Dear Commissioner Califf,

The National Network of Depression Centers (NNDC), a consortium of major academic centers with interest and expertise in mood disorders, wishes to comment on FDA’s proposed order “Neurological Devices; Reclassification of Electroconvulsive Therapy (ECT) Devices Intended for Use in Treating Severe Major Depressive Episode in Patients 18 Years of Age and Older Who are Treatment Resistant or Require a Rapid Response; Effective Date of Requirement for Premarket Approval for ECT for Certain Specified Intended Uses”. To the extent possible, NNDC’s comments draw upon new data that was not available to FDA at the time of its January, 2011 public hearing on ECT device reclassification, and on a series of discussions among experts of the 24 NNDC Centers of Excellence.

NNDC is aware of the compelling evidence supporting the safe and effective use of ECT for individuals with certain severe psychiatric disorders, and supports FDA’s proposal to reclassify ECT devices from Class III to Class II for the indication of severe major depression episodes that are either treatment resistant or require a rapid response. However, NNDC also believes that the reclassification to Class II should be extended to other disorders where there is substantial evidence supporting efficacy and safety, including catatonia, mania, and acute episodes of schizophrenia associated with severe psychotic, affective, or catatonic symptoms where such episodes are either treatment resistant or require rapid response. In addition, because of the demonstrated high relapse rates during the months following a successful acute ECT series, as well as the growing body of evidence supporting safe and effective use of subsequent intermittent ECT for prophylactic purposes, NNDC experts affirm without reservation that reclassification to Class II should also extend to the use of maintenance ECT for the diagnoses mentioned above.

Because there is no evidence that ECT treatment of acute episodes of the above disorders differs in effectiveness or safety as a function of age, NNDC experts believe that reclassification to Class II should not be limited to the treatment of individuals who are 18 or older. Rather, NNDC believes that any concerns regarding the use of ECT in adolescents and children can and should be handled via the special controls mechanism. Finally, NNDC wishes to comment on the methods by which cognitive functions should be monitored prior to and during an acute ECT course. In that regard, NNDC agrees with FDA that ongoing attention to the presence and severity of cognitive adverse effects represents an important part of the overall treatment process for those receiving ECT.
Efficacy and safety of ECT in disorders other than major depression.

Catatonia. Catatonia is most commonly found in the context of severe major depressive episodes, although it may also occur in conjunction with mania, schizophrenia, or even medical etiologies. It is well-known that ECT has a powerful anti-catatonic therapeutic effect regardless of the underlying diagnosis, with extremely high response rates. For this reason, ECT is considered the preferred treatment for patients whose response to benzodiazepines, which constitute the first line treatment for these conditions, is inadequate. Catatonia is often a life-threatening condition, and NNDC experts believe that preventing access to the only effective treatment alternative in such cases would be unethical. NNDC experts also believe that because catatonia is uncommon and is typically associated with mutism and inability to respond to questions, it would be impossible to carry out prospective controlled trials in this country. For this reason, NNDC experts believe that it would be inappropriate to withhold reclassification of ECT device use from Class III to Class II for treatment of catatonia because of the absence of such studies.

Mania: In its proposed rule, FDA noted much of the compelling data supporting the efficacy and safety of ECT in the treatment of unipolar and bipolar depression. However, because bipolar disorder is a single disorder, which may present as depression, mania, or as a mixed state, it is not surprising that ECT is as effective in the treatment of acute manic presentations as it is with depressive presentations. In this regard, a role for ECT is noted in both national and international guidelines for the treatment of acute manic episodes. There is also evidence supporting the use of maintenance ECT for patients who have had a positive response to an acute ECT course but cannot be effectively managed with maintenance medications alone. Present practice of ECT for acute mania is largely reserved for use in severely ill patients who are either treatment resistant to anti-manic psychotropic agents or require urgent response because of potentially life-threatening manic excitement or catatonic presentations. As with catatonia, NNDC experts believe that it would be unethical to withhold access to an effective treatment in these latter situations where no effective treatment alternatives exist.

Schizophrenia. A large body of literature since 1980 supports the efficacy of ECT combined with antipsychotic medications for patients with severe positive symptom (psychotic) schizophrenia and schizoaffective disorder who have not responded to antipsychotic medication alone. On the strength of these findings, both national and international treatment guidelines for treatment of acute schizophrenic episodes include ECT combined with antipsychotic medication for management of treatment resistant cases. Of particular interest is a recent study which randomly assigned clozapine nonresponders to either combined ECT and clozapine or clozapine alone. Not only did this study find a 50% responder rate in the ECT/clozapine group vs 0% responder rate in the clozapine alone group, but when the research patients in the clozapine alone group then received a course of combined ECT plus clozapine, 47% of them became responders. In addition, a recent meta-analysis of studies administering combined ECT and clozapine to schizophrenics who had failed to respond to clozapine alone reported an overall 66% responder rate. Together, these response rates are extraordinarily high for a patient population who have no effective treatment alternatives. For this reason, NNDC experts believe that reclassification of ECT devices to Class II is indicated for severely ill individuals with positive symptom schizophrenia or schizoaffective disorder who have failed a clozapine trial.

Because acute improvement with combined ECT and clozapine is difficult to maintain with continuation of clozapine alone, it is understood that it is generally necessary to enroll such patients in a maintenance ECT program to supplement psychotropic management, with an ECT frequency of 1-2 per month typically needed. If that is not done, there is a substantial likelihood that frequent acute courses of ECT combined with clozapine will be necessary.

Safety. With respect to safety, FDA itself notes in its proposed rule that there is no evidence that ECT is any less safe when used to treat any of these disorders than it is for treatment of severe depressive episodes.
Efficacy and safety of maintenance ECT.

Major depression is a prevalent and recurring illness, impacting 17% of all individuals within their lifetime, with ages of onset peaking between 15-24 years of age, and when untreated has a strong propensity to become a chronic illness with extremely high lifetime morbidity and mortality. It is universally accepted that maintenance treatment is important to sustain remission after a successful course of acute ECT. Relapse rates are high, e.g., Sackeim and colleagues reported that 84% of patients who responded to acute ECT relapsed within six months of discontinuation of an acute ECT series unless active maintenance treatment is utilized. In a recently reported multi-center follow-up study, funded by the National Institute of Mental Health (NIMH), the same group reported a six-month relapse rate of at least 50% even with aggressive pharmacotherapy with a combination of antidepressant and Lithium. In another large multicenter trial funded by NIMH and carried out by the Consortium on Research in ECT (CORE), 201 patient participants with major depressive episodes who had remitted following an acute series of ECT were randomized to six months of either maintenance ECT or maintenance pharmacotherapy with combined antidepressant medication and Lithium. Study results show that maintenance ECT alone (i.e. without concomitant pharmacotherapy) is a safe and effective treatment alternative to aggressive pharmacotherapy in decreasing relapse following an acute ECT series, although relapse was still present in a sizable minority of subjects.

The hypothesis of further lowering relapse rates by combining maintenance ECT and pharmacotherapy was then tested in a recently concluded NIMH funded multicenter trial by the CORE group, as well as in a separate Swedish trial. In both studies combined maintenance ECT and pharmacotherapy was more effective than pharmacotherapy alone. In the larger and more methodologically rigorous CORE trial, 120 patient research participants with major depressive disorder who had remitted after an acute ECT series were randomized to six-month treatment trials of either venlafaxine plus Lithium alone or maintenance ECT plus the venlafaxine/Lithium combination. At six-month follow-up, subjects receiving the maintenance ECT/pharmacotherapy combination not only had significantly lower Hamilton Depression Rating Scale (HDRS) scores than patients in the pharmacotherapy alone group, but, in addition, relapse was 1.7 times greater for subjects in the maintenance pharmacotherapy alone group. Additionally, investigators found a tendency toward shorter time to relapse for that group compared to the combined maintenance ECT/pharmacotherapy group. This study also corroborated earlier findings that cognitive functioning in research patients receiving maintenance ECT treatment did not differ from that of research patients receiving maintenance pharmacotherapy alone. Collectively, these findings clearly establish that combined maintenance ECT and pharmacotherapy offers patients a better chance to avoid relapse following ECT then does aggressive maintenance pharmacotherapy alone, and does so without impairing cognitive function.

Efficacy and safety of ECT in individuals under the age of 18.

Mood disorders, catatonia, and schizophrenia can all have onset during childhood or adolescence and although these disorders may present differently in childhood, there is no evidence that the underlying disease differs in these age groups compared with an adult population. Because ECT has been uncommonly utilized in this children or adolescents under 18, there have not been controlled research trials. However, there has been a significant growth of peer-reviewed publications focused on acute and maintenance ECT use in young patients with mood disorders, as well as other serious neuropsychiatric conditions like catatonia and psychotic disorders such as schizophrenia. In particular, retrospective case series have reported similar positive clinical response, as well as tolerability and cognitive side effects to that reported in adult ECT patients. Much of the applicable literature was summarized in 2013 by Ghaziuddin and Walter in an entire textbook titled “Electroconvulsive Therapy in Children and Adolescents.” In addition, guidelines for patient selection and use of ECT in young patients have been published by both the American Psychiatric Association and the American Association of Child and Adolescent Psychiatry. In this regard, the special controls mechanism can be used by FDA to ensure that appropriate, safe, and effective ECT treatment can be provided to individuals in this age group. Specifically, in addition to the national guidelines mentioned above, concurrence by additional independent psychiatrists
experienced in treating children and adolescents, involvement of anesthesia providers experienced with the use of
general anesthesia in this age group, and use of age-appropriate ongoing cognitive assessment would represent
reasonable special controls. In addition, it should also be noted that at present, utilization of ECT in children and
adolescents under 18 is held to higher level of indication from a treatment resistance and need for rapid response
standpoint than is the case with adults. For these reasons, NNDC experts believe that FDA should include ECT for children
and adolescents in its proposal to reclassify ECT devices from Class III to Class II, with the imposition of appropriate
special controls to ensure adequate efficacy and safety.

Assessment and monitoring of cognitive functions with ECT.
NNDC agrees with FDA that memory impairment has been the most worrisome side effect from ECT. This concern arose
predominantly from the use of unmodified ECT, which was also associated with the use of sinusoidal stimulus waveform,
bitemporal electrode placement, and non-individualized stimulus dosing. With present-day evidence-based ECT
practice, memory impairment has been substantially reduced. As such, this particular risk is outweighed by the
treatment’s compelling and sometimes life-saving benefit.

ECT is associated with both anterograde and retrograde amnesia. Studies utilizing objective measures of assessing
anterograde amnesia have consistently demonstrated that any such abnormalities disappear within several months
following completion of an acute ECT course\(^3\). Several recent studies have even demonstrated improvement in
cognitive function, compared to baseline, several weeks to months after successful treatment with ECT\(^34-38\). An even
more recently published study that reviewed 10 years of cognitive performance data in relation to ECT concluded that
there is no evidence of cumulative cognitive deficits associated with repeated ECT courses\(^39\). Studies investigating the
existence, severity, and persistence of retrograde amnesia have focused on autobiographic memory function. Objective
measures, although nonstandardized due to the challenges involved in autobiographic memory assessment, have
proven sensitive to ECT type, e.g., stimulus electrode placement and stimulus waveform, and have sometimes
demonstrated even persistent deficits with some ECT types\(^40\). Regardless of objective testing results, some patients
receiving ECT report persistent anterograde amnesia and/or persistent retrograde amnesia that is greater than what
might be expected from the results of studies utilizing objective test measures, although attempts to investigate such
reports on a scientific basis have not met with success, perhaps due to the complexity of factors known to affect such
self-ratings\(^41,42\).

Early detection of emerging cognitive side effects during the ECT course is important so that providers can adjust the
treatment approach to minimize further side-effects. Therefore, NNDC experts agree with the FDA rule that 1) cognitive
function should be evaluated before beginning ECT, 2) cognitive function should be monitored throughout the course of
treatment, and 3) the results of cognitive testing should be routinely reviewed during the course of treatment and
influence appropriate clinical decision-making (e.g., holding or ending treatment, changing ECT treatment parameters).
However, NNDC experts also believe that many patients with the most severe illnesses (e.g., catatonia, NMS, or
profound depression) will likely be unable to participate in cognitive testing. Therefore, we recommend that no patient
be denied ECT treatment due to the inability to complete cognitive testing.

With respect to formal memory testing, NNDC experts believe that simple bedside cognitive testing is adequate for the
vast majority of patients undergoing ECT. Routine requirement of extensive neuropsychological testing for all ECT
patients, on the other hand, would prove counterproductive, create an undue burden, and would commonly be
infeasible due to lack of timely availability of clinical neuropsychologist assessment in many clinical settings\(^43\), thus
limiting access to a potentially life-saving treatment. An optimal testing instrument for use with ECT would be brief, easy
to administer, simple enough for patients with limited ability to focus and complete, and sensitive to the known effects
of ECT, particularly in terms of both objective anterograde and retrograde amnesia. The instrument should also provide
an opportunity for memory self-rating by the patient. At present there are no validated ECT-sensitive instruments of this type, however, research in this area is underway. As part of this effort, NNDC investigators at multiple prominent U.S. academic locations are in process of developing a reliable, valid, brief (less than 10 min.), stand-alone cognitive screening tool meeting the above requirements that can be administered at bedside.

NNDC believes that highly selective and careful use of ECT remains a major treatment alternative for individuals with treatment resistance and/or a need for rapid response, and appreciates the opportunity to comment on FDA’s proposed reclassification rule. As the major National group of experts on the management of depressive, bipolar, and related disorders, NNDC would also welcome the opportunity to meet with FDA to provide further input during the process of developing a final reclassification rule. In this regard, NNDC experts have, as noted above, been developing a practical, sensitive cognitive assessment measure for use with individuals being treated with ECT across a broad range of clinical situations and environments.

Thank you for your consideration of our input to the ECT device reclassification rule.

Sincerely yours,

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A separate copy of this communication has been sent to:

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Citations to the scientific literature

27. Kellner et al., A randomized controlled trial of continuation electroconvulsive therapy and medication vs medication alone in geriatric depression; Phase 2 of the PRIDE study. [presented at multiple scientific meetings in 2015 and Manuscript submitted for publication]