalities and has the strongest evidence for persistent defict following ECT. While effects of UB RUL ECT on this measure have been slight (compared to retested normal controls), nonetheless we predict an advantage for FEAST in this measure of autobiographical amnesia. (4) The Attitudes Interview collects patient self-report on the effects of the treatment course on mood

and memory. A global assessment is given by the patient, akin to a clinical global impression (CGI) for each domain. Recent research has shown that these are the only self-report measures in the history of ECT research to show significant covariation with objective cognitive deficits and with type of ECT modality (Berman et al., 2008, Brakemeier et al., 2011b). We predict that the FEAST and UB RUL ECT groups will be equivalent in self-report of effects on mood, but the FEAST group will report less deleterious impact on memory.

B. 5a MRI scan

Prior to the first ECT treatment all patients in both groups will be offered an MRI scan. The scanning at MUSC will be done on a research dedicated 3T Siemens scanner across the street from the Institute of Psychiatry. At GRU scanning will be done on a 3-T Philips Scanner. In addition to a high resolution structural scan (to be used for potential modelling of current flow), patients will also have an 8 minute resting BOLD scan for assessing functional connectivity. The entire non-contrast scan will take about 30 minutes. This will be repeated as well within 24-96 hours of the last ECT session of the course. MRI scanning details follow, although these may change over time as the technology advances without requiring an ammended IDE as they pose no safety issue.

High-resolution structural images will be acquired using T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE; FOV 256mm by 256 mm; voxel size: 1x1x2mm, with 0 mm gap; TR=7.5s, TE=3.7ms, flip angle=8°).

T2-weighted functional images will be acquired with a gradient-echo echo-planar imaging (EPI) sequence (TR=2 sec, TE=29 ms, flip angle=75, 64x64 acquisition matrix, 3.75 x 3.75 x 4.55 mm voxel size, FOV=240 mm, 3.5mm slice thickness, 1mm gap). Resting state scans will be acquired over a minimum of 5 min, 16 s in duration (158 volumes).

Subjects will be instructed to keep their eyes open during the scan and stare passively at a fixation cross. Their head will be restricted with foam cushions in order to minimize head motion.

fMRI Image processing and motion correction

Artifact Detection Tools (ART, http://www.nitrc.org/projects/artifact_detect) software will be used for automatic detection of the global mean and motion outliers in the functional data.
We will exclude from the analyses individual volumes from the time series if head displacement from the median head position was greater than 1.5 mm, or if head rotation from the median head position was greater than 0.5 degrees. The functional images will be pre-processed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Slice timing correction will be applied to the data to remove signal variation due to slice acquisition temporal onset differences. The first functional image volume of each participant will be used to determine parameters for spatial normalization into Montreal Neurological Institute (MNI) standardized space employed in SPM8 using non-linear transformation.

Functional Connectivity Analysis

Two approaches can be used to perform functional network connectivity: a model-free method and a model-dependent method using seed-based correlational techniques. The first method enables the exploration of connectivity patterns without the need of defining an a priori seed region. In contrast to seed-based methods, model-free methods are designed to look for general patterns of (unique) connectivity across brain regions. We will first proceed with a model-free method (Independent Component Analysis (ICA)) and then guided by the results we will perform a seed-based method to confirm those results

Independent Component Analysis (ICA)

As a model-free method, we will use Group ICA (Calhoun et al., 2001). It will be performed using the Group ICA fMRI Toolbox (GIFT) to identify distinct brain regions with temporally coherent (functionally connected) hemodynamic signal change (Calhoun et al., 2008).

Time Series

As a seed-based method, using an in house program in Matlab or the resting state version of the Matlab-based cross-platform software CONN (http://www.nitrc.org/projects/conn), time series from the resting state scans will be extracted from specific ROIs based on the ICA analysis results by averaging the time series of all voxels in the ROIs. After scaling and filtering steps performed across all

brain voxels, the resulting times series will be correlated with the resting-state time-series of all other voxels, resulting in a functional connectivity map (fcMap).

Statistical Analysis

As correlation analysis, we will correlate the change in functional connectivity measures with the change in symptom measures for all subjects.

A two-factor MANCOVAs analysis will be conduct with Site and Treatment Group as between-subject factors, age as a covariate, and time (pre-post) and connectivity values in a priori brain regions as repeated measures factors.

Hypotheses

In contrasting resting fMRI data, we hypothesize that both connectivity methods will show that both FEAST and UB RUL ECT treatments significantly reduce connectivity between frontal cortex structures, replicating previous findings (Perrin et al., 2012, Abbott et al., 2013). However, we hypothesize that this effect is especially focal within the FEAST group (that is, FEAST patients will show a greater reduction in hyper-connectivity than will UB RUL, and these changes will be more restricted to right frontal regions.

B.6 FEAST Procedures

Medication Status. Patients will be stabilized on their medications for 7 days and will be withdrawn from lithium and anticonvulsants for at least 5 days. ECT starts after completion of the baseline battery, usually after an additional 1-2 days. PRN lorazepam is limited to 3 mg/d, and is withheld approximately 10 hr before a treatment. A daily log is kept of all medications (psychotropic or otherwise) patients receive. Introduction of any medication during the FEAST (or UB RUL ECT) will be considered a protocol violation but will not lead to termination from the study.

General Treatment Technique. After completion of the pretreatment assessment battery, treatment with FEAST will begin. FEAST will be administered only with the modified Spectrum 5000Q device approved with this IDE application. Treatments are given in the morning, 3 times per week. Pharmacological agents are standardized: atropine (0.4 mg IV), methohexital (0.75 mg/kg) and succinylcholine (0.75-1.0 mg/kg). [If methohexital is unavailable, thiopental is substituted (2.0 mg/kg).] Patients are oxygenated by mask (100% O2) prior to anesthesia and until resumption of

spontaneous respiration. Standardized procedures are used to reduce impedance at FEAST and EEG electrode sites. The impedance of the EEG electrodes is kept ~ 5k ohms.

The "cuff technique" assists in monitoring the duration of ictal motor activity (Fink and Johnson, 1982). The EEG sites are left and right frontal (F7 and F8) and a custom placement for the left and right temporal leads (to avoid overlap with the RUL ECT electrodes). Each EEG site is referenced to the ipsilateral mastoid (Weiner and Krystal, 1993). A detailed manual is available that describes detailed procedures for preparing the FEAST or RUL ECT electrode sites and the EEG sites. As indicated the primary hypothesis tested in this study concerns the ictal EEG collected at every treatment. We predict that seizure onset will be more restricted to the right frontal site with FEAST compared to UB RUL ECT.

The criterion for an adequate seizure is $\geq$ 20 s EEG duration. Subconvulsive stimuli, which occur only during titration sessions, are followed 20 s later by restimulation. Up to 5 stimulations are permitted at titration. Using these criteria, across our two of our recent studies, only 3 out of 1,372 treatment sessions were terminated without an adequate seizure (all due to very high thresholds at the first treatment). Additional monitoring includes continuous display of three channels of ECG (leads I, II, IV), heart rate, blood pressure, and pulse oximetry. At each treatment, the 4 EEG channels are digitized and along with treatment parameters automatically entered into a database using the MECTA EMR (electronic Medical Record) software. The intervals to return of spontaneous respiration and eyes opening upon command are also recorded.

FEAST Stimulus Dosing. After completion of the pretreatment assessment battery, treatment with FEAST will begin. FEAST will be administered using a modified spECTrum 5000Q device. In this study, stimulation parameters at titration will be restricted to an ultrabrief electrical stimulus (0.3 ms pulse width) and unidirectional administration. The amplitude of the constant current during each pulse will also be fixed at 800 mA. Train duration (1.5-8 s) and pulse frequency (30-80 Hz) will be the primary parameters manipulated to adjust dosage relative to seizure threshold (see Table 4). [One suprathreshold setting involves increasing pulse width to 0.5 ms].

At the first treatment, the empirical titration procedure is used to estimate ST (Sackeim et al., 1987c, Sackeim et al., 1987d, Sackeim et al., 1991). This procedure at the first session ensures that the lowest charge needed to evoke a seizure is

identified for each individual patient (Sackeim et al., 1994, American Psychiatric Association, 2001). Dosing at subsequent treatments will be substantially above seizure threshold. With traditional ECT and a RUL electrode placement, a dose of at least 6 times the initial seizure threshold (6xST) has been shown to be maximally effective (McCall et al., 2000, Sackeim et al., 2000b), with lower dosage resulting in reduced efficacy (Sackeim et al., 1987b, Sackeim et al., 1993). This is also the case when an ultrabrief stimulus is used with the RUL electrode placement (Sackeim, 2004a, Sackeim et al., 2008, Loo et al., 2012). Thus, the minimum dosage for FEAST will be approximately 6xST in treatments administered after the first session [see Table 4]. Given insufficient clinical progress after at least 5 treatments, this dosage may be increased to up to approximately 9XST prior terminating use of FEAST. Since the seizure thresholds with an ultrabrief stimulus are very low (Sackeim, 2004a, Loo et al., 2012), and are expected to be lower still with the use of FEAST, the absolute dosage administered will in almost all cases be well below that commonly administered with routine treatment in the community.

The criterion for determining ST will be EEG determined. In the past 28 patients at MUSC we are now sufficiently confident that FEAST seizures can be seen on EEG. We will also record motor movement cessation in the leg that has the BP cuff inflated.

Table 4. Titration and Dosing Schedule

Titration and Dosing Schedule

Pulse Frequency (Hz)	Pulse Width (ms)	Train Duration (s)	Current (mA)	Total Charge (mC)	Dose Relative to Initial ST
20	0.3	1	800	9.6	
20	0.3	2	800	19.2	
20	0.3	4	800	38.4	
20	0.3	8	800	76.8	
40	0.3	8	800	153.6	
80	0.3	8	800	307.2	
Subsequent Dosing: 6 X ST					
20	0.3	6	800	57.6	6
30	0.3	8	800	115.2	6
60	0.3	8	800	230.4	6
90	0.4	8	800	460.8	6
90	0.5	8	800	576	3.75
Subsequent Dosing: 9 X ST					

30	0.3	6	800	86.4	9
60	0.3	6	800	172.8	9
90	0.3	8	800	345.6	9
90	0.5	8	800	576	7.5

The titration schedule to be used in the study and the prescribed dosing at treatments following the initial titration session are presented in Table 4. The titration schedule starts with a dose of 9.6 mc, which is nearly the lowest ever used in clinical or research use of ECT, reflecting the expectation that seizure thresholds will be very low.

Only 6 parameter combinations will be used at initial titration, with a range of charge from 9.6 to 307.2 mC. If a patient does not have an adequate seizure at the highest of these settings (307.2mC) they will exit the protocol and be offered conventional ECT. [This has not occurred in any of the patients who have received FEAST.] The highest dosage that can be used in this study is 576 mC, the same as the maximal output of a standard domestic Spectrum 5000Q (576 mC).

The stimulating electrodes consist of a small (1.25″) round stainless steel electrode and a larger poster stainless steel electrode (2 x 3″) that attaches in a standard manner to the MECTA remote-treat or standard stimulus cables. This smaller electrode will be placed anteriorly with the lower boundary just above the center of the right eyebrow. The larger posterior electrode is concave in shape to better couple to the scalp. The posterior electrode will be placed tangential to the midline and extend across the right supplementary motor cortex. The medial position of this electrode will be adjacent to the line connecting the nasion and inion and with the posterior boundary 1.0″ anterior to the vertex, with the lateral portion extending over the right hemisphere. A self-adhesive locator will be used to position the anterior anode electrode, ensuring restiriction of any conductant gel to the geometry of the anode.

Unless otherwise contraindicated, all patients will be premedicated with atropine (0.4 mg IV) to block the parasympathetic effects of electrical stimulation (approximately 2 minutes prior to anesthetic induction). As indicated, methohexital (1.0 mg/kg) will be used as the general anesthetic and succinylcholine (0.75 mg/kg) will serve as the muscle relaxant. Dosing of these agents after the first treatment will be based on anesthetic response. Patients will be oxygenated from prior to the induction of anesthesia until the return of spontaneous respiration.

At MUSC, ECT sessions will be conducted in a dedicated ECT suite on the fifth floor of the Institute of Psychiatry. At GRU, ECT sessions can be either inpatient or outpatient, depending upon the patient's needs, and can occur either at Georgia Regents Medical Center in Augusta , Georgia, or at Aiken Regional Hospital in Aiken, South Carolina, depending upon patient preference. The custom device used for FEAST will not be used for any other purpose. [Patients receiving UB RUL ECT will be treated with a standard commercial MECTA Spectrum 5000Q. After the patient is medically stabilized following the administration of FEAST he/she will be moved by stretcher to an adjacent recovery room where she/he will complete neuropsychological testing (recovery of orientation, if not already obtained). Patients leave the recovery room only after being cleared by medical staff.

RUL ECT Stimulus Dosing. For the matched RUL sample, we will use the same MECTA device, but with conventional ECT settings. We will not use the FEAST electrodes, but instead will use conventional ECT electrodes. Seizure threshold will be determined at the first session, and subsequent treatments will be performed at 6 times seizure threshold. As this is a rough clinical comparison sample, all aspects of ECT treatment in these individuals will follow what is now routine clinical practice at MUSC and GRU. These details are outlined in the landmark paper regarding RUL ECT (Sackeim et al, 2008).

Number of Treatments. Duration of treatment will determined by a clinical evaluation team at each site. ECT is typically dynamically adapted to each person, attempting to deliver the necessary treatments for that patient, and no more. We incorporate that model in this IDE, similar to our algorithm in the first IDE. At MUSC that team is composed of Dr. Mark George, Dr Baron Short, and Ms. Carol Burns, Senior Nurse and ECT specialist. At GRU the ECT delivery team consists of Dr. W. Vaughn McCall and Dr. Peter Rosenquist, while depression severity, quality of life and cognitive ratings will be performed by Dr. Laryssa McCloud, Mary Anne Riley, MS, Chelsea Hodges, MS or Brittany Gubosh.

There is no stipulated minimum or maximum treatments for patients to be classified as provisional responders; the aims are to achieve maximal improvement in each patient without exposing them to unnecessary treatment. In patients who have shown substantial benefit (>40% improvement in $HRSD_{24}$ score), treatment is continued until there is a plateau over at least two treatments (i.e., change in

$HRSD_{24}$< 3 points) or it is judged that maximal improvement has been achieved (ie, $HRSD_{24}\leq$ 5). In patients who have shown more than 40% improvement, a minimum of 10 treatments will be required before classification as a nonresponder. In patients with <40 % improvement, treatment may be stopped when a plateau in improvement has obtained and the patient has received at least 6 treatments. After 5 treatments, there is the option of increasing electrical dose from 6xST to 9xST. Thus, the trajectory of symptomatic change is closely monitored. These criterion ensure an adequate trial of ECT (Sackeim, 1986b) before declaring nonresponse, while not exposing patients who respond rapidly or patients who show no benefit to excessive treatment.

Non-responders to FEAST will be offered a course of traditional ECT, first using high dosage RUL with a standard pulse width (i.e., 0.5-1.0 ms), and, if necessary, switching to bilateral ECT. The efficacy evaluation procedures will be repeated after this second (Mode 2) course.

Participation in this protocol terminates following the acute completion of the final assessments (clinical, neuropsychological, and fMRI). Patients will be followed up at 2,4, and 6 months. At that 6 month visit they are fully terminated from the study. Of note, after the acute phase is over, FEAST patients resume fully standard care at the discretion of the ECT team and the referring physicians. We will document medication changes and whether they require additional ECT during the 6 month followup.

B.7 Ultrabrief RUL ECT Treatment Procedures

FEAST and ultrabrief RUL ECT patients will be treated identically except as noted below. The traditional d'Elia electrode placement will be used for UB RUL ECT (American Psychiatric Association, 2001), with the frontotemproal electrode tangential to the midpoint of the line connecting the right auditory tragus and the canthus. The posterior electrode will be tangential to the vertex (midpoint of line connecting nasion and inion). Standard stainless steel 2" diameter electrodes will be used. If it is deemed that patients require a change in ECT modality, a switch to either brief pulse RUL or BL ECT will be implememnted, as clinically indicated.

B.8 Assessment of Efficacy

Clinician ratings. Instruments include the HRSD (24-item) (Hamilton, 1967), MADRS (Montgomery and Asberg, 1979), CGI (severity and improvement) (Guy, 1976), and the GAS (Endicott and Spitzer, 1978). A clinical evaluation team independently completes these scales on the basis of conjoint interviews, both at set time points (preECT baseline, 1-2 days after ECT termination) and the HRSD alone is also completed at spaced intervals (weekly during the ECT course). Interviews usually take place between 10 AM-12 PM to minimize variability due to diurnal variation.

The HRSD is the "gold standard" in MDE treatment trials (Depression Guideline Panel, 1993). The 3 additional items on helplessness, hopelessness, and worthlessness in the $HRSD_{24}$ are especially relevant in ECT samples. The $HRSD_{24}$ has provided the primary efficacy outcome measures for the previous ECT trials at NYSPI (Sackeim, 2004a, Sackeim et al., 1987b, Sackeim et al., 1993, Sackeim et al., 2000b, Sackeim et al., 2008), the national multisite trials that we have organized (Sackeim et al., 2001a, Prudic et al., 2004a, Sackeim et al., 2009), as well as single-site (McCall et al., 2000, Bailine et al., 2000) and multi-site ECT trials conducted by others (O'Connor et al., 2001, Petrides et al., 2001). Thus, consistency with the literature and the large databases available dictated this choice. We have demonstrated near perfect inter-rater reliability in its use (ICCs > .98) (Sayer et al., 1993, Sackeim et al., 1993), and have reported on its internal reliability, factor structure, sensitivity to change, and relations with self-report measures in ECT samples (Sayer et al., 1993). Nonetheless, studies using traditional factor analytic methods (Sayer et al., 1993, Fleck et al., 1995) or normal item response theory (IRT) models (Gibbons et al., 1993) have shown that the HRSD has several limitations. Medical illness in the elderly can contaminate HRSD scores, which are influenced by somatic symptoms (Koenig et al., 1993, Fleck et al., 1995, Legrand et al., 1995). Keeping this in mind, total HRSD scores are the primary measure in efficacy analyses. Secondary analyses will be performed on response and remission rates and on MADRS, CGI and IDS-SR scores. Dr. Sackeim has authored a detailed, structured, combined interview for the HRSD and MADRS, with new and explicit anchors for each item. A different version of this interview is used when symptoms are assessed over a one-week time frame (e.g., preECT, follow-up visits), and when the HRSD is administered twice weekly during the ECT course. In several large multisite studies of rTMS, VNS, ECT, and pharmacotherapy, ICCs between clinical raters and time-blind ratings of videotapes at NYSPI have exceeded 0.96 (Sackeim et al., 2001a).

Self-Report ratings. The Inventory of Depressive Symptoms (IDS-SR) (Rush et al., 1985) is completed at baseline, and following completion of the course. This instrument has shown strong psychometric properties and is especially broad in its coverage of depressive symtpoms. It has been used in many MDE treatment trials, including STAR*D (Rush et al., 2006).

B.9 Classification of Clinical Outcome and Dropout

Dropout. If, for any reason, there is a lapse of 3 scheduled treatments during a FEAST course (e.g., intercurrent illness, withdrawal of consent), the course is considered terminated. If, for any reason, the patient receives a prohibited psychotropic they are also considered to have dropped out. Patients who withdraw consent for research participation are immediately withdrawn from the research. The Principal Investigator or the Study Physician may withdraw a patient from the protocol at any time if it is deemed in the patient's interest to do so. Examples include emergence of a complicating medical condition, discovery of a previously undiagnosed exclusion criterion, etc.

Response Criteria. Remission is the categorical outcome that has precedence for efficacy determination. However, response status denotes that substantial, but incomplete, benefit has obtained. The a priori criteria for response are consistent across virtually all MDE clinical trials. Based on an assessment 1-2 days following ECT, patients are responders if they have a $\geq$50% reduction in $HRSD_{24}$ scores relative to preECT baseline. All other patients are nonresponders.

Remission Criteria. Especially when ECT is the treatment modality, the goal is remission and not response (Thase, 2003, Paykel, 2002, McCall, 2014, McCall, 2013). Remitters in this study must satisfy final response criteria and have a 1-wk postECT HRSD $\leq$ 10. The remitter criteria are stringent, given the use of the 24-item HRSD and the severity of illness at study entry.

B.10 Assessment of Function and Attitudes Toward Treatment

Health-Related Quality of Life (HRQOL). We hypothesize that the reduced side effect burden of FEAST translate into a HRQOL advantage. We will use the Medical Outcomes Study SF-36 (MOS SF-36) (Ware and Sherbourne, 1992). While there are depression-specific HRQOL scales (Grégoire et al., 1994, Turner, 1994), the MOS SF-36 was selected because of its widespread use (including treatment studies of MDD) (Lonnqvist et al., 1995, Lonnqvist et al., 1994), brevity, data on reliability and validity (McHorney et al., 1993), and its sensitivity to change with the treatment

of MDD (Miller et al., 1998). Its 8 dimensions have internal reliability estimates ranging from .77 to .98, and strong relative precision values compared to the full scale. The MOS SF-36 is completed at preECT baseline, and during the week following ECT. Dr. McCall ahs shown that ECT samples are especially impaired in MOS SF-36 scores at baseline, and that sustained remission following ECT results in profound improvement, with scores of remitted patients virtually indistinguishable from normative values (Rosenquist et al., 2006, McCall et al., 2013, McCall et al., 2011b, McCall et al., 2006).

Expectations and Attitudes Toward Treatment. A structured interview is conducted at baseline and during the week following FEAST/ECT. At baseline, this interview queries expectations regarding the effects of the impending course on mood and cognition. The postECT interviews is structured to make the same inquiries about the completed ECT course. Patients provide a global self-evaluation of the impact of the treatemnt on mood and memory using a 9-point Likert-type scale (i.e, +4 very much improved, 0 no change, -4 very much worsened. Post-ECT patient reports using this interview have shown strong relations with clinical outcome, extent of retrograde amnesia, and treatment modality (Brakemeier et al., 2011a, Berman et al., 2008).

B.11 Documentation of Adverse Events

Following FDA guidelines and IRB recommendations, we define an *adverse event* (AE) as any detrimental or unintended event involving a research subject. A *serious adverse event* (SAE) is any event that results in death, life threatening experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies or other serious events that may jeopardize the subject or require medical or surgical intervention to prevent any of the outcomes listed in this definition. An *unexpected adverse event* is any event that is not anticipated as a risk in the IRB-approved protocol and consent form, or occurs at a greater frequency or intensity than anticipated.

Identification of an AE will trigger completion of an AE Report. The CRF will indicate whether this is the initial report or a follow-up. It will include an event description, start date, stop date or statement that the AE is continuing, rating of frequency (once, continuous, intermittent), grade (mild, moderate severe), whether it is considered a SAE (triggering a SAE report), relationship to FEAST (definite, possible, probable, not related), relationship to other study procedures (e.g., anesthesia), and description of

actions taken. Any occasion in which a medication is administered to treat an emergent side effect or complication (e.g., headache, arrhythmia) will be considered an AE. However, administration of medication for prophylactic purposes will not, in itself, constitute an AE.

B.12 Assessment of Objective Cognitive Side Effects

Overview. For the reasons outlined above, the cognitve battery is much reduced in this study. Four key measures will be collected. The hypotheses concerning each of these measures were presented above.

Oreintation recovery time will be assessed at every treatment session. The most profound cognitive effects of ECT are expressed in the postictal period (Daniel and Crovitz, 1983a, Daniel and Crovitz, 1983b, Sackeim, 1986a). The repeated assessment (every treatment) strongly enhances reliability of measurement, and allows for examination of progressive change over the treatment course (Calev et al., 1991a, Calev et al., 1991b, Sackeim et al., 1986). The measurement of orientation recovery has been particularly sensitive to variation in ECT electrode placement, waveform, and dosage. Further, it has been been repeatedly found to be a potent predictor of the degree of retrograde amnesia following the ECT course, even in the long-term (Sobin et al., 1995b). Following seizure termination, orientation (5 items) is assessed continuously until the criterion for full recovery is met or 90 min elapse. The critierion for recovery is correct response to 4 of the 5 items. The 5 questions pertain to name, birth date, age, place, and day of the week.

The mMMS, Buschke Selective Reminding Test (BSRT) and CUAMI-SF will be administered at baseline and at follow-up (during the week following FEAST or UB RUL ECT). The modified form of the MMS provides a total socre of 57 (as opposed to 30 with the original version) and broader coverage of gross cognitive abilities (Mayeux et al., 1981, Stern et al., 1987). The primary use of the mMMS is sample characterization, epsecially since there is evidence that low baseline scores predict more severe short- and long-term retrograde amnesia (i.e., cogntively-compromised paitents are more vulnerable to the key adverse effect on memory) (Sobin et al., 1995a). No change is expected in mMMS scores in either group. However, as a safety measure, the two groups will be compared in change in mMMS scores to verify this assumption and assure that there was no change in global congtive status.

Anterograde verbal learning and memory will be assessed with the BSRT (Hannay & Levin, 1985). Impairments in verbal earning have been demonstrated with this instrument when administered during the ECT course, with impairments in retention (delayed recall) most evident shortly following the treatment course (Steif et al., 1986). BSRT scores during and immediately following ECT have been sensitive to differences in ECT electrode placement (e.g., Sackeim et al., 1993; Sackeim et al., 2007). Versions A and B (Hannay & Levin, 1985) will be used in an ABAB or BABA format over the 4 time periods, with assignment to either order randomly determined. The BSRT will follow standard scoring using a 6 trial acquisition phase, and free recall tested after a 30 min retention interval. Indeed, an invariant order of testing will be used at each time point, starting with the mMMS, then the 6-trtial acquisition phase of the BSRT, followed by administration of the CUAMI-SF during the delay interval, followed by the free recall trial of the BSRT. The dependent measures derived from the BSRT will be total recall over the 6-trial acquisition phase (learning) and the delayed total recall score (retention). We expect that the FEAST group will have superior scores on the delayed recall score relative to the comparison group at the immediate postECT time point. We do not expect group differences at the later time points, since persistent deficits following ECT on this task have not been identified (e.g., Sackeim et al., 1993; Sackeim et al., 2007).

Retrograde amnesia for autobiogrpahical information will be assessed with the CUAMI-SF (McElhiney et al., 2001). Although there has been some controversey about the reliability and validity of the measure (Semkovska and McLoughlin, 2010, Semkovska and McLoughlin, 2013, Semkovska et al., 2012{Semkovska, 2014 #23089)}, the CUAMI-SF has been remarkably sensitive to both short- and long-term effects of ECT (Sackeim, 2014a), showing, for example, long-term differences in amnesia scores as a function of electrode placement, stimulus waveform, and number of treatments (Sackeim et al., 2007, Sackeim et al., 2008). The CUAMI-SF is also the only neuropsycholopgical instrument to show signifcant covariation with pateints' subjective report of the effects of ECT on their memory (Berman et al., 2008, Brakemeier et al., 2011a). Accordingly, we expect post-course CUAMI-SF scores to be superior in the FEAST relative to the UB RUL ECT group.

Table 5: Schedule of Procedures/Assessments

Assessment or Measurement	Screening Visit (s)	MRI Visit	ECT Weekly Assessments	End Of Acute Study	MRI Visit #2	2 month, 4 month, 6 month follow-up

Informed Consent	X					
Study Information	X					
Demographics	X					
Medical Workup	X					
SCID and other treatment assessment battery (table 3)	X			X No SCID		
HRSD 24	X		X	X		X
ATHF/medications	X			X		X
Cognitive Battery	X			X		X
MRI scan		X			X	

B.13 Neurophysiology

Four-Channel Ictal EEG. At each treatment, 4 channels of EEG are recorded with the MECTA Spectrum amplifiers (1.4-48 Hz bandpass, -3dB, 12 dB/octave), and digitized and archived with MECTA EMR software. The spatial positioning of the frontal and temporal EEG electrodes, the preparation of each electrode site, and the referencing to ipsilateral linked mastoid EEG electrodes are detailed in a study manual. At each session, impedance of the each referenced pair is determined to be below 5k ohms.

The 4-channel EEG recordings are manually artifacted to remove non-encephalopathic signals. Expert visual inspection is used to define for each session the temporal periods characterized as preictal baseline (20 seconds prior to stimulus delivery), tonic phase (post-stimulus to onset of prominent low wave activity), clonic phase (end of tonic until offset of seizure activity in all channels) and postictal period (20 s following the termination of the seizure). These 4-channel ictal recordings are analyzed in a fashion identical to the procedures we have previously employed, but with the addition of measures of coherence (Luber et al., 2000, Nobler et al., 2000a). Power spectral analyses will be conducted, using a moving Hanning window and apply a Fast Fourier Transform to yield power and coherence data for each electrode site and measurement period for delta, theta, alpha, and beta frequency bands. The 4-channel recordings allow averaging across treatments to enhance reliability of measurement, and examination of cumulative effects (Krystal et al., 1998, Krystal et al., 1996a, Krystal et al., 1997, McCall et al., 1996a).

The primary aim of this study is to contrast FEAST and UB RUL ECT in these EEG measures of seizure onset and propagation. Specifically, we expect FEAST to show greater focality of seizure onset than UB RUL ECT, with seizure onset most manifest in the right frontal EEG with FEAST, and far greater activity in the left and right temporal leads with UB RUL ECT.

B.14 Quality Assurance and Data Management

A highly experienced rater will provide clinical ratings throughout the treatment period. Accuracy of the output of the FEAST device will be tested (Sackeim et al., 1994), and calibration signals regularly applied to the EEG recordings. The stimulus parameters used with the modified Spectrum 5000Q will both be recorded electronically and transferred to a database using the Spectrum's automatic EMR logging software. An experienced psychometrician will review all neurocognitive data. Data will be entered on digital forms using automatic flags for out-of-range and missing values. Any correction to a data record will be recorded in an audit notebook. The study database will be backed-up regularly.

B.15 Statistical Analyses

Data Screening. Data will be reviewed for extreme values. When distributional assumptions are not met, data will be transformed or nonparametric procedures used. Prior to statistical analyses, the study sites (MUSC vs. GRU) and treatment groups (FEAST vs. UB RUL ECT) will be compared in the baseline sociodemographic and clinical features, using ANOVA and log-linear analyses, with a liberal threshold to detect inequality ($P < 0.2$).

Hypothesis Testing. Even though this is a preliminary investigation, yielding effect sizes by which to power a subsequent randomized study, it is important to protect the Type I error rate by limiting primary analyses to a restricted and clearly specified set of hypotheses and outcome measures. The primary analyses will test the hypotheses stated below which address the objectives described in Section II. The major areas of investigation are effects on seizure threshold, electrophysiological (EEG) activity, efficacy, function, objective changes in cognition and subjective cognitive changes. The primary efficacy analyses will be conducted in the intent-to-treat sample.

Hypothesis 1.FEAST is substantially more efficient (i.e., lower ST) than traditional ECT, even when both use an ultrabrief (0.3 ms) pulse width.

An identical titration schedule is used at the first treatment in all patients. Seizure threshold, quantified at the first treatment (in mC) will be $\log_{10}$ transformed to achieve normal distributions, with adequacy of fit tested. An ANCOVA will be conducted on these values with Site (MUSC vs. GRU) and Treatment Group (FEAST vs. UB RUL ECT) as between-subject factors, and age and gender as covariates. Second order interactions will be modeled for the covariates. Gender and age were selected since they have repeatedly shown association with ST (Boylan et al., 2000, Krueger et al., 1993, Sackeim et al., 1987c, Sackeim et al., 1987d, Sackeim et al., 2008).

Hypothesis 2. In quantitative 4-lead ictal EEG measures, FEAST results in (a) less intense seizure expression (i.e., reduced amplitude especially in low frequency bands) and (b) less postictal suppression, than UB RUL ECT. In addition, the FEAST group will manifest (c) marked asymmetry in the ictal EEG as expressed in greater amplitude (total power) in right relative to left hemisphere leads. With EEG leads over traditional frontal sites and novel temporal sites, FEAST will show a pattern of (d) greatest EEG seizure expression at the right prefrontal site. In contrast, the group treated with a bidirectional stimulus and a conventional electrode configuration (UB RUL ECT) will have (e) less of a gradient between the hemispheres and in the anteroposterior plane. Quantitative measures of (f) seizure expression and postictal suppression have no or weak relations with efficacy.

The four-lead EEG digitized at each treatment will be subjected to a FFT after artifacting, and power computed in 4 frequency bands, as well as total power across bands. The baseline, tonic, clonic and postictal epochs will be averaged separately. After testing for multivariate normality, MANCOVAs will be applied to the ictal and postictal power (log10) values, using Site and Treatment Group as between-subject factors, and age as a covariate. Hypotheses 2a and 2b call for opposite main effects in the ictal and postictal analyses. Hypotheses 2c and 2e predict an interaction between Treatment Group and the laterality repeated measures factor. Thus, an asymmetry index [(r-l)/(r+l)] will be greater with FEAST than conventional stimulation. Similarly, Hypotheses 2d and 2e calls for an interaction between Treatment Group and frontal vs. temporal lead placement. Finally, Hypothesis 2f states that measures of ictal and postictal power have at most weak relations with efficacy. Percent change

in $HRSD_{24}$ scores will be added to the MANCOVAs as a covariate. Main effects of clinical improvement and first and second-order interactions will be modeled.

Hypothesis 3. In contrasting resting fMRI data, both FEAST and UB RUL ECT result in a reduction of (heightened) frontal connectivity, replicating previous findings (Abbott et al., 2013, Beall et al., 2012, Perrin et al., 2012). However, this effect is especially focal within the FEAST group, and more restricted to right frontal regions.

MANCOVAs will be conducted with Site and Treatment Group as between-subject factors, age as a covariate, and time (pre-post) and connectivity values in a priori brain regions as repeated measures factors.

Hypothesis 4. Efficacy as assessed immediately following the treatment course does not differ between the FEAST and UB RUL ECT groups.

The primary analysis for Hypothesis 4 will use all available $HRSD_{24}$ data (i.e., the intent-to-treat data) from the FEAST and UB RUL ECT samples. A random regression model will be used to examine the relationship between $HRSD_{24}$ scores and treatment group. Time will be the within-subjects repeated measures factor, site and treatment group the between-subjects factors, with medication-resistance classification and baseline $HRSD_{24}$ serving as covariates. All interactions with time will be modeled. In secondary analyses, we will also include age, gender, age-at-onset of illness, and duration of current episode as covariates, if pre-screening indicates utility. We will investigate whether $HRSD_{24}$ scores are linear in time or quadratic, cubic, or piece-wise linear (e.g., hockey-stick shaped). Indeed, in a study comparing several different statistical methods in their sensitivity to ECT treatment groups differences in rate of clinical improvement, we found that the $HRSD_{24}$ scores over time were frequently nonlinear (Nobler et al., 1997a). The type of analysis conducted on $HRSD_{24}$ scores will be repeated for secondary analyses with the MADRS, IDS-SR, and CGI-S.

FEAST and UB RUL ECT will also be compared in the categorical outcomes of final remission status ($HRSD_{24}$ of 10 or less at post-treatment) in a secondary analysis to gauge generality of the effect and clinical significance. Nominal logistic regression analysis will be used to compare the treatment groups in covariate-adjusted odds of remission. Remission status will be the dependent variable. The independent variables will be the treatment group indicator, along with site, medication resistance, and baseline $HRSD_{24}$.

Hypothesis 5. In two primary cognitive measures, orientation recovery time and CUAMI-SF scores, FEAST will have a significant advantage relative to UB RUL ECT.

The cognitive measures were described in Section B.12. Orientation time will be averaged within each patient across all treatments. An ANCOVA will be conducted on these values with Site and Treatment Group as between-subject factors, and age and number of treatments in the average as covariates. A similar ANOCA will be conducted on CUAMI-
SF scores, with Site and Treatment Group as between-subject factors, and age, number of treatments, and baseline CUAMI-SF score as the covariates.

Hypothesis 6. FEAST will have a significant advantage in the subjective global evaluation of the effects of ECT on memory.

An ANCOVA will be conducted on scores at the postECT time point. Site and Treatment Group will be the between-subject factors and age, percentage change in $HRSD_{24}$ scores and percentage change in CUAMI-SF scores will be covariates..

C. Risk Analysis

It is now clear that with our experience in 35 patients, that FEAST is a relatively well tolerated procedure. Our preliminary data suggest that its cognitive side effect profile is equal if not lower that one observed with ultrabrief pulse right unilateral ECT. In turn UB RUL ECT is now a widely, internationally used ECT modality. It is established to have a superior risk profile compared to traditional forms of ECT using bilateral or bifrontal electrode placement and/or brief pulse or sine wave stimulation (Loo et al., 2008, Loo et al., 2011, Loo et al., 2012, Loo et al., 2013, Loo et al., 2007, Sackeim et al., 2008). Thus, this study contrasts an established ECT modality with a superior side effects profile (UB RUL ECT) to an experimental treatment (FEAST) that is expected to have a further improved side effect profile.

C.1 Risks of Evaluation Procedures

The research evaluation procedures include interviews to determine diagnosis and psychiatric symptomatology, medical exams, cognitive tests, self-report questionnaires (depressive symptoms, function, subjective evaluations of mood and memory effects, etc.), electrophysiological measures (ictal EEG), and fMRI measures. These evaluation procedures involve no risks to subjects.

C.2 Risks Unique to FEAST

The major risks of the research, beyond those associated with ECT in general, are those associated with the administration of FEAST. This new modality is a form of ECT and is expected to have reduced risk of cognitive impairment compared to traditional forms of ECT. In particular, the use of a 0.3 ms pulse width is thought to markedly reduce the side effects of traditional brief pulse ECT, without impact on efficacy (Sackeim, 2004a, Sackeim et al., 2008, Loo et al., 2012). Furthermore, the FEAST condition will be administered in such a way that cognitive side effects should be less intense and/or persistent than that which regularly occurs with older methods that do not take into account variation in seizure threshold. The use of a unidirectional current and focal stimulation should additionally contribute to further reductions in cognitive side effects.

We do not anticipate that this form of ECT (unidirectional, ultrabrief pulse with spatial targeting) will have an adverse impact on efficacy, although this is not certain. Potential lack of efficacy likely constitutes the most significant risk of FEAST. Precautions have been taken in this protocol to mitigate this risk. First, patients who do show sufficient benefit after 5 treatments may receive a dosage increment, increasing the stimulus dose from 6xST to 9xST. In the community, dosing of UB RUL ST is often 8xST or more (e.g., (Loo et al., 2012)). Second, any patient who completes the research phase as a nonremitter will be offered a course of traditional ECT (UB RUL ECT, high dose RUL or BL ECT). Our preliminary experience in 35 patients clearly indicates that FEAST has potent antidepressant properties. We cannot, however, say with assurance that these properties are equivalent to traditional forms of ECT, without explicit comparison. This study provides important data in this respect, involving the first cotemporaneous comparison of FEAST and UB RUL ECT, albeit in a non-randomized and non-masked fashion. It is anticipated that the findings obtained here will provide the foundation for a subsequent RCT.

The protocol involves monitoring of objective and subjective side effects and includes provision for alternative treatment for patients who do not respond clinically. Although a large number of procedures are conducted, other than ECT, they are all noninvasive. Patients who consent to the protocol have the option of declining participation in specific procedures (e.g., fMRI studies), but can retain participation in the remaining procedures.

Finally, FEAST might present with two theoretical risks: superficial skin burn and intracerebal damamge to excessive current density). The use of an electrode with small surface area could increase the impedance in the circuit and result potentially in skin burn or prevent the passage of the stimulus. This theoretical risk is minimized by the fact that the ECT device voltage limits and immediately aborts stimulus delivery when excessive impedance in encountered. In this protocol, we are requesting that the voltage/impedance

limit be maintained at 400 V (500 ohm) for the maximal current (0.8 A). The maximal charge administered in this protocol is 576 mC. This is the same as the maximal output of a standard Spectrum 5000Q (576 mC). As indicated in Section V.D, the maximal power density with these values and the 1.25" electrode is comparable or below that commonly used in ECT.

The 2 skin burns observed in the FEAST human studies were likely a function of the electrode sizes and asymmetries rather than total energy delivered. The standard electrode sizes in Europe and many countries outside the US are approximately 1" diameter, providing an effective area of 1.57 square inches (sum of the two areas). The burns in this study occurred while using an anode of 0.75 inch diameter and cathode of 1" X 2.5". The combined effective area (see calculations elsewhere) is only 0.52 square inches, resulting in energy densities at the anode three times higher than for 1" diameter electrodes.

The second theoretical concern is that the degree of focality obtained with FEAST is so substantial that very high current densities could be achieved that may be injurious. This concern is obviated by intracranial measurements taken in nonhuman primates, contrasting FEAST with standard bilateral electroconvulsive shock (Spellman et al., 2009). The highest recorded values with FEAST were within the range of those seen with BL ECS. All observations indicated that BL ECS led to a more diffuse spread of current than FEAST. FEAST consistently showed a more marked anterior-posterior gradient than BL ECS, supporting its focality and an absence of excessively high current density. Furthermore, reviews of current density estimates with ECT (Weaver et al., 1976, Devanand et al., 1994) indicate that the values, even in the context of extremely high applied dosage, are not in the range associated with tissue injury (Agnew and McCreery, 1987, Agnew et al., 1983, McCreery et al., 1990, Yuen et al., 1981). We completed the most extensive study to date of potential neuropathological effects of ECS in non-human primates, using a randomized, double-blind, sham-controlled design. There was no histological evidence of tissue injury after 5 weeks of daily high dosage bilateral ECS (Dwork et al., 2004). Indeed, exacting glial and neuronal counts using stereological methods, failed to provide evidence of cell loss with ECS (Dwork et al., 2009).

One of the 4 nonhuman primates died 8 days after participating in the FEAST studies. This event was judged to be unrelated to the research procedures as the animal had chronic indwelling electrodes and postmortem examination revealed that he had developed an infection along the track of one of the electrodes. Infection is not an uncommon occurrence in animals with chronic implantation. There is no evidence that electrical stimulation from FEAST or ECS could cause or contribute to an infectious process. Subsequent FEAST procedures have been successfully completed in another subject with implanted electrodes with no observed ill effects.

The 35 patients treated with FEAST at NYSPI and MUSC have shown no evidence of any serious adverse event. All have tolerated the procedure well.

Thus, there is no evidence to suggest that FEAST presents an electrical danger to patients. All the safeguards of modern ECT and the Spectrum 5000Q are preserved, and the intensity of electrical stimulation is expected to be markedly less than with traditional ECT techniques.

C.3 Risks of ECT

The potential adverse effects of ECT, and the steps that can be taken to reduce risk or manage complications, were described in III.C. These risks include death, medical complications (principally cardiovascular, pulmonary, and neurological), dental injury, fracture, dislocation, muscle soreness, headache, and nausea. In addition, there can be acute, short-term and long-term adverse cognitive effects and a set of risks associated with the premedication and anesthetic agents used in ECT.

Medical Complications and Death. The risks of medical complications and death are heightened in individuals with serious and unstable medical conditions or who present with medical conditions known to markedly increase the risks of ECT, such aortic aneurysm (Devanand et al., 1990, American Psychiatric Association, 2001). Several steps are taken in this protocol to minimize these risks. First, patients believed to be at especially elevated risk for ECT induced complications are excluded. For example, history of neurological insult or disease is an exclusion, as are secondary diagnosis of a delirium, dementia, or amnestic disorder (DSM-V), pregnancy, or epilepsy. Second, all patients undergo an extensive physical and neurological exam, including blood workup, and are medically evaluated expressly for the purpose of evaluating the safety of ECT. Specialized medical consultations (i.e., cardiology consultation) are ordered as clinically indicated. Any recommendations of the medical consultant for enhancing the safety of ECT/FEAST, such as altering medication regimens, will be followed. Third, FEAST will be administered by experienced psychiatric attendings at MUSC and GRU, and by members of the Anesthesia departments at MUSC and GRU. The anesthesiologists, responsible for life support during FEAST, are privileged at each institution and each has considerable experience in the care of patients receiving ECT. In particular, residents will not be directly involved in the provision of FEAST. Fourth, the FEAST protocol is compatible with the administration of medications intended to reduce the risk of complications or the manage complications if they emerge. For example, in patients who manifest sustained hypertension prior to or following seizure induction, the anesthesiologist could recommend pretreatment with a beta-blocker, such as esmolol or labetalol, a common practice in ECT (Drop and Welch, 1989, Castelli et al., 1995).

Dental Complications. Dental injury from ECT is rare and unusually occurs in the context of compromised dentition and/or improper use of a mouth guard (bite block)

(Minneman, 1995, Morris et al., 2002). A dental exam prior to ECT will be required for patients of any age who present with significant dental vulnerability (e.g., loose or fractured teeth, dentures, gum disease, etc.). Recommendations, such as the use of a custom bite block, will be followed.

Fractures and Dislocations. With the use of muscle paralyzing agents, fracture and dislocation are extremely rare complications of ECT. Succinylcholine is the agent used in this protocol to reduce the intensity of convulsive movements. Several precautions are taken to further minimize the risk of skeletal injury. First, during the passage of the electrical stimulus there is contracture of the masseter and temporalis muscles due to direct stimulation. This could result in a vigorous clamping action of the jaw, creating dental or skeletal injury. The anesthesiologist presses upward on the chin, keeping the jaw closed and the bite block in place. Second, in case of inadequate succinylcholine dose or timing, especially at the first treatment, the patient's limbs are gently held by nursing staff to prevent excessive movement. Third, in instances where there is uncertainty about the effectiveness of the muscular paralysis (.e.g., rapid metabolism), a nerve stimulator is used to gauge the degree of relaxation. Fourth, the cuff technique is used to monitor convulsive movements in a limb in which the distribution of succinylcholine has been blocked. This can result in fracture in elderly patients with marked osteoporosis if the cuff is placed high on a limb. In this protocol, the cuff is placed on the left ankle, avoiding the possibility of such injury.

Muscle Soreness. Muscle soreness is either a consequence of excessive vigorous convulsive motor activity or intense fasciculations due to the depolarizing muscle relaxant (American Psychiatric Association, 2001). This complication is usually reported after the first treatment and commonly is not experienced again even if no change is made in treatment technique. Therefore, conservative management of this complication involves assessment of its source (fasciculations vs. excessive convulsive movements) and its severity. Mild or moderate soreness after the first treatment might result in careful observation for recurrence at the next treatment without a change in technique. Recurrent and/or severe complaints may result in (a) an increase in the muscle relaxant if excessive convulsive movements are causal; (b) premedication with a non-depolarizing agent such as curare to reduce the intensity of fasciculations; or (c) switch to a non-depolarizing agent.

Headache and Nausea. Postictal headache and nausea are common sequelae of ECT. Prediction of individuals at risk is not possible, although determining previous response to general anesthesia and ECT may be helpful. Furthermore, although not established empirically, most practitioners believe that individuals predisposed to migraine may be likely to experience headaches following ECT.

Treatment of post-ECT headache is symptomatic. Typically, aspirin, acetaminophen, or non-steroidal anti-inflammatory drugs (NSAIDs), are highly effective. If postECT

headache is severe, sumatriptan should prove effective. PostECT nausea is typically well controlled with the serotonin $5HT_3$ receptor antagonists, ondansetron.

Cognitive Side Effects. In several respects, the cognitive alterations are the most concerning risks of ECT. While it had been frequently contended that all the cognitive side effects were transient, it is now evident that many patients will experience some degree of persistent, and likely permanent, retrograde amnesia (Sackeim, 2000, American Psychiatric Association, 2001, Sackeim, 2014b). Furthermore, in some exceptional individuals, this retrograde amnesia will be profound extending back several years and involving loss of memory for substantial personal experiences and knowledge of the external events (Donahue, 2000, Lisanby et al., 2000, Sackeim, 1992, Freeman et al., 1980).

There is no empirical evidence that ECT results in long-term deficits in cognitive domains other than memory for past events (retrograde amnesia) (Sackeim, 1992, Semkovska and McLoughlin, 2010). However, in the acute and subacute period, ECT often has a deleterious effect on the retention of newly learned information (anterograde amnesia), and may acutely disrupt a variety of cognitive processes, including attention and concentration (Sackeim, 1992, Sackeim, 1986a). At its most intense, ECT can result in an organic brain syndrome (OBS) in which the patients is continuously disoriented (Miller et al., 1986). It may take several days or more for OBS to resolve after the termination of ECT (Summers et al., 1979). Consequently, the severity and persistence of the cognitive effects of ECT determine, in part, the duration of the period of convalescence that follows the treatment, during which patients should refrain from driving, use heavy equipment, or make important financial or life decisions (American Psychiatric Association, 2001).

Both patient and treatment variables are predictive of the severity and persistence of cognitive side effects. Fortunately, factors that are associated with less severe acute side effects are also predictive of less severe and persistent long-term side effects. Thus, the cognitive response of the patient to the administration of ECT during the ECT course is a strong indicator of the likelihood of long-term persistent amnesia. For example, Sobin et al. (1995b) demonstrated that the duration of disorientation in the immediate postictal period was predictive of the magnitude of retrograde amnesia two months following the completion of ECT. Thus, patients show unusually intense cognitive side effects during the receipt of ECT are especially likely to have more severe and/or persistent deficits. The predictive value of orientation recovery for

retrograde autobiographical amnesia was recently replicated in Australia by Loo and colleagues. Identifying such patients and altering methods of ECT administration, such as reducing the frequency of treatment, switching from BL to RUL ECT, or adopting use of an ultrabrief pulse width may reduce the risk of persistent impairment.

Patients with preexisting neurological or cognitive impairment appear to be at increased risk for ECT-induced cognitive side effects (Sobin et al., 1995b, Sackeim, 2004b, Sackeim et al., 2007). Consequently, the exclusion of patients with a history of neurological disease or insult should aid in mitigating against excessive cognitive side effects. Several factors in the administration of ECT also impact on the magnitude of cognitive side effects. The most important of these variables are: (a) electrode placement or the anatomical positioning of electrodes; (b) stimulus waveform; (c) stimulus dosage relative to seizure threshold; (d) spacing of treatments; (e) number of treatments; and (f) anesthetic dosage.

It is well established by the traditional bifrontotemporal (bilateral) electrode placement results in broader and more severe cognitive side effects than the right unilateral placement (Valentine et al., 1968, Lancaster et al., 1958, Costello et al., 1970, Bidder et al., 1970, Strain et al., 1968, Weiner et al., 1986, d'Elia and Perris, 1970, Lisanby et al., 2000, McElhiney et al., 1995, Sackeim et al., 1986, Sackeim et al., 1993, Sackeim et al., 2000b). Furthermore, our recent evidence, form the largest prospective long-term study of ECT cognitive side effects, indicates that severity of persistent retrograde amnesia is greater six months following ECT in patients treated with the BL than RUL electrode placement. Indeed, the number of BL treatments was linearly related to amnesia scores at this time point, while there was no relation to the number of RUL treatments (Sackeim et al., 2007).

There is substantial evidence that waveforms inefficient in producing neuronal depolarization result in more severe cognitive side effects without any advantage with respect to efficacy. Thus, compared to brief pulse stimulation, sine wave stimulation is especially likely to produce organic brain syndromes and greater deficits in a variety of cognitive domains, and recent evidence suggests that some of these untoward effects may be persistent (Scott et al., 1992, Weiner et al., 1986, Spanis and Squire, 1981, Weaver et al., 1977). In turn, the use of ultrabrief stimulation has been shown recently to have dramatic savings with respect to cognitive side effects relative to standard brief pulse stimulation, and this effect also appears to be persistent for some cognitive measures (Sackeim et al., 2008). In our most recent

randomized trial at NYSPI, coupling RUL ECT with ultrabrief pulse stimulation resulted in retrograde amnesia scores that were indistinguishable from those of healthy participants studied at comparable time intervals. In other words, there was no evidence that RUL ultrabrief ECT produced retrograde amnesia a few days following ECT. This makes the choice of UB RUL ECT as the contrast condition especially challenging and clearly minimizes the risks of study participation. It is noteworthy that the cognitive savings associated with ultrabrief stimulation have been widely replicated (Loo et al., 2012, Sienaert et al., 2010).

The absolute dose (charge) administered in ECT shows little relation to cognitive side effects. In contrast, consistent relations have been observed when quantifying the extent to which dosage exceeds seizure threshold (Sackeim et al., 1987c, Sackeim et al., 1993, McCall et al., 2000). This reflects the fact that a large component of the delivered dose is shunted away from brain and it is likely that dose relative to threshold provides a better index of intracerebral charge density than absolute dose (Sackeim et al., 1994, Deng et al., Lee et al., 2010, Peterchev et al., 2010). Treatment techniques that do not quantify the seizure threshold and which administer an arbitrary fixed dose to all patients can result in patients receiving stimulus intensities that exceed threshold by 20-50 fold (Sackeim et al., 1991). Excessive cognitive side effects are expected under these circumstances.

There is consistent evidence that treatment schedules that are closely spaced (e.g., 5 times per week) result in greater cognitive side effects, while greater spacing of treatments results, at times, in a slower rate of improvement, but with less severe postECT cognitive impairment (Lerer et al., 1995, Shapira et al., 1991, Shapira et al., 1998, Shapira et al., 2000). Thus, in patients who develop excessive cognitive side effects, reducing the treatment frequency from three to two treatments per week can be protective.

The findings that the number of BL ECT treatments is linearly related to the magnitude of retrograde amnesia at 6-month follow-up (Sackeim et al., 2007), exemplify the fact that longer treatment courses are associated with more negative cognitive outcomes. This is especially the case for forms of ECT that result in more severe acute cognitive changes (sine wave, BL placement, etc.), as recovery of function may be incomplete by the time of the next treatment, resulting in a pattern of progressive deterioration that deepens with extended treatment (Daniel and Crovitz, 1983a).

Finally, there is some evidence that excessive anesthetic dose also results in more

severe cognitive side effects, at least in the acute postictal period (Miller et al., 1985).

Each of these factors was considered when designing FEAST and the procedures used in this protocol. The guiding philosophy was to utilize knowledge of these factors to minimize adverse cognitive effects. Specifically:

1. FEAST uses a form of RUL ECT. Given the fact that it is more focal than traditional RUL ECT, with sparing of right medial temporal lobe areas expected, the electrode position should have advantages relative to both BL and traditional RUL ECT.
2. FEAST not only uses the 0.3 ms pulse width (ultrabrief) found to result in marked cognitive savings, but also uses a unidirectional waveform that is expected to confer additional advantages due to greater efficiency.
3. Stimulus dosage in this protocol is adjusted relative to the seizure threshold determined for each patient. The dosage relative to seizure threshold was selected based on evidence that this is the dose at which traditional RUL exerts maximal efficacy. A further dosage increment (9xST) is permitted only in the context of insufficient improvement.
4. FEAST will be administered at a schedule of three treatments per week. If patients show clinical benefit, but side effects are severe, the study physician may order that treatment frequency be reduced to twice per week.
5. The number of treatments administered is regulated. Treatment is continued until there is a plateau in improvement over two treatments. For patients with substantial clinical improvement ($\geq$ 40% change in $HRSD_{24}$ scores) a minimum of 10 treatments is required before declaring nonresponse. In patients with more modest improvement (< 40% change in $HRSD_{24}$ scores) the minimum is reduced to 6 treatments. Patients who manifest remission or plateau after substantial improvement can exit treatment at any time. Thus, the number of treatments is titrated to the clinical progress of patients and lack of further improvement over two treatments results in termination of the treatment course. These methods minimize the number of treatments administered

while simultaneously allowing each patient ample opportunity to attain remission. The same guidance will apply to the cotemporaneous UB RUL ECT sample.

6. Anesthetic dosage is adjusted for each patient. At the first treatment, the dose of methohexital is set at 1.0 mg/kg. Based on anesthetic response, this dose is then adjusted for the subsequent treatments.

Thus, this protocol attempts to minimize the risks of adverse cognitive effects by both attending to the patient and treatment factors that impact on cognitive outcomes. The fact that participants in this protocol will be under close observation and supervision provides another set of safeguards, allowing for rapid and sensitive detection of adverse effects and early intervention.

Psychiatric Adverse Effects. The major psychiatric adverse effects, as discussed at length in Section III.C, are the emergence of postictal delirium or agitation and a switch to hypomania or mania. As noted, it cannot be predicted which patients will manifest postictal delirium, and this state may be seen at any treatment in the course. It may occur only once or twice or it may be manifest at all treatment sessions. Depending on the severity and persistence of the agitation, various interventions will be considered. First, the patient should be made safe such that thrashing movements or attempts to leave the stretcher can be restrained without harm. Second, the IV line needs to be secured so that IV access is not lost if the agitation becomes more profound. Third, the amount of environmental stimulation should be limited, and the patient monitored in a quiet, dimly light area. Fourth, if pharmacological intervention is needed, the preferred agent is IV midazolam, although other benzodiazepines and the anesthetic agent may be used.

The induction of hypomania or mania is a relatively rare complication, almost invariably seen in patients known to have bipolar illness. There is no consensus in the field about how to manage such patients. We take a conservative approach and suspend ECT when emergent hypomania or mania is seen. Commonly, within a few days, these symptoms subside spontaneously and the depressive disorder is manifest. If the interruption is less that 3 scheduled treatments, such patients can return to the research protocol. On the other hand, if the symptoms are sufficiently prominent and concerning that immediate institution of a mood stabilizer is

warranted, these patients will be dropped from the protocol and treated on an open clinical basis.

As noted in Section III.C, worsening of depression and increased suicidality are virtually never seen during a course of ECT. Nonetheless, it is noted that all outpatient participants regularly seen at BSS and GRU will be required to have a support network and someone living with them at home responsible of monitoring them and bringing them to their treatments. Patients who do not meet remission criteria following the FEAST research phase will be offered a second course of treatment, using traditional ECT methods. Furthermore, our commitment to patients is to take all reasonable steps in treating their major depression. Thus, if patients do not benefit sufficiently from FEAST/ECT, they will be offered a series of medication trials.

Social Consequences of ECT. The review of our first application (2005) noted that we did not address the "social implications of seizure" and potential effects on employability, insurability, and driving licensure. The review also recommended that patients be given a letter documenting that their seizures were "experimentally produced."

The applicant knows of no instance in which the employability, insurability, or driving licensure of a patient was threatened due to the receipt of ECT. While it is undoubtedly the fact that there is a social stigma associated with this treatment, its receipt alone would never justify denial of employment, insurance, or driving privileges. On the other hand, providing patients with a letter documenting that they had ECT and seizures were produced for therapeutic (not experimental) purposes would likely cause more concern and distress in some patients by raising an issue that has no basis in fact.

The FEAST/ECT program involves considerable one-on-one counseling with patients about how to address the issue of their treatment and hospital stay with friends, family, employers, and medical documentation. Patients are informed about how others have dealt with these issues and the fact that ECT-induced seizures are distinct from the seizures of epilepsy. If documentation is needed, the directors of the ECT services at MUSC and GRU will readily provide it.

Premedication and Anesthesia Effects. In addition to the risks of ECT noted

above, there are additional risks to the premedication and anesthetic agents used in the procedure. Atropine is administered approximately two minutes prior to anesthetic induction to block the vagal (parasympathetic) outflow that results from electrical stimulation (independent of seizure induction). The principal reason for this agent is that subconvulsive stimulation results in vagal outflow and bradycardia, and in the absence of the catecholamine surge that accompanies the seizure, asystole may result (Decina et al., 1984, McCall, 1996). However, in patients who are tachycardic or hypertensive, atropine has the theoretical potential of aggravating these conditions. To mitigate this risk, we note that the dose of atropine that is used (0.4 mg) is the lowest reported in the field and we have found this dose to be entirely satisfactory in providing sufficient vagal blockade. This low dose also mitigates against anticholinergic effects on cognitive function. Furthermore, the anesthesiologists do a thorough examination prior to the first treatment and review the medical history and the medical exam and tests. In rare cases, due to elevated baseline heart rate or pressure, and especially in non-titration sessions, the atropine may be withheld based on the anesthesiologist's clinical judgment.

Allergic reactions to the muscle relaxant or the anesthetic agent are extremely rare. If the patient manifest prolonged apnea following seizure induction due to slow catabolism of the succinylcholine, they will be re-anesthetized and their respiration supported until spontaneous breathing returns. A pseudocholinesterase level will be obtained and the determination made for subsequent treatments to either use a very small dose of succinylcholine (e.g., 5 mg) or to switch to a non-depolarizing muscle relaxant.

The experience of being awake while still paralyzed is frightening and is especially likely to occur with treatments that result in rapid return of orientation following seizure termination. We have seen some instances of this phenomenon with Magnetic Seizure Therapy that were managed by administering an additional (half) dose of the anesthetic after seizure termination. The possibility of such a phenomenon will be closely monitored in the FEAST patients as it is expected that they have especially rapid return of orientation. In such circumstances, we will determine whether increasing the anesthetic dose prior to the electrical stimulation or giving a second post-seizure dose is the most effective strategy.

C.4 Other Risks of the Research

Three aspects of the research may involve other risks. These are the medication restrictions prior to and during the FEAST trial, the potential delay in the start of pharmacotherapy or continuation ECT following the end of the FEAST trial, and the confidentiality of the data.

Medication Washout. There is a 5-day medication washout of lithium or other anticonvulsants or stimulants prior to the start of the research evaluation procedures. All other psychotropic medications are held stable other than PRN use of lorazepam (up to 3 mg/d). The holding steady of psychotropic medications and the stopping of some medications (anticonvulsants, lithium, stimulants, excessive anxiolytic) may lead to an increase in depressive and related symptomatology, either as a withdrawal reaction or as a worsening of the psychiatric condition. Stopping lithium and anticonvulsants is standard practice for ECT, however. We limit the risks of the medication washout in the following manner. First patients who it is believed cannot tolerate medication withdrawal are excluded from the study (see Table 2). Second, any patient who finds the medication withdrawal intolerable will be withdrawn. Third, any patient who on clinical grounds requires mood stabilizers or changes in medications during the trial are withdrawn and offered the requisite treatment. Patients are in close contact with the MUSC and GRU clinicians and their primary psychiatrists. We have used these procedures in several hundred patients in our ECT clinical services and in previous ECT research at MUSC and GRU and rarely have patients had to be withdrawn from the study due to intolerance of the washout or related factors.

Delay in Start of Alternative or Continuation Therapy. Two or three days may elapse between completion of the FEAST/UB RUL ECT course and the completion of post-course research evaluations (e.g., cognitive measures, fMRI, etc.). This interval will occur regardless of clinical outcome of the FEAST/ECT course. At maximum, this delay may extend to 5 days if there are scheduling difficulties. This delay of at most 5 days before starting alternative acute treatment or continuation therapy has the theoretical risk of contributing to or accelerating later relapse. However, it should be noted that in many of our prior research studies we have routinely used a one-week medication-free interval following ECT in order to certify response and/or remission status (Sackeim et al., 2008, Sackeim et al., 1987a, Sackeim et al., 1993, Sackeim et al., 2000b, Sackeim et al., 2009). No untoward effect of this practice was noted. However, more critically, during the short delay, patients will not be medication free. They will continue on the medication regimen that was stabilized

before FEAST/ECT and maintained during the FEAST/ECT course. This should mitigate against potential clinical worsening due to the delay in instituting alternative acute treatment (e.g., nonresponders) or continuation therapy (e.g., remitters).

Confidentiality of the Data. It is always important to protect patient confidentiality, and especially so in the treatment of individuals with severe psychiatric disorders. Several steps will be taken to preserve confidentiality. When research papers are written, no participant identifying information will be reported. All records will be kept in locked files and kept confidential to the extent permitted by law. Electronically stored or transmitted information (computerized data) will not contain the name or other identifiers of participants. Participants will be identified in the electronic data by an arbitrary numeric code. The master list linking these numbers to participants' names will be kept in locked files. Any electronic transmission of information about participants will not contain the name or other personal identifiers and will be encrypted.

C.5 Risk Analysis Summary

The major risks of the research are those associated with receipt of ECT. The experimental treatment condition used here, FEAST, should have reduced risk of cognitive impairment compared to traditional forms of ECT. The use of a 0.3 ms pulse width has been shown to markedly reduce the cognitive side effects of ECT, with little impact on efficacy (Sackeim, 2004a, Sackeim et al., 2008, Loo et al., 2012). FEAST will be administered in such a way that cognitive side effects should be less intense and/or persistent than that which regularly occurs with older methods that do not take into account variation in seizure threshold (American Psychiatric Association, 2001). The use of a unidirectional current and focal stimulation should contribute to further reductions in cognitive side effects, although this is not certain.

We do not anticipate that this form of ECT (unidirectional, ultrabrief pulse with spatial targeting) will have an impact on efficacy. Were there an effect, it is anticipated that this form of treatment would confer lesser benefit. Given this possibility, provision has been made to identify early patients who do not benefit sufficiently from FEAST and offer them alternative treatment. That treatment will intensify in a stepwise manner the form of ECT administered. Specifically, as clinically indicated, patients who show insufficient benefit will have the dosage of

the unidirectional, ultrabrief pulse stimulus increased (from 6xST to 9xST), followed by a switch to high dosage RUL ECT with wide pulse width (1 ms), followed by use of traditional bilateral ECT. Thus, the protocol involves close monitoring of objective and subjective side effects and includes provision for alternative treatment for patients who do not respond clinically to initial treatment assignment. All of the assessment procedures are noninvasive, with several specifically geared to track the effects of treatment on cognition. Patients who consent to the protocol have the option of declining participation in specific procedures (e.g., fMRI), but can retain participation in the remaining procedures. Explicit provisions have been made to identify and manage complications.

Patients in the comparison group are selected from those referred for ECT and scheduled to start with ultrabrief, right unilateral (UB RUL) treatment. This treatment is routine in the US and internationally, and is considered to manifest the least short- and long-term cognitive side effects compared to other ECT modalities. Participation in this protocol presents no additional risks.

D. Device and Site Safety

Several procedures will be in place to enhance safety in use of the device at the Institute of Psychiatry at MUSC and the two facilities at the GRU (Augusta, GA and Aiken, SC) .

D.1 Controlled Access Area

The device will be used only in the dedicated area used for the delivery of ECT at the Institute of Psychiatry at MUSC on the fifth floor. When not in use, the Spectrum 5000Q FEAST device will be shut off and the room and suite housing it is locked. Identical precautions will be taken in the GRU ECT suites in Augusta, GA and Aiken, SC.

D.2 Device Calibration and Evaluation

All the quality control procedures recommended by the manufacturer in the testing and calibration of the Spectrum 5000Q will be followed, including verifying the correct operation of the circuitry that determine whether bidirectional or unidirectional stimulation is delivered. These assessments of device integrity and calibration will be conducted on each device at each site prior to first use and then again at least every 6 months.

D.3 Screening of Subjects Prior to Treatment

As described above, the screening assessment of potential subjects will identify and exclude from participation individuals with current or past medical conditions that may place them at increased risk for adverse effects from ECT or who are unlikely to benefit. Screening will involve physician evaluation, physical examination, and blood work.

D.4 Conduct of FEAST

The conduct of FEAST is detailed in Section IV.B.6. The procedures are described with respect to all aspects of the administration of FEAST, including management of concomitant medications, provision of anesthesia, stimulus dosing, physiological monitoring, and data logging. Prior to study initiation, training sessions will be held in the use of the Spectrum 5000Q FEAST device with all Study Psychiatrists. The study monitor and sponsor will regularly attend treatment sessions to document compliance with study procedures.

D.5 Adjustment of Stimulation Intensity to Individual Seizure Threshold

The most important factor determining the safe use of the device is the dosing of the electrical stimulus. Determining the seizure threshold and adjusting the dose relative to this threshold is concerned the most precise method for stimulus delivery in ECT (American Psychiatric Association, 2001). Stimulus dosing based on the empirical titration (method of limits) method is routine practice at the MUSC and the GRU, and was introduced to the field by Dr. Sackeim. The titration schedule specific to the use of FEAST was presented above (Section IV.B.6). An identical titration schedule will be used at first treatment in the UB RUL ECT group. The maximum dosage (charge) to be administered in this protocol with this device is 576 mC (see Table 4 - titration schedule), the same as the maximal output of the US marketed Spectrum 5000Q

D.6 Protection From Excessive Electrical Dosage

The Spectrum 5000Q FEAST device retains all the safety features of the commercial Spectrum 5000Q. These features include internal tests of the integrity of device operation and the accuracy of stimulus output when the device is powered on and following the completion of each treatment. A continuous static impedance measurement is provided, and the device will not arm for stimulus delivery if static impedance is below 100 or above 5,000 ohms. Under situations of inadequate electrode contact (e.g., slippage), the device automatically terminates stimulus delivery when the delivered voltage be would above the cutoff of 400 V. Each of the stimulus parameters is measured during delivery. If any parameter exceeds

specified tolerances, stimulus delivery is automatically terminated. The operator (Study Psychiatrist) can terminate stimulus delivery at any moment by releasing the treatment button.

D.7 Supervision of Patients During Treatment Sessions

Treatment sessions will be conducted under the supervision of trained personnel already privileged in the delivery of ECT at the MUSC and GRU, and further trained in the delivery of FEAST. These personnel include the Study Psychiatrist, Anesthesiologist, a nurse attending to the patient in the treatment room and another nurse attending to the patient in the recovery room. These personnel will be in visual and auditory contact with the patients at all times. The study procedures prescribe physiological monitoring of EEG, ECG, pulse oximetry, and blood pressure. The procedures for the provision of FEAST and the monitoring of patients exceed the standards recommended in the last report of the American Psychiatric Association Task Force on ECT (American Psychiatric Association, 2001).

D.8 Emergency Medical Procedures

Each treatment area is equipped and staffed to handle medical emergencies that may arise during or following the conduct of ECT. A standard crash cart is available in the treatment room. During the administration of FEAST, patients are attended to by an experienced Study Psychiatrist (credentialed in the administration of ECT at the site), an anesthesiologist, and a registered nurse. Nursing personnel are responsible for recovery room care. At each site, emergency medical facilities are readily available, if needed.

D.9 Fire Precautions

Fire extinguishers are available and easily accessible in the treatment and recovery areas. Fire precautions are in accordance with the regulations of the Institute of Psychiatry at MUSC and the Department of Psychiatry, GRU.

D.10 Environmental Impact Claim for Exclusion

We claim categorical exclusion for this study as provided for in 21 CFR section 25.24 (e) 7. The device shipped under the Investigational Device Exemption is intended to be used for clinical studies in which waste will be controlled or the amount of waste expected to enter the environment may reasonably be expected to be nontoxic.

E. Device Description (Provided by the Manufacturer)

E.1 Identification of Legally Marketed Device

The legally marketed devices, the MECTA Spectrum 5000 and 4000 series, are the current generation of MECTA Spectrum 5000 and 4000 devices. The FDA 510 K # is K965070, the regulatory class is III, and the product code is 84GXC.

E.2 Description of the Device

The MECTA Spectrum 5000* and Spectrum 4000* ECT devices are the fourth generation of MECTA ECT devices and continue technically to be the state-of-the-art ECT devices, while also continuing to offer even more safety and efficacy clinically. The 5000 devices offer up to six channels of monitoring of ECG and EEG and one Optical Motion Sensor, while the 4000 devices contain only the ECT module of the 5000 devices. As such, they are upgradeable to the 5000 series units. The 5000 Q and 4000 Q offer the user flexibility to manipulate four stimulus parameters to vary energy and charge. The 5000 M and 4000 M offer the user greater simplicity, with one single Stimulus Intensity knob, which varies all four stimulus parameters simultaneously, thus varying energy and charge.

The touch screen provides the user with an interface to set pre-treatment parameters. This provides the user with more flexibility as he can access all menus by simply touching a screen. The LCD, which illuminates the touch screen, provides the user with alphanumerics that guide her/him through self-test, treatment, and monitoring of the EEG, ECG, and OMS. The LCD/touch screen includes choices of eight set-up menus in the 5000 series and one menu in the 4000 series that can help to individualize each patient's treatment. The LCD/ touch screen also provides the user with more data that can be recorded on the patient's record regarding the self-test and treatment to ensure greater safety. Also, up to four channels of physiological monitoring can be seen on the LCD-touch screen.

The two-channel thermal chart recorder provides the user with a hard copy of the self test and treatment parameters. The simplicity of the chart recorder only requires the user to set two gain knobs as the self-test and treatment results are printed automatically. The manual on/off push button offers the user the option of also manually controlling printing. The printout provides two channels of monitoring and also provides the user with elapsed time, date, time of treatment, and patient name. The four stimulus parameters on the M series and Q series are also shown on the LCD/Touch Screen and the continuous updating of the percent

energy on the M series also helps to increase efficacy of treatment.

The hinged cover on the Stimulus Control push button prevents the user from accidentally treating. The Stimulus Status LED is illuminated to offer the user a visual confirmation that the Spectrum is enabled, that the stimulus is being delivered and finally indicates if there is a stimulus delivery fault. The three warning tones during self-test and the constant tone during treatment delivery offer the user enhanced safety during the treatment process. The continuous self-test offers the user far greater accuracy in avoiding aborted or missed seizures as this bio-feedback provides him with acceptable ranges continuously.

The EEG Data Analysis** feature provides analyses on seizure adequacy and allows the clinician to better assess the quality and presumed efficacy of each individual seizure. The Optical Motion Sensor (OMS) allows the user to monitor motor movement during the seizure and provide further valuable information in assessing seizure duration and strength. The event timer, and the leads off information all provide added information for the clinician that allows him/her to better assess and improve clinical efficacy. The event timer is printed on the chart recorder as a permanent record. The leads off feature documents that the EEG or ECG leads are off and notifies the user by providing a message on the LCD Touch Screen.

Ultrabrief ECT uses the parameter of 0.3 milliseconds ultrabrief pulse width which sharply reduces seizure threshold, thus allowing treatments to be given at much lower electrical dosage than had been previously possible. Most critically, when compared to standard brief pulse stimulation, use of ultrabrief parameters results in a profound reduction in cognitive side effects. In many domains, this advantage for ultrabrief stimulation is as large or larger than the difference between bilateral and right unilateral ECT in their cognitive effects. Right unilateral ultrabrief ECT is a clear advance for the field as patients show improvement with little sign of cognitive deficit.

The additional feature of ECT Data Management Software is provided with the devices as external software to use with a stand-alone PC. MECTA Electronic Medical Record (MEMR) software allows the clinician to view all of the traces of physiological monitoring from the Spectrum (up to four EEGs, 1 ECG, and OMS) on an external PC monitor. Up to eight traces can be displayed. These traces of monitoring are viewed in real time throughout the treatment. They can then be

stored on in a MEMR patient database that allows the clinician to store, sort, select, query, print and export multiple patient- and treatment-related variables. This software will automatically record all the treatment parameters administered in a FEAST/ECT session. It will automatically account for multiple stimulations, as often occurs in a titration session. Thus, the EMR software sued in this study will track the treatment parameters administered at each stimulation, as well as the accompanying physiological recordings and patient information.

Two features that offer the user enhanced safety are thorough device internal testing before deliveries and continuous monitoring of every pulse during delivery. All of the above features demand the most advanced technical design, as did the commitment to design to the most stringent domestic and international standards UL 60601, and IEC 60601-1, 60601-1-2, 60601-2-25, 60601-2-26 all of which resulted in far greater safety in the 4000 and 5000 devices to comply with these standards. These standards require that these devices include extensive redundant hardware and software testing and verification to confirm that they are operating correctly. The safety of these devices is unparalleled and as such are an advance that has impacted the safety and efficacy of the ECT treatment dramatically. The regulatory agency approvals that have been granted to the spECTrums are both domestic and international: cUL, UL, TUV Annex II Article 3, Health Canada, EN ISO 13485:2012, EN ISO 9001:2008, KFDA, SDA.

As the technical advances have been a result of the field's demand for greater information, efficacy, and safety, the clinical advances have primarily been ongoing in the field over the last 35 years of MECTA's device history. Therefore, the MECTA 5000, 4000 series are used in a clinical setting with modified ECT. The 5000/4000 series continues to use the constant current bi-directional square waveform and the starter kit items accompanying these devices remains the same with the exception of the hand-held electrodes that have been redesigned with the same redundant safety requirements. The patents that have been issued on the above devices and features are identified with an asterisk.

*U.S. Patent #5,755,744-U.S. Patent #6,014,587- U.K> Patent #GB 2 307 413 B
**Duke U.S. Patent #5,626,627-Duke U.K. Patent #2 304 196 B (Under exclusive license from Duke University)

A patent has also recently been approved for FEAST.

F. Monitoring Procedures

The study monitor will be Dr. Mark George, Professor, Departments of Psychiatry, Neurology, and Radiology, MUSC. Dr. George is highly experienced in the conduct of ECT and clinical trials. He will ensure the quality of the study and establish that the investigators are complying with the signed agreement, the investigational plan, and FDA and IRB regulations. Prior to the conduct of the study, the monitor will establish that the investigators understand the investigational status of the device and the requirements for accountability, the nature of the protocol and investigational plan, the obligations to obtain informed consent, and to comply with FDA and IRB regulations. The study monitor will also establish the feasibility of conducting the study at the site. Throughout the investigation, the monitor will be in regular contact with investigators at each site and will conduct monitoring no less frequently than every 4 mo. The monitor will ensure that the facilities being used continue to be acceptable for the purposes of the study, that the investigational plan is being followed, that any changes to the protocol have received IRB approval and have been reported to the sponsor, that accurate, complete, and current records are maintained, that accurate, complete and timely reports are made to the sponsor and the IRB, and that the investigators are carrying out their agreed-upon duties and are not delegating responsibilities to unspecified staff.

As indicated, in addition to the study monitor, the Brain Stimulation Service Director, Dr. Short, will review each research chart for completeness and accuracy. He will provide independent confirmation that inclusion and exclusion criteria have been met for each patient enrolled and that there is compliance with all other aspects of the investigational plan and the investigator agreement. Similarly, Dr. Rosenquist at the GRU will also review each research chart for completeness and accuracy. He will provide independent confirmation that inclusion and exclusion criteria have been met for each patient enrolled and that there is compliance with all other aspects of the investigational plan and the investigator agreement.

V. Manufacturing Information (PROVIDED BY THE MANUFACTURER)

In the FDA review of the original Spectrum 5000Q FEAST Device IDE application (6/8/05) a number of deficiencies were listed. Several of these related to the modified Spectrum units to be used in the study. These deficiencies are again addressed specifically in Sections V.C, V.D, and V.E.

Because of our preliminary work in humans, we have changed the specifications for the FEAST units from the original application. The modifications to the standard Spectrum for the FEAST IDE will include the following:

- Change voltage limits from 10-400 Volts

This change was approved and included in the ongoing IDE. As noted above, since increasing the voltage cutoff to 400 V there have been no untoward events, including no skin burns.

The 0.3 ms pulse width has been available as part of the standard marketed units since July, 2003 and thus does not constitute a modification or change for the FEAST units. See notes in Section V.C.

Reliability and validity of the manufacturing of these devices is ensured by testing each unit to validate the output of the device. The verification that the Current, Duration, Pulse Width and Frequency are within the acceptable ranges are all tested, recorded and validated in the Manual Test for each device.

Methods of manufacturing are determined by UL, cUL, TUV, ISO 9001 and FDA approvals and are identical to current methods used to manufacture, process, package, store, and install the Spectrum devices.

Facilities and Controls are determined by the UL, cUL, TUV, ISO 9001 and FDA approvals of the device and facility and are identical to current facilities and controls to manufacture, process, package, store and install the Spectrum devices.

RERERENCE APPROPRIATE SECTIONS AND APPENDICES FOR FURTHER DISCUSSION OF THE FOLLOWING DESIGN AND MANUFACTURING REQUIREMENTS:

> Design/engineering drawing of device—Reference Appendix A.1 Block Diagram

Rationale for device design—MECTA has been asked to design a modification to the existing approved Spectrum 5000Q for a research study of FEAST.

Device and Performance specifications—The Spectrum hardware specifications are identical with the exception of the rectifier on the stimulus output and a small change to allow delivery currents down to 100mA. See Section V.D for new verification and validation data. Reference Appendix A.2 and Hardware Modification Section (Section V.B).

Description of Materials- Reference Hardware Modification Section (diodes and electrodes) (Sections V.B and V.E)

Description of Function- Reference Appendix A.2 Block Diagram

Validation Testing for Subsystems and Main System- Reference Appendix A.3 and Section V.D.

Manual Test – which verifies and validates all of the settings.

A. Software Modification

The devices used for the FEAST research are modified versions of MECTA's standard Spectrum 5000 Q product. The Spectrum unit itself has been modified to allow delivery of a unidirectional pulse train (all pulses have current flow in the same direction) and to change the lowest delivery current from 500 mA down to 100 mA. The details of the hardware modifications are covered in a separate document. This document describes the software changes to the Spectrum 5000 Q units.

The software changes provide control and support for the following:

1. Enabling or disabling the hardware unidirectional feature (addition of a menu option), and
2. Extending the lower end of the delivery current range from 500 mA down to 100 mA, and
3. Change the lower voltage limit from 50 down to 10 V.

The addition of a new software "button" in the main menu screen of the Spectrum toggles the unidirectional setting between ON and OFF. The setting is saved in non-volatile memory so that it is retained while the power is off. The software simply controls the hardware line that activates the relay that controls the unidirectional feature. The software was verified by using an oscilloscope to display the delivered voltage across a load resistor for the ON and OFF settings and cycling of the power.

The changes to allow lower currents are more extensive and include the following:

1. Changes of the parameter selection settings to include currents down to 100 mA.
2. Recalibration of the current setting Pulse Width Modulator (PWM) control.
3. Changing the minimum treatment voltage limit from 50 Volts to 10 Volts.
4. Increasing the tolerance on the internal 300 Load impedance measurement from 10 % to 20%.
5. Disabling one of the redundant Energy monitor circuits.

Changes one and two were simple changes to internal tables that specify the allowed range of treatment current and duration. These allow the study to use much lower charge and energy levels than are possible on a standard spECTrum.

The delivered current circuitry utilizes a PWM to set the desired current. In a standard Spectrum, the allowed range is from 500 mA to 900 mA. A linear equation is used to determine the proper PWM setting for the desired current. Extension down to 100 mA required minor changes to the slope and offset of the linear equation (change 3).

The standard Spectrum requires that the delivered voltage be at least 50 Volts (this guarantees that the patient impedance is at least 100 Ohms). This feature detects and notifies the operator when the treatment paddles are shorted together or the current path is too low an impedance due to too much conducting gel etc. Delivery of 100 mA into 100 Ohms requires 10 Volts, so the lower voltage limit has been dropped to 10 Volts (change 4). Before delivery to a patient, the Spectrum delivers energy to an internal 300 Ohm load and verifies that the proper current, voltage,

pulse width, frequency and duration all occur. Dividing the delivered voltage by the delivered current provides a measurement of the 300 Ohm load resistance. For the standard spECTrum, the measured value must be within 10% of 300 Ohms. The PWM allows current to be set in 4 mA steps. This resolution in current constitutes a 5 times larger contribution to measurement error at 100 mA than it does at 500 mA. Similar concerns apply to the voltage measurement circuitry as well, which has a resolution of 0.5 volts. This requires somewhat larger tolerance on the measured values during this delivery test. The allowed impedance measurement variation has been increased to 20% in the FEAST units (change 5). This still puts the unit well within the required regulatory energy measurement specifications of 30% (energy is proportional to impedance).

Finally, the Spectrum includes multiple methods to ensure that excess energy is not delivered to a patient including:

1. Software monitoring of voltage, current, pulse width, frequency and duration during deliver, including verification of all of these measurement functions before treatment of each patient.
2. Independent hardware monitoring of pulse width, frequency, duration and energy, including verification of all of these functions before treatment of each patient.
3. Another software counter that monitors the energy delivery to ensure it does not exceed the expected delivery settings.

The energy monitoring in items 2 and 3 both derive from a hardware circuit that generates a pulse train whose frequency is proportional to delivered power. Counting these pulses measures the energy. The hardware counts the pulses and ensures that the energy does not exceed predetermined safety thresholds. The software (item 3) also counts the pulses as a redundant backup.

When the current setting is much lower than 500 mA, this hardware circuit fails to provide pulses for counting. As a result, the energy measurement is 0. This causes the software backup counter to register an error, since it checks for both too much and too little energy delivery. The hardware counter continues to function as an energy limiting device according to its original design. For FEAST units, the software energy counter has been disabled. This does not compromise the safety, since the

software continues to verify that current, pulse width, frequency and duration are all as specified (within a few percent for each), and that the voltage does not exceed the limit of 400 volts. This is equivalent to measuring the delivery energy. The software counter was originally included as a means to provide a simple measure of the delivered energy. This is done in the FEAST units by calculating the delivered energy from the previously mentioned parameters including the measured delivery voltage.

It is our belief that these changes provide a unit suitable for the FEAST studies, without compromising the safety features of the standard Spectrum product.

These changes simply continue the changes of the previously approved IDE. Even though the new FEAST protocol will use only 800 mA, we have maintained the 100 mA minimum rather than develop new FEAST software and hardware. This decision eliminates the need to change existing FEAST devices.

B. Hardware Modification

The modifications to the Spectrum Hardware are the addition of a full wave bridge on the output and a relay to switch between unidirectional (output passes through the bridge) and bidirectional (output bypasses the bridge). Dynamic current, voltage, impedance, pulse width and frequency are still all constantly measured during delivery.

The full wave bridge consists of four 1N4005 diodes connected in a standard bridge configuration. These parts are rated 1 Amp 600 PIV each. (Spectrum output is limited to 800mA at 400V peak for FEAST devices). The stimulus output of the spectrum is connected to a DPDT relay that connects either the rectified output of the bridge or the bi-directional output of the standard Spectrum to the stimulus connector. The stimulus connector is connected so the negative output (cathode) connects to the remote treat handle of the standard hand-held stimulus cable. The Anode connection will be to the anterior electrode. The relay is switched by writing a bit to a latch on the backplane of the Spectrum. An indication of “UNI” for unidirectional and “BI” for bidirectional mode is displayed on the LCD display of the spectrum. Output is verified by observing the output across a fixed resistor with an oscilloscope.

C. Details on Implementation of the Changes in the FEAST Device

Item 21 in the FDA review (6/8/05) addressed the implementation of two parameter changes: lowering of the minimum pulse width and lowering of the minimum current from 500 to 100 mA. The FDA requested specific details on how these changes would be implemented.

Regarding the 0.3 ms pulse width, we mistakenly included this as a new feature for the FEAST IDE. This has been a part of our standard product since July of 2003, both in the U.S. and abroad. FDA reviewed documentation on this change in preparation for the FDA two day audit of MECTA on 9/4/03 and 9/8/03. This change has been widely accepted and used throughout the world (including the U.S.A.) since then with beneficial results and no reported adverse affects.

The minimum current setting is controlled by table values in both the 386 and 80C592 processors. The minimum current setting in each table has been changed in the code for each processor and recompiled. The hardware was originally designed to operate from well below 500 mA current output to 1000 mA current output, even though the original specifications were for 500-800 mA. During testing of the desired 100 mA setting, it was found that the lowest usable current setting was about 140 mA. An op-amp used to provide a full output swing from 0 to 5 volts to cover the output current range of 0 to 1 Amp was not providing rail to rail outputs when operated between 0 and 5 Volts. The solution was to change the op-amp lower rail voltage to -5. This allowed current settings all the way down to 100 mA without problems. See the attached circuit changes for details.

D. Verification and Validation Data for the modified Spectrum 5000Q

Item 22 in the FDA review (6/8/05) requested verification and validation data for the modified Spectrum units.

Since the Spectrum is a mature product, and the change for the FEAST IDE is very minor, the verification and validation activities have been limited to the specific changes made. The FEAST units will go through our standard manual and automated testing done for every unit shipped (modified slightly for the different current range). This testing, coupled with the extensive internal testing done by each unit before each patient treatment, guarantees that each unit is functioning

properly, including all of its backup safety circuits. A copy of the Overall Quality Plan is attached. (Appendix A.4)

Verification activities for the lower current limit change were straight forward including:

1. Measurement of various delivered currents (100-400 mA) into various load impedances (100-600 ohms) (see data below). The delivered currents were calculated from measurements of the load impedances with a DMM and delivered voltages with a Tektronix TDS 320 digital storage oscilloscope. These were compared to the specified delivery current and required to be within 10%.
2. Standard automated final testing. One of the automated tests verifies accurate calibration of the delivery current.
3. Standard internal testing done by the instrument prior to every patient treatment verifies that correct currents are being delivered

The following representative data was all taken with a 0.5 second duration setting. The voltages were measured with Tektronix TDS 320 digital oscilloscope. The Load resistances were measured with a Fluke 87 True RMS Multi-meter. The worst case delivery current error is 5.0% for 100 mA into 605 Ohms for 0.3 ms.

Table VD. Representative Data Testing Accuracy of FEAST Device Output

Pulse Width	Freq.	Load Resistance	Volts/Current **@ 100** mA	Volts/Current **@ 300** mA	Volts/Current **@ 500** mA	Volts/Current **@ 600** mA	Volts/Current **@ 800** mA
0.3 ms	60 Hz	90 Ohms	Won't allow treatment	Won't allow treatment	Won't allow treatment	Won't allow treatment	Won't allow treatment
0.3 ms	60 Hz	104 Ohms	10.8/**104**	31.2/**300**	51.2/**492**	62.4/**600**	82.0/**788**
0.3 ms	60 Hz	201 Ohms	20.4/**101**	59.2/**295**	98.0/**488**	118/**587**	158/**786**

Notes:

Worst-case conditions occur for shortest pulse width at highest frequency.

The Spectrum uses adaptive current setting. During the delivery of the first 3 pulses, the delivery current is adjusted to make it as accurate as possible and must be within 22% of the expected value. After the first 3 pulses, the current must be within 10% of the expected value. If the current is more than 10% off on any delivered pulse, the Spectrum automatically terminates delivery and

notifies the operator of an error situation. Further, correct current delivery is checked by the Spectrum before each patient treatment by delivering into an internal 300 ohm resistor and verifying that the delivered voltage across the resistor is correct based upon the delivered current (within 8% of expected voltage). If this test fails, patient treatments are inhibited until this and all other internal tests pass.

These verification activities ensure that the modified Spectrum operates correctly in the 100-400 mA range.

Possible faults in the delivered current level and their consequences include:

1. Delivery system fails to turn off current pulse. Hardware pulse width limiter will automatically turn the pulse off after 2.4 ms and force the Spectrum into its error mode which notifies the operator, forces an internal testing cycle, and inhibits further treatments until all internal tests pass. This backup circuit is automatically tested by the unit before every patient treatment and must be working properly before a treatment will be allowed.
2. Delivery current level is wrong (including being too high). Delivered current is measured on every pulse and must be within tolerance or the delivery will be stopped, the operator will be notified, an internal test cycle will be started, and further treatments will be inhibited until all internal tests pass. The current measurement circuit is tested by the unit before every patient treatment and must be working properly before a treatment will be allowed.
3. Current measurement circuit fails. Delivered current is measured on every pulse and must be within tolerance or the delivery will be stopped, the operator will be notified, an internal test cycle will be started, and further treatments will be inhibited until all internal tests pass. The current measurement circuit is tested by the unit before every patient treatment and must be working properly before a treatment will be allowed. This includes a test at two different currents, both of which must pass.

Verification activities for the voltage limit changes are straight forward including:

1. Verifying the modified Spectrum will not allow any delivery into static impedances below 100 Ohms.

2. Verifying that the modified Spectrum successfully delivers 100 mA into 104 Ohms (10.4 Volts).

See the above data table summarizing these results. These verification activities ensure that the modified Spectrum operates correctly over the required voltage range and will not deliver when the voltage is outside of that range.

Possible faults in the delivered voltage level and their consequences include:

1. Delivered voltage too high (broken delivery cables, poor skin prep, etc.). The Spectrum measures the voltage on every delivered pulse and when it is out of range it will terminate the delivery, notify the user, force an internal test cycle, inhibit further treatments until all internal tests pass. The voltage measurement circuit is tested by the unit before every treatment.
2. Voltage measurement circuit fails and reports a value between 10 and 400 Volts (very unlikely failure mode). The voltage measurement circuit is tested by the unit before each treatment and must read the voltage within 8% of the expected value or treatments will be inhibited. This failure would not be detected until the next internal test cycle after the patient treatment is finished. It is then checked at two different voltage readings. This failure, in conjunction with a poor patient electrode contact, could result in a skin burn for that single treatment.
3. Voltage measurement circuit fails and reports a value below 10 or above 400 Volts. The Spectrum measures the voltage on every delivered pulse and when it is out of range it will terminate the delivery, notify the user, force an internal test cycle, inhibit further treatments until all internal tests pass. The voltage measurement circuit is tested by the unit before every treatment.

As noted under Section V.C above, no changes were made related to the pulse-width, so no additional verification or validation activities have been done in this regard for the FEAST units.

D. Feast Electrodes

The anode electrode will be made of the same material as the conventional Spectrum electrodes (stainless steel) and will be 1.25" in diameter. The commercial Spectrum electrodes are circular and 2" in diameter. The cathode electrode will connect to the handle of the current Spectrum hand held stimulus cable. It will be

made of stainless steel and be rectangular in shape (except for radius corners) and it will be 2" wide and 3" long. It will be made malleable so it can be bent to conform to the relative shape of the patient's head. Standard jell and paste will be used to improve patient contact (just as in the current Spectrum). See Appendix 4 (Electrode shapes)

The updated information related to the risk of skin burns was addressed earlier.

VI. Investigator Agreement

A signed Investigator Agreement by each of the active investigators is included in Appendix B. These agreements describe each investigator's qualifications. A copy of each investigator's curriculum vitae is attached. These agreements have been signed by:

Mark S. George, MD
Baron Short, MD
Vaughn McCall, MD
Peter Rosenquist, MD
Harold A. Sackeim, Ph.D.

A blank sample agreement is presented below:

I have examined the protocol designed by Dr. Mark George, entitled, **Focal Electrically-Administered Seizure Therapy (FEAST)** and have fully discussed the objectives of this trial and contents of this protocol with Dr. George, Sackeim and the rest of the Executive Committee. I agree to conduct this investigation in accordance with the agreement, the investigational plan, Part 812 and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB and FDA.

I understand that, should the decision be made to terminate prematurely or suspend the trial at any time for whatever reason, such decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the trial I will communicate immediately in writing to Dr. George.

I also certify that I have never been terminated from other investigational projects. If so, an explanation of the circumstances that led to termination and a statement of commitment will be attached.

Investigator Name (Please Print) _____

Investigator Address _____

_____

Telephone Number_____ Fax Number _____

Investigator Qualifications _____

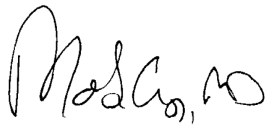
_____

_____

Signature _____Date _____

VII. INVESTIGATOR CERTIFICATION

I certify that all personnel participating in the investigation have agreed to follow the applicable clinical investigational protocol contained in this application. I have submitted the written protocol to the Institutional Review Board. All investigators participating in this investigation understand that they are bound to adhere to it as a condition of IRB approval, when granted. I certify that the list of investigators in this application identifies all current investigators. Additional participating investigators in the investigation will be added to the investigation only when they have obtained IRB approval and have signed an investigator agreement.



_____ ___2/12/15_____
Signature Date

Mark S. George, MD
Name (print)

Investigators who have signed the agreement:

Mark S George, M.D.

Harold A. Sackeim, Ph.D.
Baron Short, M.D.
Vaughn McCall, M.D.
Peter Rosenquist, M.D.

Mark George, Vaughn McCall, Peter Rosenquist, Harold A. Sackeim., or Baron Short will not promote or commercialize the device in the US during clinical investigation. There will be no charge to the subjects for use of the MECTA Spectrum 5000Q FEAST stimulator during this study.

Mark George certifies that all investigators who will take part in the study for the MECTA 5000Q FEAST stimulator will read and sign the Investigator Agreement and Certification before participating in the study. No investigator will participate in the investigation until the agreement has been signed.

Mark S. George, MD

VIII. IRB INFORMATION

MUSC IRB -I

IX. SECONDARY SITE(S)

Georgia Regents University (GRU)

X. COMMERCIALIZATION STATEMENT

The device is not commercialized. No sale will take place and no site will be charged for its use.

XI. DEVICE LABELING

The modified Spectrum 5000Q FEAST Stimulators used in this study are donated to the Institute of Psychiatry at MUSC and the Department of Psychiatry, GRU by the MECTA Corporation. These devices were obtained for research purposes and will not be sold. We request permission for investigational human use for the protocol described in this application. When IDE approval is obtained this device will be labeled, "CAUTION—Investigational Device. Limited by Federal (or United States) law to investigational use." Research subjects will not be charged for the costs of the device or for any other aspect of the research. Subject payments in this protocol are limited to reimbursement for travel expenses and time devoted to follow-up evaluations after discharge from the hospital.

XII. INFORMED CONSENTS

(We include two informed consents for MUSC, one for the FEAST patients and one for the matched RUL patients. GRU researchers will modify them slightly to conform to GRU language and verbiage but the elements will be the same across the two sites.)

Medical University of South Carolina Informed Consent Form

Focal Electrically-Administered Seizure Therapy (FEAST):

Studies at two enrolling sites to further test and refine the treatment

A. PURPOSE AND BACKGROUND:

Your doctor has recommended that you receive treatment with electroconvulsive therapy (ECT). You have been asked to participate in a research study. The study examines the effects of a new form of ECT on mood and thinking. For ECT to work, doctors have to induce a seizure during treatment. Work over the past 20 years has greatly reduced the amount of electricity needed to induce a seizure, and where the current goes in the brain. This new type of ECT attempts to restrict the brain seizure to the frontal lobe. This new type of ECT is called Focal Electrically-Administered Seizure Therapy (FEAST). Your participation in this study is purely voluntary. You are being asked to participate in this study because you have major depression that has not responded to other depression therapies. The principal investigator is Dr. Mark George (843 876 5142). This study is taking place at two sites – MUSC and Georgia Regents University and will involve 60 patients, about 30 of whom will come from MUSC.

You have been told that besides FEAST there are other treatments for depression, which include medication, psychotherapy, transcranial magnetic stimulation (TMS) and conventional forms of ECT. These alternative treatments have their own benefits and risks. The question of whether FEAST or an alternative treatment is most appropriate for you depends on your prior experience with these treatments, the nature of your psychiatric condition, and other considerations. Why ECT has been recommended for your specific case has been explained to you. ECT is available at many hospitals and you do not have to participate in this research study to receive ECT.

PROCEDURES:

If you agree to be in this study, the following will happen*:*

Overall, this study investigates FEAST in the same manner that you would normally receive conventional ECT. So, the only additional time or procedures that are purely for research are some questionnaires at the beginning and weekly through your acute course, and the 2,4 and 6 month followup visits (and the MRI scans if you elect to do those). The procedures and risks below pertain to ECT in general, as well as to the new form of ECT that we are researching, called FEAST.

In general, you can stay on most of your medications that would normally be allowed with ECT. We may suggest some changes in your medications (if any) that were used to treat your psychiatric at least five days before you receive FEAST. This is part of standard ECT practice. If there are medications that you are taking that are not allowed in this research study and you need to stop taking them in order to be in the trial, we will discuss the specific risks associated with that. The procedures used in FEAST will be identical to those used in conventional ECT except that the current will flow in one (unidirectional) instead of two directions (bidirectional) and special electrodes will be used to concentrate the current to the right frontal lobe. You will receive treatments at a rate of three a week, usually for two to six weeks, depending on your doctor's clinical judgment of what would be best for you.

During this period, if your depressive condition does not respond to treatment with FEAST, your doctor may change the treatment you receive to a traditional form of ECT. If the type of treatment is changed, all the testing procedures described below will be administered before the change, as well as following the ECT course.

At each treatment, you will be under the care of an anesthesiologist, a psychiatrist, and a nurse. To receive each treatment you will be brought to a specially equipped room. The treatments are given in the morning, before breakfast. Because the treatments involve general anesthesia, you will have had nothing to drink or eat for at least eight hours before each treatment. When you come to the treatment room, before beginning the treatment, in order to spare you the discomfort from many “needle sticks”, a thin plastic tube (an “IV line” or catheter) will be placed in your arm so that medications can be given to you. You will be given an anesthetic drug that will quickly put you to sleep. You will be given a second drug that will relax your muscles. Because you will be asleep, you will not experience pain or discomfort during the procedure. You will not feel the electrical current, and when you wake up you will have no memory of the treatment.

To prepare for the treatments, monitoring sensors will be placed on your head and other parts of your body. A blood pressure cuff will be placed on one of your limbs. This is done to monitor your brain waves, your heart, and your blood pressure. These recordings involve no pain or discomfort. After you are asleep, a small, carefully controlled amount of electricity will be passed between two electrodes that have been placed on your head. When the current is passed, a generalized seizure is produced in the brain. Because you will have been given a medication to relax your muscles, muscular contractions in your body that would ordinarily accompany a seizure will be markedly softened. The seizure will last

for approximately one minute. Within a few minutes, the anesthetic will wear off and you will awaken. During the procedure your heart rate, blood pressure, and other functions will be monitored. You will be given oxygen to breathe. After waking up from the anesthesia, you will be brought to a recovery room, where you will be observed until it is time to leave the ECT area.

You will be closely monitored in terms of the effects of the treatments on your symptoms and thinking and memory. If the evaluation team feels that you are improving at too slow a rate, they may recommend an increase in the electrical dosage administered or they may recommend that FEAST be stopped. Likewise, if excessive cognitive side effects are seen, FEAST may be stopped and a traditional form of ECT offered.

Clinical Evaluation and Neuropsychological Procedures: Before starting FEAST you will participate in interviews and will be asked questions about your current psychiatric condition, any psychological problems you may have had in the past, your family's history of psychological problems, your medical history, and your attitudes about receiving FEAST.

A member of your family may also be asked to participate in some interviews to provide further information about your psychological condition and that of members of your family. You will also be asked to complete questionnaires that assess your psychological state.

During your course of treatment and during the week following this course, you will participate in interviews to assess changes in your symptoms. Following the acute course (4 weeks of treatment), we will ask you to participate in clinical interviews at 2 months, 4 months and 6 months following your recovery. If travel is a major problem, some of these interviews may be conducted by telephone by a member of the clinical research staff. They will take place at two, four and 6 months after the end of the FEAST acute course.

To assess the effects of treatment on your cognitive abilities (thinking and memory), you will receive a battery of neuropsychological tests during the week before starting FEAST, following the sixth/seventh treatment, during the first week after treatment, and two, four, and six months following the completion of FEAST. Each administration of this battery will take about an hour. The battery includes a series of tasks to assess your memory for material that you will be asked to learn, for events that occurred in your life, and for public events. On other tasks you will be asked to repeat phrases that you have heard, solve puzzles, and other similar tests of thinking.

At each treatment session, just before you receive FEAST, you will be asked to remember a set of information. Following each treatment, after you wake up, you will be asked to recall or recognize this material and you will be administered an additional set of brief neuropsychological tasks.

EEG Procedures: The naturally occurring electrical activity of brain regions will be measured by recording the EEG (electroencephalogram). For the EEG examinations, your scalp will be

cleaned and sensors placed on your head and near your eyes. The sensors will not pass any electricity to you, but will be used to measure the brain waves that are naturally occurring. During this examination, measurements will be taken while you lie quietly with your eyes closed and while you lie quietly with your eyes open. These procedures will be conducted prior to treatment, at two or more of your treatment sessions, during the week following treatment, and at two-month follow-up sessions.

Functional Magnetic Resonance Imaging (fMRI) Procedures: You may choose to also have two MRI scans done as part of this research, one before the FEAST treatments and then one right at the end of the acute course, about 4 weeks later on average. The time between the scans will depend on how rapidly you improve, and could be as little as one week or as long as 5 weeks apart.

☐Yes, I agree to participate in the MRI scans.

☐No, I do not wish to participate in the MRI scans.

If you do not wish to participate in the MRI scans, you can skip the following paragraphs.

You are being asked to provide a brain image that will be stored for future research. The procedure used to take the brain image is called a Magnetic Resonance Imaging (MRI) scan. It uses magnetic fields and radio waves, and it is completely non-invasive and not harmful. The scan will take pictures of the brain, which will allow investigators to measure the size and shapes of parts of your brain. You will be in the scanner for less than one hour.

If you agree to participate in this fMRI part of the study, the following will happen:

MRI Procedure:

- You will first be asked questions to find out if there are any reasons as to why you might not be able to have an MRI. We will, for example, ask you questions about whether you have any metal in your body that may interfere with the scanner. This does not include things such as dental fillings or surgical pins that are stainless steel. Some people are uncomfortable in small spaces and we will also ask you about this. Women may not be pregnant or breastfeeding. Women must agree to use an effective form of birth control such as a birth control pill, birth control patch, or condoms. Women who are of childbearing age who may be pregnant will provide a urine sample for pregnancy testing.
- If there are no reasons to prevent you from having an MRI scan and you agree to participate, your first one hour MRI scan will be scheduled. The MRI scanning will occur at the MUSC Center for Advanced Imaging Research MRI scanner located at 30 Bee Street, just across the street from the Psychiatry Building.
- The night before the scan session, we encourage you to have a normal night's sleep. Please do not drink any coffee within 2 hours before the scan.

- Before the scan session, you will meet with a representative of the study (the doctor in charge or one of the research staff) to review what will happen during the scan.
- Pictures of your brain will be collected using a Magnetic Resonance Imaging (MRI) Scanner, which involves the following:
- You will be placed on a table that will slide into the scanner.
- A large plastic cylinder with holes in it will surround your head. This is the part of the scanner which will make the pictures of your brain.
- Foam or a pillow will be placed around your head to keep your head still.
- After you are made comfortable on your back on the table, the table will slide into the MRI scanner. It is wider than your body and you can see out into the room as you are lying down.
- During the scans, you will be asked to lie still and be awake. Occasionally the MRI tech or the research assistant will talk with you and instruct you in how to perform the tasks. You will be able to see the tasks on a computer screen projected into the scanner.
- You will hear loud noises from the scanner during the imaging study. These are normal operating sounds that the scanner makes. You will be given earplugs to help soften the noise. During the imaging session you will be able to talk to the investigators and the MRI technician, and they will be able to talk to you.
- Your scan will be labeled with a numerical code that does not directly identify you in any way other than that you are a research subject in this study. The scan will contain your age and the scan date/time. Your scan will then be stored on secure computers at MUSC. Your and other participants' images will be shared with the FEAST investigators and collaborators for this research study.

You may be withdrawn from this imaging study without your consent if the researchers believe it is in your best interest or if you fail to follow study procedures. For example, if there is concern that you have metal in your body we would not allow the MRI scan to proceed.

Repeat Scan – About 4-5 weeks after the first scan, we will invite you back to the MRI center to do exactly the same things as you did on the first scanning visit. We will try and coordinate this scanning session with other testing that is part of the parent study. That may not always be possible and we will then need for you to make a separate visit. Just like the first visit, the second return imaging visit should not last more than one hour.

B. DURATION:

Participation in the study will take about 3-5 weeks during the acute treatment phase, with followup visits at 2,4 and 6 months following the acute course. This research is done on top of your clinical care. The additional time required for the research aspect is several hours at the beginning in terms of questions, an additional hour each week for ratings, the MRI visits if you choose to participate in those, and the followup visits, each of which is about 2-3 hours. Thus the total duration and time of the research is about 24 hours over the 6

months.

C. RISKS/DISCOMFORTS:

Treatment Procedures: Like other medical procedures, FEAST involves some risks. The primary risk of treatment with FEAST is that it may not be effective. FEAST is a new ECT method and is still being studied and it cannot be known ahead of time whether it has the same beneficial effects as standard ECT. In the first 35 patients that we have treated so far, FEAST appears to have antidepressant effects similar to conventional ECT. However, if you do not benefit from FEAST, you will be offered treatment with a standard form of ECT. We will be monitoring your clinical response each visit and there is a formula or algorithm for switching you back to conventional ECT if you are not making progress. We will talk with you about this progress at each visit.

A common side effect of ECT is decreased memory functioning. This may also occur with FEAST, although the effect on memory is expected to be less than with traditional forms of ECT. The degree of disruption of memory is likely to be related to the number and type of treatments given. A smaller number of treatments are likely to produce less memory impairment than a larger number of treatments. The memory difficulties with ECT have a characteristic pattern. Shortly following a treatment, the problems with memory are most pronounced. As time from treatment increases, memory functioning improves. Shortly after the course of FEAST, you may experience difficulties remembering events that happened before and while you received FEAST. Your spottiness in memory for past events may extend back to several months before you received FEAST, and in rare instances, to one, two, or more years. Many of these memories will return during the first few months following the FEAST course. However, you may be left with permanent gaps in memory, particularly for events that occurred close in time to the FEAST course. In addition, for a short period following FEAST, you may experience difficulty in learning and remembering new events. This difficulty in forming new memories should be transient and will most likely subside within several weeks following the FEAST course.

Individuals vary considerably in the extent to which they experience confusion and memory problems during and shortly following treatment with ECT. However, in part because psychiatric conditions themselves produce impairments in learning and memory, most patients report that their learning and memory functioning is improved after ECT compared to their functioning prior to the treatment course. Objective tests indicate that many aspects of thinking are improved following ECT, but that, nonetheless, there are specific problems in memory, as described above. While it is expected that FEAST will have reduced negative effects on thinking and memory compared to ECT, this cannot be guaranteed. A small minority of patients treated with ECT report severe problems in memory that remain for months or even years. The reasons for these exceptional reports of long-lasting impairment are not fully understood. However, as with any medical treatment, individuals who receive ECT differ in the extent to which they experience side effects. Rarely, ECT may result in permanent and extensive gaps in memory.

Because of the possible problems with confusion and memory, it is important that you not make important personal or business decisions during the FEAST course or immediately following the course. This may mean postponing decisions regarding financial or family matters. After the treatment course, you will begin a "convalescence period," usually one to three weeks, but which varies from patient to patient. During this period, you should refrain from driving, transacting business, or other activities for which impairment of concentration or memory may be problematic, until so advised by your doctor.

When you awaken after each FEAST treatment, you may experience confusion. The confusion usually goes away within an hour. Shortly after the treatment, you may have a headache, muscle soreness, or nausea. These side effects usually respond to simple treatment, such as Tylenol® for muscle soreness or headache and Reglan® for nausea. More serious medical complications with ECT are rare, and should be very infrequent with FEAST. With modern anesthetic techniques, dislocations or bone fracture, and dental complications very rarely occur. As with any general anesthetic procedure, there is a remote possibility of death. It is estimated that fatality associated with ECT occurs approximately one per 10,000 patients treated. While also rare, the most common medical complications with ECT are irregularities in heart rate and rhythm, which can be effectively treated in nearly all cases. FEAST should have similar complications to ECT, although it is anticipated that their frequency and/or severity will be reduced with FEAST when compared to ECT.

To reduce the risk of medical complications, you will receive a careful medical evaluation prior to starting FEAST. However, in spite of precautions there is a small chance that you might experience a medical complication. Should this occur, medical care and treatment will be instituted immediately and facilities are available to handle emergencies.

Clinical Evaluation Procedures: There are no anticipated risks to you. You may find the interviews about your psychological condition upsetting, but no more so than the psychiatric interviews you would undergo as part of your care.

EEG Procedures: There are no anticipated risks associated with the EEG examinations.

fMRI Procedures: (The following pertains only to those also doing the fMRI study).MRI tests are non-invasive and painless. 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. There are no known additional risks associated with high-speed MRI. Both the conventional and the high speed MRI systems have been approved by the U.S. Food and Drug Administration (FDA) and will be operated within the standards reviewed and accepted by the FDA.

However, an MRI may cause you to feel claustrophobic (uncomfortable in a small space) or anxious from the banging noises made by the machine. Most subjects find the procedure

easy, and often fall asleep during the scanning. We ask that you try to stay awake since if you fall asleep and suddenly wake up, you may move and this will affect the image.

Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during your examination, which could in the process possibly, harm you. Precautions have been taken to prevent such an event from happening; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have a MRI.

Having an MRI may mean some added discomfort to you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the study. Temporary hearing loss has been reported from the loud noise. You will wear earplugs during the scan to help prevent this.

This MRI scan will be used to answer research questions, not to examine your brain medically. This MRI scan is not a substitute for one a doctor would order. It may not show problems that would be picked up by a medical MRI scan. Nevertheless, a neuroradiologist (a doctor trained in reading MRI brain scans) will review all scans and if they believe that there may be a medical problem in your MRI scan, we will ask your permission to contact your primary care physician. If you do not have a primary care physician, we will assist you in finding a doctor to follow up on any finding that may not be normal.

Another risk relates to the loss of privacy as images will be shared with other scientists. Additional data included with the image are the date and time of the scan and your age at the time of the scan. We will make every effort to protect your confidentiality and make sure that your identity does not become known. All written information will be stored in a locked file cabinet, and electronic data will be encrypted. A limited number of staff members will have access to the data. However, there is a slight risk of a breach of security.

Your brain scan will be labeled with a numeric code only and will not contain your name, initials, date of birth, social security number, or any other information that could identify you directly. The image will contain the date/time of your scan and your age at the time of the scan. The scans will be securely stored at the Center for Biomedical Imaging (CBI) Archive at MUSC.

Research records will be kept confidential to the extent allowed by law. Federal Privacy Regulations provide safeguards for the privacy, security, and authorized access. Research records may be reviewed by the Institutional Review Board, the Office of Human Research Protection, and the Food and Drug Administration (FDA).

Unknown Risks: The experimental treatments may have unknown side effects to you or to an embryo or fetus should you become pregnant. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

D. BENEFITS:

The potential benefit of the treatment component of this study is that it may lead to improvement in your psychiatric condition.

The neuropsychological procedures, the neurophysiology procedures, and the MRI procedures will not benefit you directly. Many people suffer from the same type of psychiatric condition and many people receive ECT. The information obtained from this study may benefit others, although there is no way to know for sure if this will be so.

E. COSTS:

There is no cost to participate in this research. Specifically, the MRI scans, and additional assessments are paid for by the study.

ECT is a medical procedure covered by almost all insurance carriers. You or your insurance company will be billed for the routine clinic visits, and all standard laboratory tests (e.g. routine blood counts and blood chemistry tests) and ECT treatments. You will not be billed for tests required for purposes of research (e.g. MRI exams).

F. PAYMENT TO PARTICIPANTS:

When you participate in the two-, four-, and six-month follow-up procedures, you will be paid $20.00 for each hour of time that you contribute. For each MRI scan you will be paid $50.00. If you discontinue your participation you will be paid for the amount of time you have contributed to that point. Payments will be made in cash at the visit. If you complete these follow-up assessments, which typically involve up to 3 hours, the total compensation would be $180. With two MRI scans at $50 each, the total possible would be $280.

Payments that you receive from MUSC for participating in a research study are considered taxable income per IRS regulations. Payment types may include, but are not limited to: checks, cash, gift certificates/cards, personal property, and other items of value. If the total amount of payment you receive from MUSC reaches or exceeds $600.00 in a calendar year, you will be issued a Form 1099.

G. ALTERNATIVES:

If you choose not to participate in this study, you could receive other treatments for your condition. The standard therapies for your condition are talking therapy, medications, transcranial magnetic stimulation, or conventional ECT. You and your doctor have discussed why ECT is likely the next best treatment for you and your depression. If you elect

not to participate in this FEAST study, you may still receive standard clinical care and standard ECT.

H. NEW INFORMATION: If there are significant new findings during the course of the study, you will be notified.

I. RELEASE OF MEDICAL RECORDS TO ANYONE OTHER THAN THE INVESTIGATORS: You will be asked to sign a separate release for the release of your medical records.
J. STUDENT PARAGRAPH: Your participation or discontinuance will not constitute an element of your academic performance nor will it be a part of your academic record at this Institution.
K. EMPLOYEE PARTICIPATION: Your participation or discontinuance will not constitute an element of your job performance or evaluation nor will it be a part of your personnel record at this Institution.
L. CLINICAL TRIAL REGISTRY DATABANK: A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

Results of this research will be used for the purposes described in this study. This information may be published, but you will not be identified. Information that is obtained concerning this research that can be identified with you will remain confidential to the extent possible within State and Federal law. The sponsor and the Food and Drug Administration (FDA) will receive copies of the research records. The investigators associated with this study, employees of the sponsor, the FDA, and the MUSC Institutional Review Board for Human Research will have access to identifying information. All records in South Carolina are subject to subpoena by a court of law.

In the event of a study related injury, you should immediately go to the emergency room of the Medical University Hospital, or in case of an emergency go to the nearest hospital, and tell the physician on call that your are in a research study. They will call your study doctor who will make arrangements for your treatment. If the study sponsor does not pay for your treatment, the Medical University Hospital and the physicians who render treatment to you will bill your insurance company. If your insurance company denies coverage or insurance is not available, you will be responsible for payment for all services rendered to you.

Your participation in this study is voluntary. You may refuse to take part in or stop taking part in this study at any time. You should call the investigator in charge of this study if you decide to do this. The data collected on you to this point remains part of the study database and may not be removed. Your decision not to take part in the study will not affect your current or future medical care or any benefits to which you are entitled.

The investigators and/or the sponsor may stop your participation in this study at any time if they decide it is in your best interest. They may also do this if you do not follow the investigator's instructions.

Volunteers Statement

I have been given a chance to ask questions about this research study. These questions have been answered to my satisfaction. If I have any more questions about my participation in this study or study related injury, I may contact _____. I may contact the Medical University of SC Hospital Medical Director (843) 792-9537 concerning medical treatment.

If I have any questions, problems, or concerns, desire further information or wish to offer input, I may contact the Medical University of SC Institutional Review Board for Human Research IRB Manager or the Office of Research Integrity Director at (843) 792-4148. This includes any questions about my rights as a research subject in this study.

I agree to participate in this study. I have been given a copy of this form for my own records.

If you wish to participate, you should sign below.

Signature of Person Obtaining Consent	Date	Signature of Participant	Date

Capacity to Consent Addendum

I have discussed the proposed research with this patient and, in my opinion, this patient understands the benefits and risks and is capable of freely consenting to participate in this research.

DATE

SIGNATURE _____
Study Physician

PRINT NAME _____
Study Physician

I have examined on _____ for the purpose of determining whether he/she is capable of understanding the purpose, nature, risks, benefits and alternatives (including non-participation) of the research, making a decision about participation, and understanding that the decision about participation in the research will involve no penalty or loss of benefits to which the patient is otherwise entitled, for Dr. Mark George's research project "FEAST: Studies at two enrolling sites to further test and refine the treatment". On the basis of this examination I have arrived at the conclusion that:

_____ A. This patient has this capacity at this time.

_____ B. There is a question about this patient's capacity at this time.

_____ C. This patient clearly lacks this capacity.

DATE

SIGNATURE _____
Member of Treatment Team
(M.D. or Ph.D.; Not a co-investigator)

PRINT NAME _____
Member of Treatment Team

Focal Electrically-Administered Seizure Therapy (FEAST):

Studies at two enrolling sites to further test and refine the treatment:

Right Unilateral Ultrabrief ECT as a Comparison to FEAST

M. PURPOSE AND BACKGROUND:

Your doctor has recommended that you receive treatment with electroconvulsive therapy (ECT). You have been asked to participate in a research study. The study seeks to document your clinical progress and brain changes in order to compare a new form of ECT against the current state of the art. **You will be receiving standard state of the art ECT**. The only aspect of your treatment that is research are some additional questions and tests, two MRI scans, and followup visits at 2,4 and 6 months after treatment. The new type of ECT is called Focal Electrically-Administered Seizure Therapy (FEAST). YOU WILL NOT BE GETTING FEAST but will instead be getting standard care. Your participation in this study is purely voluntary. You are being asked to participate in this study because you have a diagnosis of major depression and you have not responded to, or have been intolerant to, other depression therapies. The principal investigator is Dr. Mark George. (843 876 5142) This study is taking place at two sites – MUSC and Georgia Regents University and will involve 60 patients, about 30 of whom will come from MUSC.

You have been told that besides ECT there are other treatments for depression, which include medication, psychotherapy, transcranial magnetic stimulation (TMS) and conventional forms of ECT. These alternative treatments have their own benefits and risks. Why ECT has been recommended for your specific case has been explained to you. ECT is available at many hospitals and you do not have to participate in this research study to receive ECT.

N. PROCEDURES:

If you agree to be in this study, the following will happen*:*

Overall, this study simply follows your clinical progress as you receive ECT. So, the only additional time or procedures that are purely for research are some questionnaires at the beginning and weekly through your acute course, and the 2,4 and 6 month followup visits (and the MRI scans if you elect to do those). The procedures and risks below pertain to ECT in general. The only part that is research are the additional questionnaires and scans.

In general, you can stay on most of your medications that would normally be allowed with ECT. We may suggest some changes in your medications (if any) that were used to treat your psychiatric at least five days before you receive FEAST. This is part of standard ECT practice. If there are medications that you are taking that are not allowed in this research study and you need to stop taking them in order to be in the trial, we will discuss the specific risks associated with that. The procedures used in FEAST will be identical to those used in conventional ECT except that the current will flow in one (unidirectional) instead of two directions (bidirectional) and special electrodes will be used to concentrate the current to the right frontal lobe. You will receive treatments at a rate of three a week, usually for two to six weeks, depending on your doctor's clinical judgment of what would be best for you.

During this period, if your depressive condition does not respond to treatment with right unilateral ultrabrief ECT (which is the current standard), your doctor may change the treatment so that you receive an older form of traditional ECT. If the type of treatment is changed, all the testing procedures described below will be administered before the change, as well as following the ECT course.

At each treatment, you will be under the care of an anesthesiologist, a psychiatrist, and a nurse. To receive each treatment you will be brought to a specially equipped room. The treatments are given in the morning, before breakfast. Because the treatments involve general anesthesia, you will have had nothing to drink or eat for at least eight hours before each treatment. When you come to the treatment room, before beginning the treatment, in order to spare you the discomfort from many “needle sticks”, a thin plastic tube (an “IV line” or catheter) will be placed in your arm so that medications can be given to you. You will be given an anesthetic drug that will quickly put you to sleep. You will be given a second drug that will relax your muscles. Because you will be asleep, you will not experience pain or discomfort during the procedure. You will not feel the electrical current, and when you wake up you will have no memory of the treatment.

To prepare for the treatments, monitoring sensors will be placed on your head and other parts of your body. A blood pressure cuff will be placed on one of your limbs. This is done to monitor your brain waves, your heart, and your blood pressure. These recordings involve no pain or discomfort. After you are asleep, a small, carefully controlled amount of electricity will be passed between two electrodes that have been placed on your head. When the current is passed, a generalized seizure is produced in the brain. Because you will have been given a medication to relax your muscles, muscular contractions in your body that would ordinarily accompany a seizure will be markedly softened. The seizure will last for approximately one minute. Within a few minutes, the anesthetic will wear off and you will awaken. During the procedure your heart rate, blood pressure, and other functions will be monitored. You will be given oxygen to breathe. After waking up from the anesthesia, you will be brought to a recovery room, where you will be observed until it is time to leave the ECT area.

You will be closely monitored in terms of the effects of the treatments on your symptoms and thinking and memory. If the evaluation team feels that you are improving at too slow a rate, they may recommend an increase in the electrical dosage administered or they may recommend that FEAST be stopped. Likewise, if excessive cognitive side effects are seen, Right Unilateral ECT may be stopped and a traditional form of ECT offered.

Clinical Evaluation and Neuropsychological Procedures: Before starting ECT you will participate in interviews and will be asked questions about your current psychiatric condition, any psychological problems you may have had in the past, your family's history of psychological problems, your medical history, and your attitudes about receiving ECT.

A member of your family may also be asked to participate in some interviews to provide further information about your psychological condition and that of members of your family. You will also be asked to complete questionnaires that assess your psychological state.

During your course of treatment and during the week following this course, you will participate in interviews to assess changes in your symptoms. Following the acute course (4 weeks of treatment), we will ask you to participate in clinical interviews at 2 months, 4 months and 6 months following your recovery. If travel is a major problem, some of these interviews may be conducted by telephone by a member of the clinical research staff. They will take place at two, four and 6 months after the end of the ECT acute course.

To assess the effects of treatment on your cognitive abilities (thinking and memory), you will receive a battery of neuropsychological tests during the week before starting ECT, following the sixth/seventh treatment, during the first week after treatment, and two, four, and six months following the completion of ECT. Each administration of this battery will take about an hour. The battery includes a series of tasks to assess your memory for material that you will be asked to learn, for events that occurred in your life, and for public events. On other tasks you will be asked to repeat phrases that you have heard, solve puzzles, and other similar tests of thinking.

At each treatment session, just before you receive ECT, you will be asked to remember a set of information. Following each treatment, after you wake up, you will be asked to recall or recognize this material and you will be administered an additional set of brief neuropsychological tasks.

EEG Procedures: The naturally occurring electrical activity of brain regions will be measured by recording the EEG (electroencephalogram). For the EEG examinations, your scalp will be cleaned and sensors placed on your head and near your eyes. The sensors will not pass any electricity to you, but will be used to measure the brain waves that are naturally occurring. During this examination, measurements will be taken while you lie quietly with your eyes closed and while you lie quietly with your eyes open. These procedures will be conducted prior to treatment, at two or more of your treatment sessions, during the week following treatment, and at two-month follow-up sessions.

Functional Magnetic Resonance Imaging (fMRI) Procedures: You may choose to also have two MRI scans done as part of this research, one before the ECT treatments and then one right at the end of the acute course, about 4 weeks later on average. The time between the scans will depend on how rapidly you improve, and could be as little as one week or as long as 5 weeks apart.

☐Yes, I agree to participate in the MRI scans.

☐No, I do not wish to participate in the MRI scans.

If you do not wish to participate in the MRI scans, you can skip the following paragraphs.

You are being asked to provide a brain image that will be stored for future research. The procedure used to take the brain image is called a Magnetic Resonance Imaging (MRI) scan. It uses magnetic fields and radio waves, and it is completely non-invasive and not harmful. The scan will take pictures of the brain, which will allow investigators to measure the size and shapes of parts of your brain. You will be in the scanner for less than one hour.

If you agree to participate in this fMRI part of the study, the following will happen:

MRI Procedure:

- You will first be asked questions to find out if there are any reasons as to why you might not be able to have an MRI. We will, for example, ask you questions about whether you have any metal in your body that may interfere with the scanner. This does not include things such as dental fillings or surgical pins that are stainless steel. Some people are uncomfortable in small spaces and we will also ask you about this. Women may not be pregnant or breastfeeding. Women must agree to use an effective form of birth control such as a birth control pill, birth control patch, or condoms. Women who are of childbearing age who may be pregnant will provide a urine sample for pregnancy testing.
- If there are no reasons to prevent you from having an MRI scan and you agree to participate, your first one hour MRI scan will be scheduled. The MRI scanning will occur at the MUSC Center for Advanced Imaging Research MRI scanner located at 30 Bee Street, just across the street from the Psychiatry Building.
- The night before the scan session, we encourage you to have a normal night's sleep. Please do not drink any coffee within 2 hours before the scan.
- Before the scan session, you will meet with a representative of the study (the doctor in charge or one of the research staff) to review what will happen during the scan.
- Pictures of your brain will be collected using a Magnetic Resonance Imaging (MRI) Scanner, which involves the following:
- You will be placed on a table that will slide into the scanner.
- A large plastic cylinder with holes in it will surround your head. This is the part of the scanner which will make the pictures of your brain.

- Foam or a pillow will be placed around your head to keep your head still.
- After you are made comfortable on your back on the table, the table will slide into the MRI scanner. It is wider than your body and you can see out into the room as you are lying down.
- During the scans, you will be asked to lie still and be awake. Occasionally the MRI tech or the research assistant will talk with you and instruct you in how to perform the tasks. You will be able to see the tasks on a computer screen projected into the scanner.
- You will hear loud noises from the scanner during the imaging study. These are normal operating sounds that the scanner makes. You will be given earplugs to help soften the noise. During the imaging session you will be able to talk to the investigators and the MRI technician, and they will be able to talk to you.
- Your scan will be labeled with a numerical code that does not directly identify you in any way other than that you are a research subject in this study. The scan will contain your age and the scan date/time. Your scan will then be stored on secure computers at MUSC. Your and other participants' images will be shared with the ECT investigators and collaborators for this research study.

You may be withdrawn from this imaging study without your consent if the researchers believe it is in your best interest or if you fail to follow study procedures. For example, if there is concern that you have metal in your body we would not allow the MRI scan to proceed.

Repeat Scan – About 4-5 weeks after the first scan, we will invite you back to the MRI center to do exactly the same things as you did on the first scanning visit. We will try and coordinate this scanning session with other testing that is part of the parent study. That may not always be possible and we will then need for you to make a separate visit. Just like the first visit, the second return imaging visit should not last more than one hour.

O. DURATION:

Participation in the study will take about 3-5 weeks during the acute treatment phase, with followup visits at 2,4 and 6 months following the acute course. This research is done on top of your clinical care. The additional time required for the research aspect is several hours at the beginning in terms of questions, an additional hour each week for ratings, the MRI visits if you choose to participate in those, and the followup visits, each of which is about 2-3 hours. Thus the total duration and time of the research is about 24 hours over the 6 months.

P. RISKS/DISCOMFORTS:

Treatment Procedures: Like other medical procedures, ECT involves some risks. The primary risk of treatment with ECT is that it may not be effective.

A common side effect of ECT is decreased memory functioning. The degree of disruption of memory is likely to be related to the number and type of treatments given. A smaller number of treatments are likely to produce less memory impairment than a larger number of treatments. The memory difficulties with ECT have a characteristic pattern. Shortly following a treatment, the problems with memory are most pronounced. As time from treatment increases, memory functioning improves. Shortly after the course of ECT, you may experience difficulties remembering events that happened before and while you received ECT. Your spottiness in memory for past events may extend back to several months before you received ECT, and in rare instances, to one, two, or more years. Many of these memories will return during the first few months following the ECT course. However, you may be left with permanent gaps in memory, particularly for events that occurred close in time to the ECT course. In addition, for a short period following ECT, you may experience difficulty in learning and remembering new events. This difficulty in forming new memories should be transient and will most likely subside within several weeks following the ECT course.

Individuals vary considerably in the extent to which they experience confusion and memory problems during and shortly following treatment with ECT. However, in part because psychiatric conditions themselves produce impairments in learning and memory, most patients report that their learning and memory functioning is improved after ECT compared to their functioning prior to the treatment course. Objective tests indicate that many aspects of thinking are improved following ECT, but that, nonetheless, there are specific problems in memory, as described above. A small minority of patients treated with ECT report severe problems in memory that remain for months or even years. The reasons for these exceptional reports of long-lasting impairment are not fully understood. However, as with any medical treatment, individuals who receive ECT differ in the extent to which they experience side effects. Rarely, ECT may result in permanent and extensive gaps in memory.

Because of the possible problems with confusion and memory, it is important that you not make important personal or business decisions during the ECT course or immediately following the course. This may mean postponing decisions regarding financial or family matters. After the treatment course, you will begin a "convalescence period," usually one to three weeks, but which varies from patient to patient. During this period, you should refrain from driving, transacting business, or other activities for which impairment of concentration or memory may be problematic, until so advised by your doctor.

When you awaken after each ECT treatment, you may experience confusion. The confusion usually goes away within an hour. Shortly after the treatment, you may have a headache, muscle soreness, or nausea. These side effects usually respond to simple treatment, such as Tylenol® for muscle soreness or headache and Reglan® for nausea. More serious medical complications with ECT are rare, and should be very infrequent with FEAST. With modern anesthetic techniques, dislocations or bone fracture, and dental complications very rarely occur. As with any general anesthetic procedure, there is a remote possibility of death. It is estimated that fatality associated with ECT occurs approximately one per 10,000 patients

treated. While also rare, the most common medical complications with ECT are irregularities in heart rate and rhythm, which can be effectively treated in nearly all cases.

To reduce the risk of medical complications, you will receive a careful medical evaluation prior to starting ECT. However, in spite of precautions there is a small chance that you might experience a medical complication. Should this occur, medical care and treatment will be instituted immediately and facilities are available to handle emergencies.

Clinical Evaluation Procedures: There are no anticipated risks to you. You may find the interviews about your psychological condition upsetting, but no more so than the psychiatric interviews you would undergo as part of your care.

EEG Procedures: There are no anticipated risks associated with the EEG examinations.

fMRI Procedures: (The following pertains only to those also doing the fMRI study).MRI tests are non-invasive and painless. 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. There are no known additional risks associated with high-speed MRI. Both the conventional and the high speed MRI systems have been approved by the U.S. Food and Drug Administration (FDA) and will be operated within the standards reviewed and accepted by the FDA.

However, an MRI may cause you to feel claustrophobic (uncomfortable in a small space) or anxious from the banging noises made by the machine. Most subjects find the procedure easy, and often fall asleep during the scanning. We ask that you try to stay awake since if you fall asleep and suddenly wake up, you may move and this will affect the image.

Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during your examination, which could in the process possibly, harm you. Precautions have been taken to prevent such an event from happening; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have a MRI.

Having an MRI may mean some added discomfort to you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the study. Temporary hearing loss has been reported from the loud noise. You will wear earplugs during the scan to help prevent this.

This MRI scan will be used to answer research questions, not to examine your brain medically. This MRI scan is not a substitute for one a doctor would order. It may not show problems that would be picked up by a medical MRI scan. Nevertheless, a neuroradiologist

(a doctor trained in reading MRI brain scans) will review all scans and if they believe that there may be a medical problem in your MRI scan, we will ask your permission to contact your primary care physician. If you do not have a primary care physician, we will assist you in finding a doctor to follow up on any finding that may not be normal.

Another risk relates to the loss of privacy as images will be shared with other scientists. Additional data included with the image are the date and time of the scan and your age at the time of the scan. We will make every effort to protect your confidentiality and make sure that your identity does not become known. All written information will be stored in a locked file cabinet, and electronic data will be encrypted. A limited number of staff members will have access to the data. However, there is a slight risk of a breach of security.

Your brain scan will be labeled with a numeric code only and will not contain your name, initials, date of birth, social security number, or any other information that could identify you directly. The image will contain the date/time of your scan and your age at the time of the scan. The scans will be securely stored at the Center for Biomedical Imaging (CBI) Archive at MUSC.

Research records will be kept confidential to the extent allowed by law. Federal Privacy Regulations provide safeguards for the privacy, security, and authorized access. Research records may be reviewed by the Institutional Review Board, the Office of Human Research Protection, and the Food and Drug Administration (FDA).

Unknown Risks: The experimental treatments may have unknown side effects to you or to a fetus or embryo if you were to become pregnant during the acute phase of the study. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

Q. BENEFITS:

The potential benefit of the treatment component of this study is that it may lead to improvement in your psychiatric condition.

The neuropsychological procedures, the neurophysiology procedures, and the MRI procedures will not benefit you directly. Many people suffer from the same type of psychiatric condition and many people receive ECT. The information obtained from this study may benefit others, although there is no way to know for sure if this will be so.

R. COSTS:

There is no cost to participate in this research. Specifically, the MRI scans, and additional assessments are covered by the study.

ECT is a medical procedure covered by almost all insurance carriers. You or your insurance company will be billed for the routine clinic visits, and all standard laboratory tests (e.g.

routine blood counts and blood chemistry tests) and ECT treatments. You will not be billed for tests required for purposes of research (e.g. MRI exams).

S. PAYMENT TO PARTICIPANTS:

When you participate in the two-, four-, and six-month follow-up procedures, you will be paid $20.00 for each hour of time that you contribute. For each MRI scan you will be paid $50.00. If you discontinue your participation you will be paid for the amount of time you have contributed to that point. Payments will be made in cash at the visit. If you complete these follow-up assessments, which typically involve up to 3 hours, the total compensation would be $180. With two MRI scans at $50 each, the total possible would be $280.

Payments that you receive from MUSC for participating in a research study are considered taxable income per IRS regulations. Payment types may include, but are not limited to: checks, cash, gift certificates/cards, personal property, and other items of value. If the total amount of payment you receive from MUSC reaches or exceeds $600.00 in a calendar year, you will be issued a Form 1099.

T. ALTERNATIVES:

If you choose not to participate in this study, you could receive other treatments for your condition. The standard therapies for your condition are talking therapy, medications, transcranial magnetic stimulation, or conventional ECT. You and your doctor have discussed why ECT is likely the next best treatment for you and your depression. If you elect not to participate in this ECT study, you may still receive standard clinical care and standard ECT.

U. NEW INFORMATION: If there are significant new findings during the course of the study, you will be notified.

V. RELEASE OF MEDICAL RECORDS TO ANYONE OTHER THAN THE INVESTIGATORS: You will be asked to sign a separate release for the release of your medical records.

W. STUDENT PARAGRAPH: Your participation or discontinuance will not constitute an element of your academic performance nor will it be a part of your academic record at this Institution.

X. EMPLOYEE PARTICIPATION: Your participation or discontinuance will not constitute an element of your job performance or evaluation nor will it be a part of your personnel record at this Institution.

Y. CLINICAL TRIAL REGISTRY DATABANK: A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

Results of this research will be used for the purposes described in this study. This information may be published, but you will not be identified. Information that is obtained concerning this research that can be identified with you will remain confidential to the extent possible within State and Federal law. The sponsor and the Food and Drug Administration (FDA) will receive copies of the research records. The investigators associated with this study, employees of the sponsor, the FDA, and the MUSC Institutional Review Board for Human Research will have access to identifying information. All records in South Carolina are subject to subpoena by a court of law.

In the event of a study related injury, you should immediately go to the emergency room of the Medical University Hospital, or in case of an emergency go to the nearest hospital, and tell the physician on call that your are in a research study. They will call your study doctor who will make arrangements for your treatment. If the study sponsor does not pay for your treatment, the Medical University Hospital and the physicians who render treatment to you will bill your insurance company. If your insurance company denies coverage or insurance is not available, you will be responsible for payment for all services rendered to you.

Your participation in this study is voluntary. You may refuse to take part in or stop taking part in this study at any time. You should call the investigator in charge of this study if you decide to do this. The data collected on you to this point remains part of the study database and may not be removed. Your decision not to take part in the study will not affect your current or future medical care or any benefits to which you are entitled.

The investigators and/or the sponsor may stop your participation in this study at any time if they decide it is in your best interest. They may also do this if you do not follow the investigator's instructions.

Volunteers Statement

I have been given a chance to ask questions about this research study. These questions have been answered to my satisfaction. If I have any more questions about my participation in this study or study related injury, I may contact _____. I may contact the Medical University of SC Hospital Medical Director (843) 792-9537 concerning medical treatment.

If I have any questions, problems, or concerns, desire further information or wish to offer input, I may contact the Medical University of SC Institutional Review Board for Human Research IRB Manager or the Office of Research Integrity Director at (843) 792-4148. This includes any questions about my rights as a research subject in this study.

I agree to participate in this study. I have been given a copy of this form for my own records.

If you wish to participate, you should sign below.

Signature of Person Obtaining Consent	Date	Signature of Participant	Date

Revised: 2/11/15

Capacity to Consent Addendum

I have discussed the proposed research with this patient and, in my opinion, this patient understands the benefits and risks and is capable of freely consenting to participate in this research.

DATE

SIGNATURE _____
Study Physician

PRINT NAME _____
Study Physician

I have examined on _____ for the purpose of determining whether he/she is capable of understanding the purpose, nature, risks, benefits and alternatives (including non-participation) of the research, making a decision about participation, and understanding that the decision about participation in the research will involve no penalty or loss of benefits to which the patient is otherwise entitled, for Dr. Mark George's research project "FEAST: Studies at two enrolling sites to further test and refine the treatment". On the basis of this examination I have arrived at the conclusion that:

_____ A. This patient has this capacity at this time.

_____ B. There is a question about this patient's capacity at this time.

_____ C. This patient clearly lacks this capacity.

DATE

SIGNATURE _____
Member of Treatment Team
(M.D. or Ph.D.; Not a co-investigator)

PRINT NAME _____
Member of Treatment Team

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