Subcallosal cingulate deep brain stimulation for treatment-resistant depression

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Abstract: Background: Deep brain stimulation (DBS) of the subcallosal cingulate white matter (SCC) has shown promise as an intervention for patients with chronic, unremitting depression (TRD). To test the safety and efficacy of DBS for TRD, a prospective, randomized, sham-controlled trial was conducted.
Methods: Participants with TRD were implanted with a DBS system targeting bilateral SCC white matter and randomized to six months of active versus sham DBS followed by six months open-label SCC DBS. The primary outcome was response rate at the end of the six-month double-blind phase. Response was defined as a 40% or greater reduction in depression severity from baseline. A futility analysis was performed when approximately half of the proposed sample received DBS implantation and completed the double-blind phase. At the conclusion of the 12-month study, a subset of patients continued to be followed for up to 24 months.
Findings: Prior to the futility analysis, 90 participants were randomized to active (N=60) versus sham (N=30) stimulation. Both groups showed improvement, but there was no statistically significant difference in response rate during the double-blind, sham-controlled phase. Participants continued to improve during the six months open-label phase. Long-term response and remission rates for all participants receiving active DBS open-label were, respectively, 40% and 19% at 12 months, 51% and 17% at 18 months, and 48% and 25% at 24 months. Twenty-eight patients

experienced 39 adverse events; eight of these (in seven patients) were deemed to be related to the study device and/or surgery.
Interpretation: This study confirmed the safety and feasibility of SCC DBS as a treatment for TRD but failed to show statistically significant antidepressant efficacy in a six months double-blind, sham-controlled trial. Long-term (up to 24 months) open-label SCC DBS was associated with a response rate of nearly 50%, with 25% of participants remitted. These rates are clinically meaningful and higher than those expected in this patient population with treatment-as-usual.

Introduction

Brodmann Area 25 (BA25) within the subcallosal cingulate has been strongly implicated in the pathophysiology of treatment-resistant depression.[1] In depressed patients who respond to antidepressant treatments, BA25 activity shows a consistent change associated with antidepressant response. However, in patients with treatment-resistant depression, BA25 activity does not change with adequate antidepressant treatment compared to treatment responders. Anatomically, BA25 shows a pattern of structural connectivity that supports its role in the pathophysiology of depression and treatment-resistant depression, with monosynaptic connections to the medial prefrontal cortex, perigenual and dorsal anterior cingulate gyri, hippocampus/amygdala, ventral striatum, thalamus, hypothalamus and monoaminergic nuclei within the brain stem.[1] Therefore, direct modulation of BA25, and especially its white matter connections to other brain regions involved in depression, is a potential treatment target for patients with treatment-resistant depression.

Deep brain stimulation (DBS) of the subcallosal cingulate white matter has shown promising safety and efficacy for patients with treatment-resistant depression.[2-9] Open-label, chronic, high-frequency (>100 Hz) subcallosal cingulate DBS has demonstrated six-month response rates of about 50% and long-term remission rates (over two to six years) around 50%.[4-7, 10] Patients enrolled in these studies were highly treatment-resistant (typically not responding to at least four antidepressant medications in the current episode, and no consistent response to psychotherapy and/or electroconvulsive therapy (ECT)), chronically depressed (average episode duration of about five years) and severely ill due to their treatment-resistant depression, with the vast majority effectively disabled. These preliminary findings are clinically meaningful and compare favorably to response and remission rates in patients with treatment-resistant depression receiving treatment-as-usual, other neuromodulation interventions or ablative procedures such as cingulotomy.[11-17] Given these encouraging open-label data, a

prospective, randomized, double-blind sham-controlled trial of subcallosal cingulate DBS for treatment-resistant depression was conducted. It was hypothesized that six months of subcallosal cingulate DBS would be associated with statistically significant antidepressant efficacy compared to sham stimulation.

Methods

Study overview

A six-month, multi-center, randomized, double-blind, sham-controlled trial was conducted to evaluate the safety and efficacy of subcallosal cingulate DBS (Libra®XP Deep Brain Stimulation System, St. Jude Medical, Plano, Texas) for patients with treatment-resistant depression. A six-month open-label phase followed the double-blind phase. Planned enrollment was 201 participants randomized at up to 20 sites. The study was registered at clinicaltrials.gov (NCT00617162). Study procedures were approved by the Institutional Review Board at each site and the U.S. Food and Drug Administration under an Investigational Device Exemption (G070107, sponsored by St. Jude Medical). The study was monitored by an independent Data and Safety Monitoring Board. Recruitment occurred from April 10, 2008 to November 21, 2012.

Participants

Inclusion criteria included: 1) men and women aged 21-70 years; 2) unipolar, non-psychotic major depressive disorder (MDD) diagnosed before age 45 with a current episode >12 months duration; 3) lack of antidepressant response (via medical and/or pharmacy records) to a minimum of four adequate antidepressant treatments, including at least three medications from three different classes, evidence-based

psychotherapy, and/or ECT, 4) lack of sustained response to a course of psychotherapy; 5) Montgomery-Asberg Depression Rating Scale (MADRS) score >22 at each of three separate baseline visits, rated by two separate psychiatrists; baseline visits 2 and 3 were separated by no more than 6 weeks, and eligible participants must have demonstrated absence of notable improvement (≤20% lessening of MADRS score) between these visits; 6) Global Assessment of Function (GAF) score <50; 7) Mini-Mental State Examination (MMSE) score >24; 8) medication free or current antidepressant/ psychotropic medication regimen stable for >4 weeks prior to study entry; 9) able and willing to give written informed consent.

Exclusion criteria included: 1) bipolar or psychotic disorder; 2) obsessive compulsive disorder, post-traumatic stress disorder, panic disorder, bulimia or anorexia nervosa; 3) generalized anxiety disorder (GAD) as the primary diagnosis during the current depressive episode; 4) substance use disorder (excluding caffeine, nicotine) within the last 12 months; 5) borderline or antisocial personality disorder; 6) substantial risk of suicide; 7) received ECT within 3 months prior to enrollment, or likely to require ECT during the study; 8) central nervous system disease impairing motor, sensory or cognitive function or requiring intermittent or chronic medication; 9) fibromyalgia, chronic fatigue syndrome or current condition requiring chronic narcotic use; 10) unstable, uncontrolled medical illness; 11) past ablative or other intracranial surgery; 12) contraindication to magnetic resonance imaging (MRI) scanning; 13) contraindication to general anesthesia or deep brain stimulation surgery; 14) pregnant, intending to get pregnant during the study or breastfeeding; 15) currently participating in another investigational device, drug or surgical trial; and 16) unable to comply with study visit schedule and timeline.

Concomitant treatments

Participants could continue psychotherapy and medications during the study but were required to maintain a stable medication regimen as well as regularly scheduled psychotherapy visits. Medication changes or the initiation of psychotherapy were not allowed during the six-month double-blind phase. Minor adjustments to sedative/hypnotic and anxiolytic medications were allowed.

Screening and baseline assessments

Potential participants were screened according to the eligibility criteria above. At least two years of medical records were reviewed. Potential participants were provided a detailed informed consent document, had an initial screening, and completed three baseline evaluations. These evaluations occurred no less than two weeks apart from each other, and baseline visits 2 and 3 were not separated by more than six weeks. The first two baseline visit evaluations were performed by independent psychiatrists. Baseline assessments included the MADRS; the 17-item Hamilton Depression Rating Scale (HRSD-17); the Self-Rated Quick Inventory of Depressive Symptomatology (QIDS-SR); subsection for cluster B personality disorder of the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II); Systematic Assessment for Treatment Emergent Events (SAFTEE); the 30 item Inventory of Depressive Symptomatology (IDS-C30); the Young Mania Rating Scale (YMRS); the Work and Social Adjustment Scale (WSAS); GAF; the short form Quality of Life Enjoyment and Satisfaction Questionnaire (QOL); Clinical Global Impression of Severity and Improvement (CGI); Patient Global Impression Index (PGI); Health and Labor Questionnaire (HLQ); Hamilton Anxiety Rating Scale (HAM-A) and Columbia Suicide Severity Rating Scale (C-SSRS). After the baseline visit was completed, the lead study psychiatrist (PEH) performed an external review of the participant's data to ensure eligibility. After the third baseline visit, a neuropsychological

battery was administered to assess attention/working memory and other executive functions. A high-resolution magnetic resonance imaging (MRI) scan and pre-surgical evaluation were also performed.

Surgery and target localization

The DBS system consisted of two leads, extension wires and an implantable pulse generator (IPG). Each DBS lead consisted of a four electrode array with a 3 mm electrode at the tip and three 1.5 mm electrodes, each separated by 1.5 mm. At least two of three experts (HSM, CH, PEH) manually selected and agreed upon the optimal surgical target, defined as a region in the subcallosal cingulate white matter approximately 75% of the distance from the anterior commissure to the plane defined by the gray matter edge of the genu of the corpus callosum and in the transition from the white matter to the gray matter in the medial-lateral axis.[2, 3, 18] Target selection was performed in native MRI space (i.e., not in an atlas-defined space) and involved identifying a target region at the gray matter-white matter transition area in the subcallosal cingulate gyrus. Optimal target location was provided to the site neurosurgeon to assist with surgical targeting, and each neurosurgeon was trained on targeting by a team of experts (HSM, CH, AML).

Bilateral DBS system implantation occurred no less than two weeks and no more than four weeks after the final baseline evaluation using the standard stereotactic surgical procedures at each site. Impedance of the system was tested intraoperatively, but no stimulation was delivered during surgery.

Post-operative computed tomography (CT) was obtained to assess for intracranial hemorrhage and lead localization. The post-operative CT scan was then merged with the pre-operative high-resolution MRI used for initial target selection. At least two of three expert consultants

(HSM, CH, PEH) reviewed these merged images and selected an optimal contact sequence for chronic monopolar stimulation. The first contact chosen was the one in closest proximity to the predefined target (described above), and the second contact chosen was the one in the next closest proximity to the predefined target. No participant had more than two contacts within the predefined target region. Four subjects had an additional surgery to reposition the leads due to the leads not being in the ideal target region; in all cases, this occurred prior to randomization. Post-operative CT scans were merged with baseline MRI scans.

Randomization

Approximately two weeks after device implantation, participants were randomized to receive immediate active stimulation (Stimulation group) or 6-month delayed stimulation (sham; Control group) using a ratio of 2:1 (Stimulation:Control). Randomization was computer-generated (SAS version 9.2) with a block size of three at each site before the site started the study. At each site, an unblinded DBS programmer was informed of treatment allocation; all other team members and the patient were blinded to treatment allocation.

DBS programming

For participants randomized to the Stimulation group, stimulation was initiated at the completion of the randomization visit (week 2 following implantation). Initial parameters included monopolar stimulation at the optimal first contact selected on each side at 130 Hz, 91 microsecond pulse width (PW), 4 milliamperes (mA). For Controls, a sham programming session was performed, but stimulation was not initiated. Participants were not formally assessed for whether they had acute effects from stimulation.

For participants receiving active stimulation, programming changes were made based on the change in MADRS from the previous rating. Two weeks after the initial programming session, no parameter changes were made if the MADRS score reduction was ≥10% from the previous evaluation. If the MADRS value was ≤10% lower than that on the previous evaluation, amplitude was increased to 6 mA. After another four weeks (if the MADRS was again ≤10% lower than that from the previous evaluation), the amplitude was increased to 8 mA. After another four weeks, if the MADRS was again ≤10% lower than that from the previous evaluation, the second contact from the pre-selected contact sequence would be added for monopolar stimulation (i.e., the patient would have two contacts providing active monopolar [8 mA] stimulation in each hemisphere). If intolerable side effects occurred following a parameter change, parameters were returned to the previous settings. No modifications were allowed in pulse width or frequency. No further parameter changes were allowed beyond 10 weeks following initiation of stimulation. Participants randomized to sham had similar programming visits, but stimulation remained off during the double-blind phase.

Randomized, double blind, sham-controlled phase

Following randomization, participants returned for evaluations at weeks 4, 6, and 8, then every month until the 6-month endpoint. At each visit, the following evaluations were completed: MADRS; SAFTEE; DBS programming form; IDS-C30; QIDS-SR; WSAS; GAF; CGI; PGI; HAM-A; and C-SSRS. At the 3 month and 6 month visits, the following additional evaluations were completed: HRSD-17; YMRS; QOL; and HLQ. The neuropsychological battery was repeated at the 6 month visit. Outside of regularly scheduled, in-person evaluations, each patient was contacted by phone or in person by study personnel every one to two weeks to assess for safety. Participants experiencing worsening of suicidal ideation could remain in the study if stability (“rescue”) could be achieved within seven days. Participants experiencing a ≥25% worsening in MADRS

score from baseline were considered treatment failures, exited from this phase of the study and enrolled in the open-label or long-term follow-up study based on whether they were already receiving active stimulation.

Open-label phase

Following the 6-month double-blind phase, participants entered the 6-month open-label phase. All participants in the Control group (including responders and remitters) had stimulation initiated at this time with the identical algorithm employed for contact and parameter selection and changes as described above for the active treatment group. Participants in the Stimulation group continued with active stimulation. In the open-label phase, patients and study staff (except the unblinded programmer) were not provided any information about randomization status during the first 6 months of the study. At each monthly visit the following evaluations were completed: DBS programming form; MADRS; IDS-C30; QIDS-SR; WSAS; GAF; CGI; PGI; HAM-A; and C-SSRS. At the 9 month and 12 month visits, the following additional evaluations were completed: SAFTEE; YMRS; QOL; and HLQ. The neuropsychological battery was performed again at the 12 month visit. Parameter adjustments were constrained as described above. Changes in medications and psychotherapy were allowed in this open-label phase.

Long-term follow-up phase

Participants completing the 12 month study were invited to continue in a long-term, naturalistic follow-up study. Study visits occurred every six months. Changes in stimulation parameters, medications and psychotherapy were allowed. For patients continuing with chronic DBS, a rechargeable battery was provided as needed.

Efficacy measures

The primary efficacy endpoint for the study was defined as difference in response rate between the Stimulation and Control groups. Response was defined as a ≥40% reduction in MADRS and no worsening in GAF from baseline (average of 3 baseline MADRS assessments) to the average scores at months 4, 5, and 6. The average of months 4, 5, and 6 was chosen as the primary endpoint due to the aim to assess for a sustained change over time. Secondary measures of efficacy included changes from baseline to endpoint for the HRSD-17, IDS-C30, QIDS-SR, WSAS, PGI, CGI, QOL and HAM-A. For the 6-month open-label and long-term follow-up studies, response was defined as a ≥40% reduction in MADRS from the baseline average to the score at the time point of interest (e.g., 12 months, 18 months, 24 months). Remission at all time points was defined as a MADRS score ≤10.

Safety measures

The incidence of all adverse events (e.g., hospitalization due to worsening depression, suicidal ideation or behavior, unanticipated medical treatment for psychiatric reasons, and device related events) that occurred over study duration were used as the primary safety endpoints for the study.

Statistical considerations and data analyses

Based on preliminary data[7], a ≥40% response rate was anticipated for the active subcallosal cingulate DBS group. A ≤18.5% response rate for the Control group was expected.[12] Therefore, 159 participants randomized 2:1 (106 in the active group and 53 in the sham group) would provide 80% power to reject the primary efficacy null hypothesis at a 5% significance level. Sample size calculations were performed based on the Z test method with pooled variance using PASS 2005. To allow for a dropout rate as high as 20%, the sample size for recruitment was increased to 201 participants (134 in the active stimulation group and 67 in the sham stimulation group).

The primary efficacy outcome assessed was difference in response rate between the groups (as defined above). Participants who were missing one or two of the assessments at months 4, 5 or 6 had data from the available visits used. Participants missing MADRS scores for Months 4, 5 and 6 were considered non-responders. A logistic regression model including effects of treatment group, study site, level of treatment resistance (as defined by ATHF criteria), and baseline MADRS was fitted. Data from study sites with fewer than three participants in either treatment group were pooled.

Planned futility analysis

In approving this study, the U.S. FDA required a futility analysis be completed once ≥75 participants had reached the primary endpoint by either completing the month 6 visit or exiting the study. No more than 125 participants could be enrolled prior to the futility analysis. The futility analysis was performed using the average of the revised alternative hypothesis and the observed interim results. With the current sample size of 201 participants, the alternative hypothesis was a 40% response rate for participants receiving active stimulation and a 20.7% response rate for participants receiving sham (the proportions providing 80% power to reject the primary hypothesis given the smaller sample size at the

time of the futility analysis). Based on these revised population proportions, 5000 sets of simulation results among the remaining approximately 84 stimulation participants and 42 control group participants were run. Each set of simulated results was added to the observed results, and a two-tailed Fisher's exact p-value was calculated. The probability of a successful outcome of the study was the proportion of these p-values <0.05. If the probability of a successful study outcome was <10%, the study would be stopped for futility. Additionally, the study could be stopped at the sponsor's discretion, even if this formal definition for futility was not met.

Results

A total of 128 participants were enrolled (i.e., signed informed consent) from 15 investigational sites prior to the completion of the futility analysis (Figure 1). Of the 128 participants enrolled into the study, only 90 from 13 investigational sites received DBS system implantation and were randomized to treatment. Of these, 60 participants were randomized to active stimulation, and 30 were randomized to sham stimulation. There were no statistically significant differences between the groups in demographic or clinical variables (Table 1).

On average, patients in both groups showed a statically significant improvement in depression and global functioning over 6 and 12 months. At the endpoint for the 6-month blinded, controlled phase, there was no statistically significant difference in efficacy between the Stimulation group (20% response rate; 10% remission rate) and the Control group (17% response rate; 7% remission rate)(Figure 2, Tables 2 and 3; analyses of primary and secondary outcome measures are shown in Supplementary Tables S1-S8). In participants randomized to sham stimulation for the first six months of the study, six months of active stimulation did not result in additional statistically significant within group antidepressant efficacy (i.e., no statistically significant decrease in MADRS score from month 6 to month 12). By the 12 month visit, response and

remission rates did not statistically significantly increase compared to the 6 month visit in either group, though response rates numerically increased in both groups (Stimulation group: 30% response rate; Control group: 27% response rate), and remission rates remained stable to slightly increased (Stimulation group: 18%; Control group: 7% remission rate). Medication and/or psychotherapy changes were only allowed in the 6 month open-label phase, but did not correlate with efficacy or differential efficacy in the groups.

Adequacy of blinding was confirmed based on questioning participants about which group they were assigned to after 4 weeks, 8 weeks, 3 months and 6 months of the blinded, randomized, controlled phase of the study. There was no difference between the Stimulation and Control group in proportion of participants guessing they were receiving active stimulation, with approximately 30%-40% of each group (Stimulation, Control) guessing they were receiving active stimulation at each time point. About 50% of participants in each group guessed accurately, and there was no difference in accuracy of guessing between the groups. No participant reported any acute effects with the initiation of active stimulation, nor were any effects of initial activation of stimulation observed by study staff, including the unblinded programmer.

For the futility analysis, based on the first six months' data, the response rate for the Stimulation group was predicted to be 40%, and the response rate for the Control group was predicted to be 18.5% (see Methods above). In the actual futility analysis, the Stimulation group showed a 20% response rate, and the Control group showed a 17% response rate. It was concluded that the study had a 17% chance of success if continued. Although this did not meet the formal definition for futility described above (<10% chance of success), the sponsor chose to end study enrollment following the futility analysis.

Following the initial 12-month study, seventy-seven (77) participants entered into a four-year follow-up study. Eight participants from the Active group and five participants from the Control group dropped out; all were nonresponders at the 12 month endpoint. For long-term

assessment of efficacy, response was defined as a ≥40% decrease in MADRS score from baseline to each endpoint, and remission was defined as a MADRS score ≤10. For assessment of long-term efficacy, patients in both groups (Stimulation and Control) were combined for analysis; therefore and by example, six months of stimulation refers to six months of active stimulation regardless of whether this started initially (in the Stimulation group) or six months later (in the Control group). With long-term, active subcallosal cingulate DBS, response and remission rates were 40% and 19% at 12 months, 51% and 17% at 18 months, and 48% and 25% at 24 months, respectively. Mean MADRS and GAF scores by months of stimulation are shown in Figure 3.

To assess whether stimulation parameter and/or medication changes were associated with efficacy, two post-hoc analyses were performed. For the first 12 months data, a generalized linear mixed effects model was fitted that included treatment group, medication change and stimulation parameter change at each follow-up visit as independent fixed effects, subject as a random effect and responder status at each follow-up visit as the dependent variable. Based on this model, neither stimulation parameter change nor medication change was associated with response rate ($p=0.2176$ and $p=0.4891$, respectively). Separately, a generalized linear mixed effects model was fitted for the 18-30 months (open-label) data that included medication change and stimulation parameter change at each follow-up visit as independent fixed effects, subject as a random effect and responder status at each follow-up visit as the dependent variable. This analysis showed that stimulation parameter change was associated with increased response rate ($p=0.0127$), but medication change was not ($p=0.3955$).

Twenty eight (28) participants experienced 39 serious adverse events (SAE) during the 12 month study (Table 3). Eight (8) SAEs occurring in seven patients were judged to be definitely related to the study device and/or surgery, including six infections (in five patients), one skin erosion over the extension wires, and one post-operative seizure. The remainder of SAEs were attributed to the primary mood disorder and

deemed unrelated to the device or active stimulation; i.e., there appeared to be no clear temporal relationship between the onset and resolution of these events and the initiation or adjustment of stimulation. There were two deaths by suicide in the study; both were in the Control group during the 6-month open-label phase. No unanticipated device related adverse events were reported. No episodes of hypomania or mania occurred during the study. There were no adverse neuropsychological effects at 6 or 12 months; a full description of neuropsychological findings will be reported separately. No side effects occurred with DBS programming, and no parameter adjustments were required due to side effects following a parameter change.

Ten out of 90 participants receiving DBS system implantation terminated the study early (five prior to the primary endpoint/six-month visit and five before the 12-month visit). Six early exits were due to adverse events (worsening depression [n=1], suicide attempt [n=1], increased suicidal ideation with failed "rescue" (see Methods) [n=1], death by suicide [n=2], and head pain [n=1]). Three early exits were due to patient preference and one was due to the sponsor closing the study. Four out of the 10 subjects that exited the study early chose to have the device fully explanted shortly after study exit.

No demographic or clinical characteristics were associated with 6 month, 12 month or 24 month response or remission rates. Presence of melancholic features, duration of illness and/or current episode, history of ECT did not differ between responders and nonresponders at any time point. Eventual responders versus non-responders did not differ in use or change in psychotherapy, medications or stimulation parameter adjustments. No systematic difference in electrode placement between responders and non-responders was identified, consistent with prior studies.[18, 19] Additionally, distance between actual vs. planned target placement did not differ significantly between eventual responders versus nonresponders, and there were no significant differences between sites in accuracy of electrode placement.

Discussion

This study helps confirm the feasibility and safety of subcallosal cingulate DBS as a treatment for treatment-resistant depression patients. However, this study failed to demonstrate that six months of active versus sham stimulation was associated with statistically significant antidepressant effects. Additionally, participants initially treated with sham stimulation during the first six months of the study did not show statistically significant antidepressant benefit with an additional six months of open-label active stimulation. In participants with up to two years of open-label active DBS stimulation, 48% achieved an antidepressant response and 25% achieved remission. These long-term outcomes are clinically meaningful and greater than would be expected with treatment-as-usual in this highly treatment-refractory patient population.[12]

These findings are disappointing given the encouraging data from earlier open-label studies of subcallosal cingulate DBS, and no demographic or clinical characteristics were associated with response versus nonresponse. However, it is noted that participants in this study had an average current episode duration of about 12 years. This is much longer than the average duration of current episode in prior subcallosal cingulate DBS studies (approximately five years)[3, 6] and may have contributed to the low overall response rate. Although subcallosal cingulate DBS has shown enduring, open-label efficacy in chronic depression,[4, 6] it is possible that this intervention is less effective for patients with extremely chronic depression.

Interpreting these findings must also consider study design. For studies of invasive interventions for neuropsychiatric disorders, placebo effects can be surprisingly high and may actually be quite long-lasting.[20, 21] However, the placebo response rate in this study was not significantly greater than what was anticipated; in fact it was lower than projected. Indeed, the major difference in this study compared to prior subcallosal

cingulate DBS studies was the lower response rate to active stimulation during the blinded phase of the study. Again, this may be due to the more chronic nature of disease in this cohort compared to prior samples. Additionally, it is not uncommon for the response to active treatment to be lower in a randomized, blinded, placebo-controlled trial than in open-label studies. Additionally, prior studies and data from this cohort suggest delayed and progressive antidepressant effects over time with subcallosal cingulate DBS. Therefore, it is possible that differences in benefit between active and sham stimulation may not be seen until after one to two years of treatment in this group. However, such a time frame makes sham-controlled studies much more challenging. Other study designs may need to be considered, such as open-label stimulation followed by blinded discontinuation.[22]

Targeting for this study was based on an algorithm derived from early subcallosal cingulate DBS studies.[18] Neurosurgical placement of the DBS electrodes, based on this algorithm, was highly accurate and did not differ between eventual responders and nonresponders. However, gross anatomical placement of subcallosal cingulate DBS electrodes may not be adequate for optimal treatment delivery. Recently, important subtleties in electrode placement have been described based on the white matter tracts impacted.[19] These data suggest that, for maximal efficacy, the active subcallosal cingulate DBS electrode must be placed such that it impacts a critical network of white matter tracts connecting key brain regions, including the forceps minor, cingulum bundle and uncinate fasciculus. Therefore, it is possible that prospective targeting based on individual DTI tractography could optimize subcallosal cingulate DBS electrode placement.[23, 24]

Given the strength of the preliminary data leading to this study, and the emerging data suggesting ways to optimize targeting for this intervention, the negative outcome of this trial should not be simply interpreted as a failure of subcallosal cingulate DBS for treatment-resistant depression. Subsequent studies are merited to determine whether active subcallosal cingulate DBS failed to differentiate from sham due to

clinical features of the patient population (e.g., extremely chronic depression) or suboptimal electrode placement. Additionally, identification and use of a physiological metric to verify engagement of the appropriate neural circuit could assist with targeting. Importantly, the long term response and remission rates in this and prior studies suggest that this intervention continues to have promise.

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Table 2. Depression severity over time.

Table 3. Response/remission by study visit.

Table 4. Serious adverse events and non-serious adverse events by group.

FIGURE LEGENDS

Figure 1. Participant disposition.

Figure 2. Depression severity over time in each treatment arm. Note that at months 9 and 12, the Control group was receiving active stimulation; therefore, for the Control group, 9 months refers to 3 months of active stimulation, and 12 months refers to 6 months of active stimulation.

Figure 3. Overall function over time in each treatment arm. Note that at months 9 and 12, the Control group was receiving active stimulation; therefore, for the Control group, 9 months refers to 3 months of active stimulation, and 12 months refers to 6 months of active stimulation.

Figure 4. Long-term outcomes (depression severity and overall function) in all participants receiving active stimulation during the study. These results include participants initially randomized to active stimulation and participants initially randomized to no stimulation for the double-blind phase of the study. For the participants initially randomized to no stimulation, the data used for this graph are solely those collected after active stimulation had been initiated in the open-label study phase.

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Dr. Holtzheimer receives grant support from NIMH, BBRF and Janssen Pharmaceuticals. He receives royalties from UpToDate and Oxford University Press. He previously consulted for St. Jude Medical Neuromodulation but has not received consulting fees since 2014.

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Dr. Lisanby is co-inventor on a patent, assigned to Columbia University, on an unrelated technology. This patent is not licensed and generates no royalties.

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Dr. Slavin is a member of advisory board and / or consultant for Abbott (previously known as St. Jude Medical), Baxter, Biotronik, Boston Scientific, Insightec, Medtronic, Neuramodix, Nevro, Nuvectra, SPR Therapeutics, StimRelieve; he has received research and/or fellowship funding from Abbott, Autonomic Technologies, Boston Scientific, Medtronic, Neuros and Pfizer.

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Dr. Abosch has performed ad hoc consulting for Medtronic.

Dr. Lam is a consultant for Allergan, Asia-Pacific Economic Cooperation, Bristol Myers Squibb, Canadian Depression Research and Intervention Network, Canadian Network for Mood and Anxiety Treatments, Janssen, Lundbeck, Medscape, Pfizer, Takeda. He receives speaker honoraria from AstraZeneca, Canadian Network for Mood and Anxiety Treatments, Canadian Psychiatric Association, Lundbeck, Lundbeck Institute,

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Ms. Peichel is employed by Abbott (previously known as St. Jude Medical).

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Dr. Hamani was a consultant for Abbott (previously known as St. Jude Medical), and has received honoraria from Medtronic.

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Drs. Berman, Espinoza, Pandurangi, Holloway, McKhann and Whitworth have no disclosures.

AUTHOR CONTRIBUTIONS

Dr. Holtzheimer made substantial contribution to design and conduct of this study as well as interpretation of the data. He had primary responsibility for drafting this manuscript. He gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Dr. Rothschild made a substantial contribution to the acquisition of study data and the critical revision of the manuscript. He gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Ms. Peichel made substantial contributions to the design and conduct of this study. She supervised all aspects of data acquisition and analysis and contributed to the interpretation of the results. She assisted in the drafting of the manuscript and its critical revision. She gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Gross made substantial contributions to the design and conduct of this study. He assisted in drafting the manuscript and its critical revision. He gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Hamani made substantial contributions to the design and conduct of this study. He assisted in drafting the manuscript and its critical revision. He gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Lozano made substantial contributions to the design and conduct of this study. He assisted in drafting the manuscript and its critical revision. He gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Mayberg made substantial contributions to the design and conduct of this study. She assisted in drafting the manuscript and its critical revision. She gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Introduction

Brodmann Area 25 (BA25) within the subcallosal cingulate ~~(SCC)~~ has been strongly implicated in the pathophysiology of treatment-resistant depression ~~(TRD)~~.[1] In depressed patients who respond to antidepressant treatments, BA25 activity shows a consistent change associated with antidepressant response. However, in patients with ~~TRD~~treatment-resistant depression ~~patients~~, BA25 activity does not change with adequate antidepressant treatment compared to treatment responders. Anatomically, BA25 shows a pattern of structural connectivity that supports its role in the pathophysiology of depression and ~~TRD~~treatment-resistant depression, with monosynaptic connections to the medial prefrontal cortex, perigenual and dorsal anterior cingulate gyri, hippocampus/amygdala, ventral striatum, thalamus, hypothalamus and monoaminergic nuclei within the brain stem.[1] Therefore, direct modulation of BA25, and especially its white matter connections to other brain regions involved in depression, is a potential treatment target for patients with ~~TRD~~treatment-resistant depression.

Deep brain stimulation (DBS) of the subcallosal cingulate white matter ~~(SCC)~~ has shown promising safety and efficacy for patients with ~~TRD~~treatment-resistant depression.[2-9] Open-label, chronic, high-frequency (>100 Hz) ~~SCC~~subcallosal cingulate DBS has demonstrated six-month response rates of about 50% and long-term remission rates (over two to six years) around 50%.[4-7, 10] Patients enrolled in these studies were highly treatment-resistant (typically not responding to at least four antidepressant medications in the current episode, and no consistent response to psychotherapy and/or electroconvulsive therapy (ECT)), chronically depressed (average episode duration of about five years) and severely ill due to their ~~TRD~~treatment-resistant depression, with the vast majority effectively disabled. These preliminary findings are clinically meaningful and compare favorably to response and remission rates in patients with ~~TRD~~treatment-resistant depression receiving treatment-as-usual, other neuromodulation interventions or ablative procedures such as cingulotomy.[11-17] Given these encouraging open-label data, a

prospective, randomized, double-blind sham-controlled trial of ~~SCC~~subcallosal cingulate DBS for ~~TRD~~treatment-resistant depression was conducted. It was hypothesized that six months of ~~SCC~~subcallosal cingulate DBS would be associated with statistically significant antidepressant efficacy compared to sham stimulation.

Methods

Study overview

A six-month, multi-center, randomized, double-blind, sham-controlled trial was conducted to evaluate the safety and efficacy of ~~SCC~~subcallosal cingulate DBS (Libra®XP Deep Brain Stimulation System, St. Jude Medical, Plano, Texas) for patients with ~~TRD~~treatment-resistant depression. A six-month open-label phase followed the double-blind phase. Planned enrollment was 201 participants randomized at up to 20 sites. The study was registered at clinicaltrials.gov (NCT00617162). Study procedures were approved by the Institutional Review Board at each site and the U.S. Food and Drug Administration under an Investigational Device Exemption (G070107, sponsored by St. Jude Medical). The study was monitored by an independent Data and Safety Monitoring Board. Recruitment occurred from April 10, 2008 to November 21, 2012.

Participants

Inclusion criteria included: 1) men and women aged 21-70 years; 2) unipolar, non-psychotic major depressive disorder (MDD) diagnosed before age 45 with a current episode >12 months duration; 3) lack of antidepressant response (via medical and/or pharmacy records) to a minimum of four adequate antidepressant treatments, including at least three medications from three different classes, evidence-based

psychotherapy, and/or ECT, 4) lack of sustained response to a course of psychotherapy; 5) Montgomery-Asberg Depression Rating Scale (MADRS) score >22 at each of three separate baseline visits, rated by two separate psychiatrists; baseline visits 2 and 3 were separated by no more than 6 weeks, and eligible participants must have demonstrated absence of notable improvement (≤20% lessening of MADRS score) between these visits; 6) Global Assessment of Function (GAF) score <50; 7) Mini-Mental State Examination (MMSE) score >24; 8) medication free or current antidepressant/ psychotropic medication regimen stable for >4 weeks prior to study entry; 9) able and willing to give written informed consent.

Exclusion criteria included: 1) bipolar or psychotic disorder; 2) obsessive compulsive disorder, post-traumatic stress disorder, panic disorder, bulimia or anorexia nervosa; 3) generalized anxiety disorder (GAD) as the primary diagnosis during the current depressive episode; 4) substance use disorder (excluding caffeine, nicotine) within the last 12 months; 5) borderline or antisocial personality disorder; 6) substantial risk of suicide; 7) received ECT within 3 months prior to enrollment, or likely to require ECT during the study; 8) central nervous system disease impairing motor, sensory or cognitive function or requiring intermittent or chronic medication; 9) fibromyalgia, chronic fatigue syndrome or current condition requiring chronic narcotic use; 10) unstable, uncontrolled medical illness; 11) past ablative or other intracranial surgery; 12) contraindication to magnetic resonance imaging (MRI) scanning; 13) contraindication to general anesthesia or deep brain stimulation surgery; 14) pregnant, intending to get pregnant during the study or breastfeeding; 15) currently participating in another investigational device, drug or surgical trial; and 16) unable to comply with study visit schedule and timeline.

Concomitant treatments

Participants could continue psychotherapy and medications during the study but were required to maintain a stable medication regimen as well as regularly scheduled psychotherapy visits. Medication changes or the initiation of psychotherapy were not allowed during the six-month double-blind phase. Minor adjustments to sedative/hypnotic and anxiolytic medications were allowed.

Screening and baseline assessments

Potential participants were screened according to the eligibility criteria above. At least two years of medical records were reviewed. Potential participants were provided a detailed informed consent document, had an initial screening, and completed three baseline evaluations. These evaluations occurred no less than two weeks apart from each other, and baseline visits 2 and 3 were not separated by more than six weeks. The first two baseline visit evaluations were performed by independent psychiatrists. Baseline assessments included the MADRS; the 17-item Hamilton Depression Rating Scale (HRSD-17); the Self-Rated Quick Inventory of Depressive Symptomatology (QIDS-SR); subsection for cluster B personality disorder of the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II); Systematic Assessment for Treatment Emergent Events (SAFTEE); the 30 item Inventory of Depressive Symptomatology (IDS-C30); the Young Mania Rating Scale (YMRS); the Work and Social Adjustment Scale (WSAS); GAF; the short form Quality of Life Enjoyment and Satisfaction Questionnaire (QOL); Clinical Global Impression of Severity and Improvement (CGI); Patient Global Impression Index (PGI); Health and Labor Questionnaire (HLQ); Hamilton Anxiety Rating Scale (HAM-A) and Columbia Suicide Severity Rating Scale (C-SSRS). After the baseline visit was completed, the lead study psychiatrist (PEH) performed an external review of the participant's data to ensure eligibility. After the third baseline visit, a neuropsychological

battery was administered to assess attention/working memory and other executive functions. A high-resolution magnetic resonance imaging (MRI) scan and pre-surgical evaluation were also performed.

Surgery and target localization

The DBS system consisted of two leads, extension wires and an implantable pulse generator (IPG). Each DBS lead consisted of a four electrode array with a 3 mm electrode at the tip and three 1.5 mm electrodes, each separated by 1.5 mm. At least two of three experts (HSM, CH, PEH) manually selected and agreed upon the optimal surgical target, defined as a region in the subcallosal cingulate white matter approximately 75% of the distance from the anterior commissure to the plane defined by the gray matter edge of the genu of the corpus callosum and in the transition from the white matter to the gray matter in the medial-lateral axis~~Targeting the SCC for DBS for TRD has been previously described~~.[2, 3, 18] Target selection was performed in native MRI space (i.e., not in an atlas-defined space) and involved identifying a target region at the gray matter-white matter transition area in the subcallosal cingulate gyrus. Optimal target location was provided to the site neurosurgeon to assist with surgical targeting, and~~E~~ each neurosurgeon was trained on targeting by a team of experts (HSM, CH, AML).

~~Each neurosurgeon was trained on targeting by a team of experts (HSM, CH, AML). At least two experts (HSM, CH, PEH) manually selected and agreed upon the optimal bilateral SCC DBS targets for each patient using the baseline MRI scan. These data were provided to the site neurosurgeon to assist with surgical targeting.~~ Bilateral DBS system implantation occurred no less than two weeks and no more than four weeks after the final baseline evaluation using the standard stereotactic surgical procedures at each site. Impedance of the system was tested intraoperatively, but no stimulation was delivered during surgery.

Post-operative computed tomography (CT) was obtained to assess for intracranial hemorrhage and lead localization. The post-operative CT scan was then merged with the pre-operative high-resolution MRI used for initial target selection. ~~Four subjects had an additional surgery to reposition the leads due to the leads not being in the ideal target for stimulation; in all cases, this occurred prior to randomization. Post-operative CT scans were merged with baseline MRI scans.~~ At least two of three expert consultants (HSM, CH, PEH) reviewed these merged images and selected an optimal contact sequence for chronic monopolar stimulation. The first contact chosen was the one in closest proximity to the predefined target (described above), and the second contact chosen was the one in the next closest proximity to the predefined target. No participant had more than two contacts within the predefined target region.

Four subjects had an additional surgery to reposition the leads due to the leads not being in the ideal target region~~for stimulation~~; in all cases, this occurred prior to randomization. Post-operative CT scans were merged with baseline MRI scans.

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Randomization

Approximately two weeks after device implantation, participants were randomized to receive immediate active stimulation (Stimulation group) or 6-month delayed stimulation (sham; Control group) using a ratio of 2:1 (Stimulation:Control). Randomization was computer-generated (SAS version 9.2) with a block size of three at each site before the site started the study. At each site, an unblinded DBS programmer was informed of treatment allocation; all other team members and the patient were blinded to treatment allocation.

DBS programming

For participants randomized to the Stimulation group, stimulation was initiated at the completion of the randomization visit (week 2 following implantation). Initial parameters included monopolar stimulation at the optimal first contact selected on each side at 130 Hz, 91 microsecond pulse width (PW), 4 milliamperes (mA). For Controls, a sham programming session was performed, but stimulation was not initiated. Participants were not formally assessed for whether they had acute effects from stimulation.

For participants receiving active stimulation, programming changes were made based on the change in MADRS from the previous rating. Two weeks after the initial programming session, no parameter changes were made if the MADRS score reduction was ≥10% from the previous evaluation. If the MADRS value was ≤10% lower than that on the previous evaluation, amplitude was increased to 6 mA. After another four weeks (if the MADRS was again ≤10% lower than that from the previous evaluation), the amplitude was increased to 8 mA. After another four weeks, if the MADRS was again ≤10% lower than that from the previous evaluation, the second contact from the pre-selected contact sequence would be added for monopolar stimulation (i.e., the patient would have two contacts providing active monopolar [8 mA] stimulation in each hemisphere). If intolerable side effects occurred following a parameter change, parameters were returned to the previous settings. No modifications were allowed in pulse width or frequency. No further parameter changes were allowed beyond 10 weeks following initiation of stimulation. Participants randomized to sham had similar programming visits, but stimulation remained off during the double-blind phase.

Randomized, double blind, sham-controlled phase

Following randomization, participants returned for evaluations at weeks 4, 6, and 8, then every month until the 6-month endpoint. At each visit, the following evaluations were completed: MADRS; SAFTEE; DBS programming form; IDS-C30; QIDS-SR; WSAS; GAF; CGI; PGI; HAM-A;

and C-SSRS. At the 3 month and 6 month visits, the following additional evaluations were completed: HRSD-17; YMRS; QOL; and HLQ. The neuropsychological battery was repeated at the 6 month visit. Outside of regularly scheduled, in-person evaluations, each patient was contacted by phone or in person by study personnel every one to two weeks to assess for safety. Participants experiencing worsening of suicidal ideation could remain in the study if stability ("rescue") could be achieved within seven days. Participants experiencing a ≥25% worsening in MADRS score from baseline were considered treatment failures, exited from this phase of the study and enrolled in the open-label or long-term follow-up study based on whether they were already receiving active stimulation.

Open-label phase

Following the 6-month double-blind phase, participants entered the 6-month open-label phase. All participants in the Control group (including responders and remitters) had stimulation initiated at this time with the identical algorithm employed for contact and parameter selection and changes as described above for the active treatment group. Participants in the Stimulation group continued with active stimulation. In the open-label phase, patients and study staff (except the unblinded programmer) were not provided any information about randomization status during the first 6 months of the study. At each monthly visit the following evaluations were completed: DBS programming form; MADRS; IDS-C30; QIDS-SR; WSAS; GAF; CGI; PGI; HAM-A; and C-SSRS. At the 9 month and 12 month visits, the following additional evaluations were completed: SAFTEE; YMRS; QOL; and HLQ. The neuropsychological battery was performed again at the 12 month visit. Parameter adjustments were constrained as described above. Changes in medications and psychotherapy were allowed in this open-label phase.

Long-term follow-up phase

Participants completing the 12 month study were invited to continue in a long-term, naturalistic follow-up study. Study visits occurred every six months. Changes in stimulation parameters, medications and psychotherapy were allowed. For patients continuing with chronic DBS, a rechargeable battery was provided as needed.

Efficacy measures

The primary efficacy endpoint for the study was defined as difference in response rate between the Stimulation and Control groups. Response was defined as a ≥40% reduction in MADRS and no worsening in GAF from baseline (average of 3 baseline MADRS assessments) to the average scores at months 4, 5, and 6. The average of months 4, 5, and 6 was chosen as the primary endpoint due to the aim to assess for a sustained change over time. Secondary measures of efficacy included changes from baseline to endpoint for the HRSD-17, IDS-C30, QIDS-SR, WSAS, PGI, CGI, QOL and HAM-A. For the 6-month open-label and long-term follow-up studies, response was defined as a ≥40% reduction in MADRS from the baseline average to the score at the time point of interest (e.g., 12 months, 18 months, 24 months). Remission at all time points was defined as a MADRS score ≤10.

Safety measures

The incidence of all adverse events (e.g., hospitalization due to worsening depression, suicidal ideation or behavior, unanticipated medical treatment for psychiatric reasons, and device related events) that occurred over study duration were used as the primary safety endpoints for the study.

Statistical considerations and data analyses

Based on preliminary data[7], a ≥40% response rate was anticipated for the active ~~SCC~~subcallosal cingulate DBS group. A ≤18.5% response rate for the Control group was expected.[12] Therefore, 159 participants randomized 2:1 (106 in the active group and 53 in the sham group) would provide 80% power to reject the primary efficacy null hypothesis at a 5% significance level. Sample size calculations were performed based on the Z test method with pooled variance using PASS 2005. To allow for a dropout rate as high as 20%, the sample size for recruitment was increased to 201 participants (134 in the active stimulation group and 67 in the sham stimulation group).

The primary efficacy outcome assessed was difference in response rate between the groups (as defined above). Participants who were missing one or two of the assessments at months 4, 5 or 6 had data from the available visits used. Participants missing MADRS scores for Months 4, 5 and 6 were considered non-responders. A logistic regression model including effects of treatment group, study site, level of treatment resistance (as defined by ATHF criteria), and baseline MADRS was fitted. Data from study sites with fewer than three participants in either treatment group were pooled.

Planned futility analysis

In approving this study, the U.S. FDA required a futility analysis be completed once ≥75 participants had reached the primary endpoint by either completing the month 6 visit or exiting the study. No more than 125 participants could be enrolled prior to the futility analysis. The futility analysis was performed using the average of the revised alternative hypothesis and the observed interim results. With the current sample size of 201 participants, the alternative hypothesis was a 40% response rate for participants receiving active stimulation and a 20.7% response rate for participants receiving sham (the proportions providing 80% power to reject the primary hypothesis given the smaller sample size at the time of the futility analysis). Based on these revised population proportions, 5000 sets of simulation results among the remaining approximately 84 stimulation participants and 42 control group participants were run. Each set of simulated results was added to the observed results, and a two-tailed Fisher's exact p-value was calculated. The probability of a successful outcome of the study was the proportion of these p-values <0.05. If the probability of a successful study outcome was <10%, the study would be stopped for futility. Additionally, the study could be stopped at the sponsor's discretion, even if this formal definition for futility was not met.

Results

~~*Participants and study flow*~~

A total of 128 participants were enrolled (i.e., signed informed consent) from 15 investigational sites prior to the completion of the futility analysis (Figure 1). Of the 128 participants enrolled into the study, only 90 from 13 investigational sites received DBS system implantation and were randomized to treatment. Of these, 60 participants were randomized to active stimulation, and 30 were randomized to sham stimulation. There were no statistically significant differences between the groups in demographic or clinical variables (Table 1).

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~~*Efficacy of randomized, controlled DBS (6 months) followed by open-label treatment (6 months)*~~

On average, patients in both groups showed a statically significant improvement in depression and global functioning over 6 and 12 months. At the endpoint for the 6-month blinded, controlled phase, there was no statistically significant difference in efficacy between the Stimulation group (20% response rate; 10% remission rate) and the Control group (17% response rate; 7% remission rate)(Figure 2, Tables 2 and 3; analyses of primary and secondary outcome measures are shown in Supplementary Tables S1-S8). In participants randomized to sham stimulation for the first six months of the study, six months of active stimulation did not result in additional statistically significant within group antidepressant efficacy (i.e., no statistically significant decrease in MADRS score from month 6 to month 12). By the 12 month visit, response and remission rates did not statistically significantly increase compared to the 6 month visit in either group~~improve~~, though response rates numerically~~had~~ increased in both groups (Stimulation group: 30% response rate; Control group: 27% response rate), and remission rates remained stable to slightly increased (Stimulation group: 18%; Control group: 7% remission rate). Medication and/or psychotherapy changes were only allowed in the 6 month open-label phase, but did not correlate with efficacy or differential efficacy in the groups.

Adequacy of blinding was confirmed based on questioning participants about which group they were assigned to after 4 weeks, 8 weeks, 3 months and 6 months of the blinded, randomized, controlled phase of the study. There was no difference between the Stimulation and Control group in proportion of participants guessing they were receiving active stimulation, with approximately 30%-40% of each group (Stimulation, Control) guessing they were receiving active stimulation at each time point. About 50% of participants in each group guessed

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accurately, and there was no difference in accuracy of guessing between the groups. No participant reported any acute effects with the initiation of active stimulation, nor were any effects of initial activation of stimulation observed by study staff, including the unblinded programmer.

~~*Futility analysis*~~

For the futility analysis, based on the first six months' data, the response rate for the Stimulation group was predicted to be 40%, and the response rate for the Control group was predicted to be 18.5% (see Methods above). In the actual futility analysis, the Stimulation group showed a 20% response rate, and the Control group showed a 17% response rate. It was concluded that the study had a 17% chance of success if continued. Although this did not meet the formal definition for futility described above (<10% chance of success), the sponsor chose to end study enrollment following the futility analysis.

~~*Long-term outcomes*~~

Following the initial 12-month study, seventy-seven (77) participants entered into a four-year follow-up study. Eight participants from the Active group and five participants from the Control group dropped out; all were nonresponders at the 12 month endpoint. For long-term assessment of efficacy, response was defined as a ≥40% decrease in MADRS score from baseline to each endpoint, and remission was defined as a MADRS score ≤10. For assessment of long-term efficacy, patients in both groups (Stimulation and Control) were combined for analysis; therefore and by example, six months of stimulation refers to six months of active stimulation regardless of whether this started initially (in the Stimulation group) or six months later (in the Control group). With long-term, active ~~SCC~~subcallosal cingulate DBS, response and remission rates

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were 40% and 19% at 12 months, 51% and 17% at 18 months, and 48% and 25% at 24 months, respectively. Mean MADRS and GAF scores by months of stimulation are shown in Figure 3.

To assess whether stimulation parameter and/or medication changes were associated with efficacy, two post-hoc analyses were performed. For the first 12 months data, a generalized linear mixed effects model was fitted that included treatment group, medication change and stimulation parameter change at each follow-up visit as independent fixed effects, subject as a random effect and responder status at each follow-up visit as the dependent variable. Based on this model, neither stimulation parameter change nor medication change was associated with response rate (p=0.2176 and p=0.4891, respectively). Separately, a generalized linear mixed effects model was fitted for the 18-30 months (open-label) data that included medication change and stimulation parameter change at each follow-up visit as independent fixed effects, subject as a random effect and responder status at each follow-up visit as the dependent variable. This analysis showed that stimulation parameter change was associated with increased response rate (p=0.0127), but medication change was not (p=0.3955). ~~Stimulation parameter, medication and/or psychotherapy changes were allowed during the follow-up study, but these changes, when they occurred, had no discernible impact on efficacy over time.~~

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~~*Safety*~~

Twenty eight (28) participants experienced 39 serious adverse events (SAE) during the 12 month study (Table 3). Eight (8) SAEs occurring in seven patients were judged to be definitely related to the study device and/or surgery, including six infections (in five patients), one skin erosion over the extension wires, and one post-operative seizure. The remainder of SAEs were attributed to the primary mood disorder and

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deemed unrelated to the device or active stimulation; i.e., there appeared to be no clear temporal relationship between the onset and resolution of these events and the initiation or adjustment of stimulation. There were two deaths by suicide in the study; both were in the Control group during the 6-month open-label phase. No unanticipated device related adverse events were reported. No episodes of hypomania or mania occurred during the study. There were no adverse neuropsychological effects at 6 or 12 months; a full description of neuropsychological findings will be reported separately. No side effects occurred with DBS programming, and no parameter adjustments were required due to side effects following a parameter change.

Ten out of 90 participants receiving DBS system implantation terminated the study early (five prior to the primary endpoint/six-month visit and five before the 12-month visit). Six early exits were due to adverse events (worsening depression [n=1], suicide attempt [n=1], increased suicidal ideation with failed "rescue" (see Methods) [n=1], death by suicide [n=2], and head pain [n=1]). Three early exits were due to patient preference and one was due to the sponsor closing the study. Four out of the 10 subjects that exited the study early chose to have the device fully explanted shortly after study exit.

~~*Response predictors*~~

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No demographic or clinical characteristics were associated with 6 month, 12 month or 24 month response or remission rates. Presence of melancholic features, duration of illness and/or current episode, history of ECT did not differ between responders and nonresponders at any time point. Eventual responders versus non-responders did not differ in use or change in psychotherapy, medications or stimulation parameter adjustments. No systematic difference in electrode placement between responders and non-responders was identified, consistent with prior

studies.[18, 19] Additionally, distance between actual vs. planned target placement did not differ significantly between eventual responders versus nonresponders, and there were no significant differences between sites in accuracy of electrode placement. ~~Although not statistically significant, it was noted that nonresponders tended to have an electrode placement that was more posterior and inferior to that of responders based on review by two experts (HSM, RG, CH).~~

Discussion

This study helps confirm the feasibility and safety of ~~SCC~~subcallosal cingulate DBS as a treatment for ~~TRD~~treatment-resistant depression patients. However, this study failed to demonstrate that six months of active versus sham stimulation was associated with statistically significant antidepressant effects. Additionally, participants initially treated with sham stimulation during the first six months of the study did not show statistically significant antidepressant benefit with an additional six months of open-label active stimulation. In participants with up to two years of open-label active DBS stimulation, 48% achieved an antidepressant response and 25% achieved remission. These long-term outcomes are clinically meaningful~~, similar to those seen in earlier open-label studies~~ and greater than would be expected with treatment-as-usual in this highly treatment-refractory patient population.[12]

These findings are disappointing given the encouraging data from earlier open-label studies of ~~SCC~~subcallosal cingulate DBS, and no demographic or clinical characteristics were associated with response versus nonresponse. However, it is noted that participants in this study had an average current episode duration of about 12 years. This is much longer than the average duration of current episode in prior ~~SCC~~subcallosal cingulate DBS studies (approximately five years)[3, 6] and may have contributed to the low overall response rate. Although

~~SCC~~subcallosal cingulate DBS has shown enduring, open-label efficacy in chronic depression,[4, 6] it is possible that this intervention is less effective for patients with extremely chronic depression.

Interpreting these findings must also consider study design. For studies of invasive interventions for neuropsychiatric disorders, placebo effects can be surprisingly high and may actually be quite long-lasting.[20, 21] However, the placebo response rate in this study was not significantly greater than what was anticipated; in fact it was lower than projected. Indeed, the major difference in this study compared to prior ~~SCC~~subcallosal cingulate DBS studies was the lower response rate to active stimulation during the blinded phase of the study. Again, this may be due to the more chronic nature of disease in this cohort compared to prior samples. Additionally, it is not uncommon for the response to active treatment to be lower in a randomized, blinded, placebo-controlled trial than in open-label studies. Additionally, ~~As~~ prior studies and data from this cohort suggest delayed and progressive antidepressant effects over time with ~~SCC~~subcallosal cingulate DBS. Therefore, ~~,~~ it is possible that differences in benefit between active and sham stimulation may not be seen until after one to two years of treatment in this group. However, such a time frame makes sham-controlled studies much more challenging. Other study designs may need to be considered, such as open-label stimulation followed by blinded discontinuation.[22]

Targeting for this study was based on an algorithm derived from early ~~SCC~~subcallosal cingulate DBS studies.[18] Neurosurgical placement of the DBS electrodes, based on this algorithm, was highly accurate and did not differ between eventual responders and nonresponders. However, gross anatomical placement of ~~SCC~~subcallosal cingulate DBS electrodes may not be adequate for optimal treatment delivery. Recently, important subtleties in electrode placement have been described based on the white matter tracts impacted.[19] These data suggest that, for maximal efficacy, the active ~~SCC~~subcallosal cingulate DBS electrode must be placed such that it impacts a critical network of white matter tracts

connecting key brain regions, including the forceps minor, cingulum bundle and uncinate fasciculus~~. It is notable that SCC DBS responders in this study tended to have a more anterior and superior electrode placement compared to nonresponders – a placement that, in theory, would be more likely to allow direct stimulation of the forceps minor~~. Therefore, it is possible that prospective targeting based on individual DTI tractography could optimize ~~SCC~~subcallosal cingulate DBS electrode placement.[23, 24]

Given the strength of the preliminary data leading to this study, and the emerging data suggesting ways to optimize targeting for this intervention, the negative outcome of this trial should not be simply interpreted as a failure of ~~SCC~~subcallosal cingulate DBS for ~~TRD~~treatment-resistant depression. Subsequent studies are merited to determine whether active ~~SCC~~subcallosal cingulate DBS failed to differentiate from sham due to clinical features of the patient population (e.g., extremely chronic depression) or suboptimal electrode placement. Additionally, identification and use of a physiological metric to verify engagement of the appropriate neural circuit could assist with targeting. Importantly, the long term response and remission rates in this and prior studies suggest that this intervention continues to have promise.

LIST OF TABLES

Table 1. Demographics and clinical characteristics.

Table 2. Depression severity over time.

Table 3. Response/remission by study visit.

Table 4. Serious adverse events and non-serious adverse events by group.

FIGURE LEGENDS

Figure 1. Participant disposition.

Figure 2. Depression severity over time in each treatment arm. Note that at months 9 and 12, the Control group was receiving active stimulation; therefore, for the Control group, 9 months refers to 3 months of active stimulation, and 12 months refers to 6 months of active stimulation.

Figure 3. Overall function over time in each treatment arm. Note that at months 9 and 12, the Control group was receiving active stimulation; therefore, for the Control group, 9 months refers to 3 months of active stimulation, and 12 months refers to 6 months of active stimulation.

Figure 4. Long-term outcomes (depression severity and overall function) in all participants receiving active stimulation during the study. These results include participants initially randomized to active stimulation and participants initially randomized to no stimulation for the double-blind phase of the study. For the participants initially randomized to no stimulation, the data used for this graph are solely those collected after active stimulation had been initiated in the open-label study phase.

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Dr. Holtzheimer receives grant support from NIMH, BBRF and Janssen Pharmaceuticals. He receives royalties from UpToDate and Oxford University Press. He previously consulted for St. Jude Medical Neuromodulation but has not received consulting fees since 2014.

Dr. Husain receives research grant support from NIH, NIMH, NIDA, NINDS, NIA**,** NARSD, Stanley Medical Foundation**,** Cyberonics, Neuronetics, Abbott (previously known as St. Jude Medical), MagStim (equipment only), Brainsway, NeoSync**,** Alkermes, Assurex, and Avanir. He is on the Speaker Bureau/Research consultant for Acadia and AltheaDx.

Dr. Lisanby is co-inventor on a patent, assigned to Columbia University, on an unrelated technology. This patent is not licensed and generates no royalties.

Dr. Taylor received research support from Neuronetics, Abbott (previously known as St. Jude Medical), and Vanguard Research Group.

Dr. McClintock receives research support from NIH. He has also received a teaching honorarium from TMS Health Solutions.

Dr. Slavin is a member of advisory board and / or consultant for Abbott (previously known as St. Jude Medical), Baxter, Biotronik, Boston Scientific, Insightec, Medtronic, Neuramodix, Nevro, Nuvectra, SPR Therapeutics, StimRelieve; he has received research and/or fellowship funding from Abbott, Autonomic Technologies, Boston Scientific, Medtronic, Neuros and Pfizer.

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Dr. Abosch has performed ad hoc consulting for Medtronic.

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Dr Henderson is a consultant for Nevro Corp., Circuit Therapeutics, Enspire DBS, and Proteus Biomedical. He serves on the Surgical Advisory Board for Neuropace.

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AUTHOR CONTRIBUTIONS

Dr. Holtzheimer made substantial contribution to design and conduct of this study as well as interpretation of the data. He had primary responsibility for drafting this manuscript. He gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Husain made a substantial contribution to the acquisition of study data and the critical revision of the manuscript. He gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Dr. Rothschild made a substantial contribution to the acquisition of study data and the critical revision of the manuscript. He gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Pilitsis made a substantial contribution to the acquisition of study data and the critical revision of the manuscript. She gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Espinoza made a substantial contribution to the acquisition of study data and the critical revision of the manuscript. He gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Petrides made a substantial contribution to the acquisition of study data and the critical revision of the manuscript. He gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Mogilner made a substantial contribution to the acquisition of study data and the critical revision of the manuscript. He gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Professor Matthews made a substantial contribution to the acquisition of study data and the critical revision of the manuscript. He gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ms. Peichel made substantial contributions to the design and conduct of this study. She supervised all aspects of data acquisition and analysis and contributed to the interpretation of the results. She assisted in the drafting of the manuscript and its critical revision. She gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Gross made substantial contributions to the design and conduct of this study. He assisted in drafting the manuscript and its critical revision. He gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Hamani made substantial contributions to the design and conduct of this study. He assisted in drafting the manuscript and its critical revision. He gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Lozano made substantial contributions to the design and conduct of this study. He assisted in drafting the manuscript and its critical revision. He gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dr. Mayberg made substantial contributions to the design and conduct of this study. She assisted in drafting the manuscript and its critical revision. She gave final approval of the submitted manuscript and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Manuscript reference number: THELANCETPSYCH-D-17-00261

Title: Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multi-site, randomized, sham-controlled trial

Dear Dr. Marsh,

Please see our responses to the editor's and reviewers' comments below.

1. All Lancet group journals should contain a Research in context panel.
***Done.

2. Can you include a statement that the neuropsychiatric findings will be published separately.
***This has been added to the safety section of the results.

3. For each author, please provide just one (highest) degree.
***Done

4. We need written confirmation, including a signature, from everyone who is mentioned in the Acknowledgments section to confirm that they are happy to be quoted in your paper. The following format can be used:

"I permit <corresponding author> et al to list my name in the acknowledgments section of their manuscript and I have seen a copy of the paper <full article title>"

All authors are required to provide a signed author contribution statement form, available to be downloaded from http://download.thelancet.com/flatcontentassets/authors/tlp-author-signatures.pdf .

All authors should complete and return an ICMJE conflict of interest form, available from http://www.icmje.org/conflicts-of-interest/

***These should have been sent to you directly by DeLea Peichel from Abbott (formerly St. Jude Medical Neuromodulation). If you have not received, please let me know ASAP.

5. Please remove subheadings from the Results section
***Done.

6. Please write out TRD and SCC.
***Done throughout, though this is awkward in some places.

7. Please give details of the safety outcomes in the abstract and check that the abstract contains all information required by CONSORT.
***We have added information on safety in the abstract.

8. Please state the role of the funder.
***Abbott previously known as St. Jude Medical was the study Sponsor. This role included protocol design with assistance of the consultants, FDA negotiations and communication, study execution including monitoring, data analysis, and statistical analysis.

9. Please provide the appendix as a pdf file with numbered pages.
***This is supplied as a separate document.

10. One of my editorial colleagues requested: please add to the discussion the fact that methods vary a lot between DBS trials so can't really say they work / don't work as a general rule unless you know the methods, as they are very heterogenous and perhaps some techniques work and others don't. E.g., “the methods could use more info on precise lead localisation measurements, types of electrodes used, how variability between surgeons was rated, etc. Or, if this level of detail is not available, the discussion could use a bit on how things like missing the target, variability between surgeons, etc could have affected the outcome.”

***More detail is provided on the parameters of the electrode array and targeting. As described in the manuscript, lead placement was assessed by a team of experts; in four cases, leads were repositioned due to inadequate placement. This team of experts also identified the optimal sequence of contacts to be used for active/sham stimulation; this is now described in more detail. We did perform a post-hoc imaging analysis of lead placement and location of the contacts used for stimulation. In terms of gross anatomical location, there was no statistically significant difference in lead placement between responders and nonresponders. This is described in the last paragraph of the results section.

***Results for all secondary outcome measures are now provided in Supplementary Tables S2-S8.

Reviewer #2:

1. I think these results deserve some more discussion than it currently receives. On p.16 the authors state: "Indeed, the major difference in this study compared to prior SCC DBS studies was the lower response rate to active stimulation during the blinded phase of the study." I completely agree with this statement, but the authors explain this difference by stating "(…) it is possible that differences in benefit between active and sham stimulation may not be seen until after one to two years of treatment". However, I miss a direct comparison between this study and previous open-label studies. For instance, in Lozano et al (2008, Biological Psychiatry) the response rate after 6 months was 60% (12/20), in Holtzheimer et al (2012, Archives of General Psychiatry), response was 58,9% (10/17), in Puigdemont et al (2012, Internation Journal of Neuropsychopharmacology) it was 87.5% (7/8). These are all substantially higher response rates, which did not take 1-2 years to reach. Even after 6 months of open-label stimulation in this study (i.e. the 12-month point), the response rates were approximately 30% in both groups. Could the authors discuss this point some more? Might there be some essential differences with these open-label studies, e.g. other ways of DBS programming or more supportive or psychotherapeutic sessions?

***We share the reviewers perplexity, yet it is not uncommon for placebo-controlled studies to show lower response rates to active treatment compared to prior open-label studies (please refer to the VNS studies in depression, where placebo-controlled response rates to active VNS over 3 months was half of what was seen in the prior open-label study). However, this alone does not fully explain the overall lower response rate even at the later time points. It is plausible that the more chronic nature of these patients compared to prior samples plays some role, as this cohort has a notably longer duration of the index episode compared to the average duration of other published small studies. These points have been emphasized in the discussion.

2. One explanation given in the discussion is the longer episode duration. Do you have any evidence from this study that patients with shorter episode duration responded better or faster? If so, could this be added to the paper?

***In this study, episode duration did not correlate with response, and we likely did not have the power to adequately test for this. However, it is notable that this sample had, on average, a much longer duration of current episode than in previous studies. This may have impacted the response rate to active stimulation, but this is purely speculative at this point.

3. In addition to the long episode duration, Table 1 shows participants in the active group are on average 67.73 years (3.8) and in the control group 67.37 years (3.29). This means the patients in this study are on average 20 years older than the patients in the open-label studies. I think this and its possible influence on the results should be mentioned in the discussion.

***This was an error in the original table. This has been corrected.

4. The response rates do seem to increase after one year of open-label stimulation to approximately 50% (i.e. at the 18-month point). On p.14, the authors state: "Stimulation parameter, medication and/or psychotherapy changes were allowed during the follow-up study, but these changes, when they occurred, had no discernible impact on efficacy over time." Could the authors explain how this was measured or analyzed, and also add this analysis to the manuscript? Can the authors give any indication what did cause the increase in response rates?

***Below we provide a full description of the data analyses, and we have added this to the results section. We defer to the editors whether to include all of this text in the manuscript. As stated in the original manuscript, neither stimulation parameter nor medication changes were associated with efficacy for the first two phases of the study (6 month sham-controlled phase and 6 month open-label phase). However, an analysis of the 18-30 month period (when all participants had received active stimulation for 12-24 months) did show that stimulation parameter changes associated with efficacy (including reevaluating contact location and stimulating at a single contact (different from the initial optimal contact)). Details of the analyses include:

“For the first 12 months data, a generalized linear mixed effects model was fitted that included treatment group, medication change and stimulation parameter change at each follow-up visit as independent fixed effects, subject as a random effect and responder status at each follow-up visit as the dependent variable. Neither stimulation parameter change nor medication change were associated with response rate ($p=0.2176$ and $p=0.4891$, respectively). Separately, a generalized linear mixed effects model was fitted for the 18-30 months data (open-label stimulation) that included medication change and stimulation parameter change at each follow-up visit as independent fixed effects, subject as a random effect and responder status at each follow-up visit as the dependent variable. Stimulation parameter change was associated with increased response rate ($p=0.0127$), but medication change was not ($p=0.3955$).”

5. Some details of the surgery and target localization (p.6) were a bit unclear. Which electrodes were implanted and how many contacts did the electrode have? How was the targeting done (by use of an anatomical landmark or axon bundles?) and can you give a short description of where the contacts were approximately placed? If possible, could you add a figure or schematic of a typical placement? On p.6

the following remark is made: "(…) using the standard stereotactic surgical procedures at each site." Were there any systematic differences between sites?

***Details on the electrode array/lead and target selection have been added to the Methods. The same targeting approach was used at every site; differences in stereotactic surgical procedures between sites did not affect target selection or location of the implanted leads and primarily involved the surgeon's preference regarding details of the procedure unrelated to target placement (e.g., location of scalp incision, angle of lead insertion).

6. In addition, I had some question on the DBS programming (p.7). I understand no more than four different settings (4, 6 and 8 mA and addition of contact?) were allowed and no changes were made after 10 weeks. What happened in case of side effects? Did you change it to a previous setting or was a setting in between allowed?

***In the case of side effects, parameters could be changed to those used previously. However, this occurred in no cases. (But, this clarification has been added to the manuscript.)

7. And assuming the use of a 4-contact electrode, why was decided not to try different contacts besides these two contacts?

***This has been clarified by providing a more detailed description of targeting, as above. Prior studies of SCC DBS strongly suggested that the optimal contact for chronic stimulation was the contact best situated in the subcallosal cingulate white matter. The contact selection was guided by this. The contact best situated in the SCC white matter was selected as the first contact to be used. The contact next best situated in the SCC white matter was selected as the second contact to be added. In no case were the third or fourth contacts situated in or near the SCC white matter so there were never considered as viable options for long term stimulation. Additionally, due to the experience that antidepressant effects of SCC DBS occur over weeks to months, we chose to limit parameter changes to the first 10 weeks of the study, and this necessarily limited the number of steps included in the algorithm.

8. Furthermore, no DBS parameters were changed in case of >10% decrease on MADRS. Does this mean: once >10% decrease has been achieved, DBS parameters were fixed? Or could amplitude be increased two weeks later, if no further improvement had been achieved? As a concrete example: if a patient decreases from 40 to 36 on the MADRS on 4 mA after 2 weeks, is the amplitude fixed on 4 mA, or did you have the opportunity to increase to 6 mA if the patient did not show further improvement in the weeks after?

***As described in the methods, the 10% MADRS change was assessed based on the previous MADRS assessment. So yes, the amplitude could continue to be increased if the MADRS following 4 weeks was less than 10% lower than the MADRS at 4 weeks' time point.

9. Table 3 presents the responder rates. At 18, 24 and 30 months percentages are presented out of a total of 52 and 25 patients. What about the 8 and 5 dropping out? Were these responders / non-responders? Could the authors add the intent-to-treat percentages (e.g. by using the response status at last follow-up)?

***The response rates presented are the intent-to-treat percentages. Of the eight patients that dropped out of the Active group, all were nonresponders at all time points up to the 12 month endpoint. Of the

five patients that dropped out of the Control group, three were nonresponders at all time points up to the 12 month endpoint. One was a responder at 3, 6, and 9 months, but not at the 12 month endpoint. One was a responder at the 9 month time point but not at any other time point. We believe this level of detail is not needed in the manuscript. However, we have added the following to the Results section: "Eight participants from the Active group and five participants from the Control group dropped out; all were nonresponders at the 12 month endpoint."

Reviewer #3:

1. Why did the authors choose MADRS rather than the more standard (eg in the pilot papers) HAMD? Table 2 is missing HAMD data from months 9 and 12 and it's not explained why.

***The MADRS was chosen as the primary measure because it has been shown to be unifactorial, hence more sensitive to symptom change. Per the protocol, the HAMD and several other secondary measures were were only administered every 6 months per the FDA approved protocol.

2. Authors state that expert consultants selected optimal contact sequences for monopolar stimulation. What constituted an optimal sequence? Proximity to anatomic SCC?

***The optimal sequence essentially included the first and second contacts best situated in or near the SCC white matter. Please see response to Reviewer 2 above. More detail on targeting has been added to the Methods, as described above.

3. Did the authors assess the effect, if any, of cumulative stimulation dose, i.e compare outcomes of those who were stimulated the longest compared to the shortest?

***Response and remission rates increased over time, though a few participants responded sooner than others. From the data collected, there is no meaningful way to assess the effect of cumulative dose beyond noting that antidepressant efficacy increased over time in the sample.

4. I would consider removing or re-wording the line in the Discussion that intervention may be less effective in the extremely chronically depressed. The authors state in the preceding paragraph that no demographic or other features predicted clinical response to DBS, and duration of illness is an illness feature. For many in the psychiatry community, brain surgery ought to be specifically for patients who are extremely chronically depressed, to justify it's risk and invasiveness. Is this not the very definition of TRD?

***We included this comment to reflect the difference in duration of current episode between this current cohort and the samples enrolled in prior studies of SCC DBS for TRD. We do believe this is a potential explanation for active DBS not achieving a mean effect as large as that seen in prior studies. If SCC DBS were clinically available, we do not think this comment implies that it should not be considered for patients with extremely chronic depression. However, this should perhaps be considered as a potentially negative prognostic factor (as it currently is when considering ECT and TMS).

5. Only one reference is made to DBS trials done at targets other than the SCC. Several have been tried, including the VC/VS, NAcc, Habenula, and MFB. In addition SCC DBS has been tried in different indications, including bipolar disorder and anorexia nervosa. Do the authors feel a different target should be tried? Why or why not?

***We feel it is most appropriate to focus this manuscript on the findings of this trial. We believe it is beyond the scope of this manuscript to weigh in on the relatively strengths of the various DBS targets for TRD, and that this discussion is more appropriate for a commentary or later review. However, we defer to the editors on this and would be happy to include more discussion on this point if the editors feel it would strengthen the manuscript.

Reviewer #4:

1. It is a little frustrating that the authors did not ensure a more similar patient population to prior studies.

***As noted above, the age of this sample was incorrectly reported in the previous manuscript. The mean age for this sample is similar to that of prior studies. All other clinical features are also similar to previous studies except for duration of current episode. This was unanticipated, since no limits for episode duration were used in prior studies, and therefore the same approach was used in this study. This approach unexpectedly resulted in a sample with a longer mean duration of current episode than seen in prior studies.

2. Despite no advantage of 6 months DBS when comparing to sham to active, transition to open-label DBS showed marked improvement over 2 years. It is unclear whether there are significant differences when compared to baseline in this open-label phase but this would be worth indicating.

***There was an overall statistically significant within group decrease in depression severity over time. This comment has been added to the manuscript in the Results section.

2. It is certainly reasonable that a microlesion effect was durable and that a better design would have been open-label stimulation followed by blinded discontinuation as the authors indicated as the authors indicate.

***We agree that this is an interesting alternative design. However, this was not the FDA-approved protocol for this study.

3. Could there not have been a significant change between groups because there was frequent, supportive contact (every 1-2 weeks) from the study team? Any involvement in clinical trials has been found to improve outcomes in patients across disciplines.

***This is indeed possible, though the change in depression severity over the first 6 months in the sham group was not dramatic.

4. Might the clinical scales used not be sensitive to detect a clinically meaningful effect in very ill subjects?

***It is possible that the MADRS may not capture the meaningful symptom change in these very ill patients. However, the use of standard depression rating scales is typically expected from the field at large, and especially the FDA.

5. Interestingly, this study was like the Reclaim VC/VS depression study in that it used the MADRS, showed no effect, and was halted by study sponsor. Also, could lack of more robust response be the result of not changing DBS settings after 10 weeks?

***This is possible. However, we chose to err in favor of longer stimulation time at what were deemed to be optimal settings (based on prior studies) versus additional settings changes that would not have allowed for a longer period of stimulation at the final parameters.

6. The authors indicate that the demographics did not impact outcome - I was curious however how closely they looked at sex differences?

***Change in primary and secondary measures were compared between men and women in the study and were not found to be statistically significantly different. A logistic regression model was used to examine the effect of treatment (Stimulation or Control) while adjusting for the baseline demographic variables (study site, level of treatment resistance as defined by ATHF criteria and baseline MADRS). Based on the logistic regression model results, gender did not impacted the outcomes (p=0.3164). The full model for the primary outcome measure (MADRS) is provided below and is now included as Supplementary Table S1.

Source	DF	Chi-Square	Pr > ChiSq	Method
Treatment group	1	0.12	0.7274	LR
Sex	1	1.00	0.3164	LR
Site category	2	5.65	0.0593	LR
Average Baseline MADRS	1	0.39	0.5303	LR
Total number of lifetime antidepressant medications and acceptable medication augmentation strategies	1	0.68	0.4087	LR
Total number of lifetime antidepressant medications rated 3 or higher with at least good confidence	1	0.00	0.9686	LR
Total number of lifetime antidepressant treatments rated 3 or higher (can include psychotherapy, ECT, VNS, TMS)	1	0.19	0.6602	LR
Total number of lifetime treatments for depression (including all others listed on this document	1	1.81	0.1783	LR

7. The inclusion of patients with medication-free or stable regimens for only >4 weeks may have been too little?

***Presuming the reviewer means that 4 weeks of medication stability may be too short for "true" stability, we partially agree. However, for clinical and practical reasons, a longer period of stability was deemed not feasible. Also, a four week period of medication stability is common in depression clinical trials, including studies of patients with TRD.

8. Did revision patients have any difference in outcomes on average? There were 4 revisions. Would be interesting to know if there was a more robust lesion effect in these revisions as well. The authors have not proven that DBS is better than implant alone, so ruling out lesion effects by looking at patients with perhaps MORE robust lesion effects would help.

***There was no difference in efficacy in patients with and without revisions. In these 4 revisions, 3 were in the control group and 1 was in the treatment group. Their responder status at each visit was summarized in the below table.

Study Subject ID	Responder based on 4,5,6M average	Responder 6m open-label	Responder 9m open-label	Responder 12m open-label	group
074005	Non-responder	Non-responder	Non-responder	Non-responder	Ctrl
278003	Non-responder	Non-responder	Responder	Non-responder	Ctrl
214002	Non-responder	Non-responder	Non-responder	Responder	Ctrl
277015	Non-responder	Non-responder	Non-responder	Non-responder	Stim

Within the control group, a logistic model which included an indicator of system revision as independent variable and responder status at 6M as dependent variable was fitted to the data. It shows that there was no difference in efficacy in patients with and without system revisions (p-value = 0.2817). A generalized linear mixed-effect model was fitted to the longitudinal data and it shows that was no difference in long-term efficacy in patients with and without system revision (p=0.6792).

9. Given this staggered randomized onset design, were revision patients in each group?

***Yes.

10. Why wouldn't the treatment/control groups be of the same size? They were 2:1 I believe - is this ethically driven as more patients in the experimental group will be exposed to potential therapy earlier on?

***In consultation with the FDA, this design was chosen to reduce the chances of patients receiving sham treatment. Statistical analyses accounted for this difference in group size.

11. For patients who needed increase in mA during the blinded phase, were there outcome differences?

***There were not.

12. Are certain patients simply super responsive but those who don't respond at a low dose, don't respond or worsen at a higher dose? This would support a blinded randomization of responders.

***This is unknown, and the study was not designed to test this.

13. How many subjects worsened and moved to open label?

***None.

14. How many had revisions were in the control group?

***There were 4 subjects who had revisions: 3 were in the control group and 1 was in the stimulation group.

15. To me it seems disease stability is necessary before interpreting a stimulated response. Shouldn't the investigators have waited until the subjects returned to a predefined baseline? It seems patients in the control group were improving as I am sure the stimulated group would have had they not been stimulated. I recognize it must be challenging to wait and funding was likely a major limitation, but if patients are on a downward trend in disease severity without stimulation, I feel the design compromised any interpretation of stimulation induced effects on depression severity. Some discussion is needed on this.

***This is an interesting design option, but again, this was not the protocol approved by the FDA. A more standard, prospective, randomized, controlled trial was deemed to be most appropriate for testing the hypotheses, especially given the state of the field at the time the study was designed. This is already mentioned in the discussion.

16. "Stimulation parameter, medication and/or psychotherapy changes were allowed during the follow-up study, but these changes, when they occurred, had no discernible impact on efficacy over time." How was this confirmed to be true?

***Please see the response to Reviewer 2 above.

17. "However, it is noted that participants in this study had an average current episode duration of about 12 years. This is much longer than the average duration of current episode in prior SCC DBS studies (approximately five years)3, 6." But this wasn't significant as a correlation, right? The authors seem to be looking for trends (and I understand why) but they stated previously that demographics did not impact outcome. Have they consulted with a statistician to ensure these correlations were not significant?

***As stated in the manuscript, there was no correlation between duration of current episode and efficacy in this study; this was indeed confirmed by statistical analyses. It is possible we did not have power to show an association of episode duration and efficacy. However, this sample, as a whole, had a mean duration of current episode much longer than prior studies which we believe is an important point to note as a potential explanation for why patients in this study were less responsive to active DBS than in prior trials.

18. "It is notable that SCC DBS responders in this study tended to have a more anterior and superior electrode placement compared to nonresponders - a placement that, in theory, would be more likely to allow direct stimulation of the forceps minor. Therefore, it is possible that prospective targeting based on individual DTI tractography could optimize SCC DBS electrode placement." I agree - but wonder why this targeting is such a challenge across institutions. It is a bit concerning that if targeting is difficult, that this potential therapy could not be broadly adopted. I suspect this is not the case, but it would provide clarity if the authors could explain why this error occurred despite the training they claimed was performed.

***Since lead placement did not differ significantly (only a slight trend) between responders and nonresponders, we have taken this statement out of the manuscript. Regarding surgical targeting, there are a number of reasons why this might vary within and between sites. A full discussion of this is beyond the scope of this manuscript. To be clear, there was no systematic error in targeting and this is described in the last paragraph of the results section.

Reviewer #5:

1. This study mainly reported descriptive statistics and simple comparison results between means. Multilevel modeling is a standard analysis method for longitudinal data, which is known to be more powerful than simple comparison between two time points. In the Section Statistical Consideration and Data Analysis, a logistic regression model was mentioned. However it is not clear what is the outcome variable in this logistic regression. Was it used to examine responders versus non-responders? No results from this logistic regression were reported in the Results Section.

***The full logistic regression model is provided above in response to Reviewer 4. This is now included in the supplementary information as Table S1.

2. Efficacy measures were collected at baseline (weeks 4, 6, ad 8) and at months 4, 5, and 6. To evaluate efficacy, average of 3 baseline MADRS assessments and average of months 4, 5, and 6 were used. For this type of longitudinal data, it is a common practice to use multilevel modeling to examine the change trajectory. The stimulation group can be added as a moderator to see whether the trajectory is significantly different between the two groups. Multilevel modeling has advantages of handling missing data and is known to be a more powerful analysis method than simple averaging.

***A linear mixed effects model was constructed which included treatment group and visit as fixed effects and subject as a random effect and was fitted to the MADRS assessment over the first 12 months (Figure 2 in the manuscript). It shows that MADRS decreased over time (p-value <0.0001) in both groups and the Control group have a 2.95 point higher MADRS score across all visits as compared to the Stimulation group (p=0.0038), however there was no significant difference in change over time between the groups. A similar model was fitted to the GAF and it shows that GAF improved over time (p-value <0.0001) in both groups and there was no difference between two groups over time (p=0.2417).

Treatment effects on MADRS in the first 12 months based on Linear mixed effect models

Effect	GROUP	VISIT	Estimate	Standard Error	Pr > |t|
GROUP	Ctrl	.	2.9474	1.0123	0.0038
GROUP	Stim	.	0	.	.

Treatment effects on GAF in the first 12 months based on Linear mixed effect models

Effect	GROUP	VISIT	Estimate	Standard Error	Pr > |t|
GROUP	Ctrl	.	-1.4687	1.2528	0.2417
GROUP	Stim	.	0	.	.
VISIT		0	-12.5339	1.8961	<.0001
VISIT		3	-7.1333	1.8912	0.0002
VISIT		6	-3.0101	1.9168	0.1171
VISIT		9	-1.7980	1.9336	0.3530
VISIT		12	0	.	.

4. When examining long-term outcomes, it makes more sense to run multilevel models for data shown in Figure 3. Words describing change trajectories such as "efficacy over time" and "temporal relationship" appeared several times in the paper. It seems that the authors were trying to investigate the change trajectory. If so, I strongly recommend multilevel modeling as an effective approach for longitudinal data.

***Please see the above responses.

Reviewer #7:

1. To my mind, using a responder criteria of 40% improvement is problematic. I realize that 40% improvement in this refractory population is significant. However, essentially ALL prior depression studies use 50% improvement as a measure of response. For example, you reference Lozano (2012) which is reference #7. Using 50% criteria, the one year response rate in that study was 29%. With the 40% criteria, it was 62%! The more lenient criteria makes comparison to prior and future studies highly problematic. A greater explanation needs to be given for choosing this threshold. It also makes

comparison to the only other sham controlled trial (Dougherty, 2015, Reclaim) very difficult. In looking at that study, there appear to be a number of patients who would be responders at 2 years at 40%, but were not at 50%. I'm not sure how to resolve this given that the 40% threshold was chosen a priori. I would like to see the response rate results given for the 50% threshold as well, if for nothing more than comparative purposes. At a minimum, the difference has to be completely clear when comparing to prior studies. It also needs to be very clearly addressed in the discussion.

*** The requested 50% response rate data has been added to the table.

2. Per Table 1, the mean age in this study was over 67 years. I'm assuming this is an error, given that the inclusion criteria were ages 21-70. My apologies if I am misreading the Table. Please explain. Obviously, an average age of 67 would make this population dramatically different than other DBS studies or your own open label trials.

***This was an error in the Table and has been corrected. The mean age of this group is very similar to prior studies of DBS for TRD.

3. Please provide mean reductions in MADRS scores and increases in GAF scores for Figure 3. These appear to be much less than in prior open-label studies. This would allow for some direct comparison to other studies that used different response threshold criteria. I would also suggest adding a 2-year time point for Table 2.

***Since not all patients at 12 months entered the long-term follow-up study, we deemed it not appropriate to put the 2 year data in Table 2 and the Figures. Long term effects are presented in Table 3. As discussed in the manuscript, the change over time with active stimulation is less than that seen in prior studies. We do not believe reporting the percent change in MADRS and GAF adds much to the presentation of results since these could easily be calculated from the data presented. However, we defer to the editors on this, and could easily add these to Table 2 (though we feel this would make the table much more visually complicated).

4. How was your stimulation adjustment paradigm arrived at? Was it based on data from prior studies or more on clinical experience? Please explain.

***This was based on prior studies showing that a single contact in the SCC white matter was sufficient for antidepressant benefit and that no more than 8 mA was typically needed to achieve effects.

5. The first paragraph of the discussion states that response/remission rates here are similar to open label studies. This really isn't true, especially when the 40% threshold is considered. Please rephrase.

***This sentence has been revised.

6. The only other sham controlled trial of DBS in TRD(Dougherty, 2015) isn't even referenced in the discussion. Granted, it is a different target. However, it appears to have a very similar design, and many similarities in the results. It is critical to emphasize and discuss why two sham controlled studies based on solid open label data both failed to demonstrate efficacy. This group of highly experienced authors must at least comment on where this treatment sits after these two trials and where the field goes from here.

***We believe it is beyond the scope of this paper to comment on the other sham-controlled trial given the major differences between these studies (different targets, different time points, different programming paradigms, etc.). To us, this discussion seems more appropriate for a commentary or review. We have focused this manuscript on describing the results of this clinical trial and prefer to defer to others on placing this in the broader context of DBS for TRD. However, we see this as an editorial decision. If the editors believe that this discussion should be added to this manuscript, we will add it.

7. Were both suicides on active stimulation at the time of suicide? Please clarify.

***As stated in the results, both deaths by suicide occurred in the Control group during the open-label phase, so both patients were receiving active stimulation but had previously received sham stimulation.

8. One patient was exited due to sponsor study closure. Was this decision forced upon the patient or did they concur with exiting? Did they want to continue but weren't able? This concern has been brought up in several ethics commentaries on DBS. It's a crucial point when designing future studies and what the funding agencies will be responsible for. Please clarify and discuss.

***This patient was exited from the 12-month study but was enrolled in the long-term follow-up study. Therefore, the sponsor continues to provide care related to DBS for this patient.

9. Please explain why a 2:1 randomization was chosen.

***In consultation with the FDA, this design was chosen to reduce the chances of patients receiving sham treatment. Statistical analyses accounted for this difference in group size.

Clinical Protocol

Protocol Number: C-07-01, Revised with Amendment I-IX, 10/05/2011

Protocol Title: A clinical evaluation for the management of patients with Major Depressive Disorder, single or recurrent episode, with deep brain stimulation.

Investigator: _____, MD
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Approval Signatures:

Investigator _____ **Date** _____

Director, Clinical Research _____ **Date** _____

Study Monitor _____ **Date** _____

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Confidentiality Statement

The confidential information in the following document is provided to you as an Investigator, potential Investigator, or Consultant for review by you, your staff and an appropriate Institutional Review Board or Independent Ethics Committee. By accepting the document you agree that the information contained herein will not be disclosed to others without written authorization from Advanced Neuromodulation Systems, Inc., except to the extent necessary to obtain informed consent from those persons to whom the products may be administered.

Protocol Summary

Title: A clinical evaluation for the management of patients with Major Depressive Disorder, single or recurrent episode, with deep brain stimulation.

Test Articles: ANS Libra® Deep Brain Stimulation System

Objectives: To demonstrate the safety and efficacy of deep brain stimulation (DBS) to the subgenual white matter (Brodmann Area 25WM) as an adjunctive treatment for single or recurrent Major Depressive Disorder (MDD).

Patient Population: Patients who have single or recurrent Major Depressive Disorder (MDD) complying with specific inclusion/exclusion criteria.

Sample Size: A total of 201 patients will be randomized to treatment from up to 20 investigational sites.

Structure: Prospective, controlled, multi-centered, double blind, randomized, study with endpoint evaluation at 6 months post device implantation. Control group patients will not have the investigational device activated for the first 6 months of study.

Method of Assignment: All patients who meet the inclusion/exclusion criteria will be randomized.

Randomization: Randomization will be performed according to a computer generated scheme after device implant in a 2:1 ratio (Active Stimulation vs. Control Group).

Statistical Analysis: The primary endpoint, at least a 40% decrease from baseline to 6 months in Montgomery and Asberg Depression Rating Scale (MADRS) and no worsening in Global Assessment of Functioning, will be analyzed by logistic regression that includes the effects of treatment group, study site, and baseline MADRS, and will be tested at the 5% level of significance.

Adverse Events: Volunteered and solicited.

1 Introduction

Depression, also known as major depressive disorder (MDD), is a serious medical illness that affects a person's physical and mental state. When a person is clinically depressed, his or her ability to function both mentally and physically is drastically affected. This impaired functional and symptomatic state may last for weeks, months, or even years. Typical symptoms of depression include: an "empty" feeling, sadness and anxiety, tiredness, lack of energy or interest in activities, sleep disturbances, including early morning awakening or oversleeping, and thoughts of death or suicide, a suicide attempt. These problems can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of their daily responsibilities. MDD is one of the leading causes of disability in the United States and established market economies worldwide (Murray et al. 1996). The World Health Organization (2006) estimates that at its worst, depression can lead to suicide, a tragic fatality associated with approximately 850,000 lives every year.

Major depressive disorder affects approximately 9.9 million American adults or about 5.0 percent of the U.S. population age 18 and older in a given year (Narrow 1998). While MDD can develop at any age, the average age of onset is the mid-20s (American Psychiatric Association – APA, 1994). Among this disease population, a large number of patients are consistently resistant to the many and different therapies utilized to treat depression. This subgroup is diagnosed as having treatment resistant depression (TRD) and treatment alternatives are desperately needed for this growing population of severely depressed patients.

Modern brain imaging technologies are revealing that in depression, neural circuits responsible for the regulation of moods, thinking, sleep, appetite, and behavior fail to function properly, and that critical neurotransmitters—chemicals used by nerve cells to communicate—are out of balance (Nestler et al. 2002). Genetic research indicates that vulnerability to depression results from the influence of multiple genes acting together with environmental factors (NIMH Genetics Workgroup). Ongoing studies of brain chemistry and of mechanisms of action with antidepressant medications continue to inform the development of new and better treatments.

Antidepressant medications are widely used and often partially effective treatments for depression (Mulrow et al. 1998). Available antidepressant drugs influence the functioning of certain neurotransmitters in the brain, primarily serotonin and norepinephrine, known as monoamines. Older medications such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), affect the activity of both of these neurotransmitters simultaneously. The disadvantage of these older medications is that they can be difficult to tolerate due to side effects or, in the case of MAOIs, dietary and medication restrictions. Newer medications, such as the selective serotonin reuptake inhibitors (SSRIs) or selective serotonin/norepinephrine reuptake inhibitors (SNRIs), appear to have fewer side effects than the older drugs, making it easier for patients to adhere to treatment. Unfortunately, no single medication is effective for all depressed patients as

various groups of patients will respond to one drug while other patients will require different agents. Fava (2003) states that treatment resistant depression typically refers to an occurrence of an inadequate response following adequate antidepressant therapy among patients suffering from unipolar depressive disorders; which further shows that adequate treatment strategy is extremely difficult for this group of depressed patients. A recent, overall assessment of the nation's largest real world study of treatment-resistant depression (Sequenced Treatment Alternatives to Relieve Depression – STAR*D) suggests that a patient with persistent depression can get well after trying multiple treatment strategies, but his or her odds of "beating" depression lessen as additional strategies are needed (Rush et al. 2006). The STAR*D study, which has studied thousands of patients, further proves that the task of finding the correct treatment for severely depressed patients, can be extremely daunting.

Certain types of psychotherapy can be an effective treatment option for depression. Cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT) have shown to be particularly useful. Approximately two thirds of adults with depression improve when they receive appropriate treatment with medication, psychotherapy, or the combination (Hollon et al. 2006), whereas only one third of treatments result in a full remission.

Despite available pharmacologic and psychotherapeutic treatments, a large number of depressed patients do not have an acceptable or sustained response to these treatments. Despite the advances in brain-neurobiology research and the growing number of available antidepressant therapies, fewer than 50% of these patients achieve remission, and up to 20% develop treatment resistant depression (Kennedy & Lam, 2003). Not only do these patients remain treatment resistant, they are also chronically and severely disabled.

For these severely ill patients who do not respond to psychotherapy and medication, Electroconvulsive Therapy (ECT), is often prescribed. Although this therapy has been shown to have short-term efficacy, many patients experience acute or sustained side effects as a result of the feature (Fink, 2001). Some patients indicate memory loss which can occur for days, weeks and even months after ECT sessions. More recently, other somatic interventions such as Transcranial Magnetic Stimulation (rTMS) and Vagus Nerve Stimulation (VNS) have become available, although sustained response rates are relatively modest according to research studies.

Although still investigational, the rTMS method appears to only provide temporary relief of symptoms; thus many aspects will need to be refined for programming parameters and targeting of regional locations when utilizing this technology, if it is ultimately approved by FDA. A recent FDA panel meeting addressing rTMS' safety and efficacy, showed that rTMS has a favorable safety profile but did not show efficacy at the specific primary endpoint of the clinical trial. The FDA panel recommended to FDA that this therapy not be approved for the treatment of Major Depressive Disorder (FDA Panel Meeting, January 2007).

Alternatively, vagus nerve stimulation has been used for the indication of Epilepsy

in the United States since 1997 (George 2000 and Sackeim et al. 2007). Due to the fact that many epileptic drugs also work for bipolar depressed patients, there was belief that there may be a correlation in the disease process between these two conditions (Elger 2000). These hypotheses led to clinical trials researching the use of the VNS system for major depressive disorder. VNS was ultimately evaluated and approved by the FDA in July of 2005, for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age and older, who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments (Cyberonics Labeling). VNS is now one of the limited new options for this depressed, treatment resistant patient population. Although this therapy was recently approved by the FDA, longer-term, well designed clinical trials are needed to confirm the safety and efficacy of this treatment alternative. Furthermore, since the VNS device has shown limited efficacy in small numbers of patients, it has certainly not proven to be the ultimate solution for treatment of these severely depressed patients.

For the most severely, treatment resistant of these patients, several invasive ablative neurosurgical procedures have also been available; although they are now infrequently used due to perceived side effects and the unfortunate irreversibility of the treatment. Well-established procedures involve the production of lesions that interrupt distinct frontal-cingulate, fronto-striatal, and thalamo-frontal white matter tracts, resulting in therapeutic benefit for some patients (Cosgrove et al. 1995; and Sachdev and Sachdev, 2005). Several of these procedures, including subcaudate tractotomy, cingulotomy and anterior capsulotomy have been found to be effective in some patients, although all involve the permanent destruction of neural structures. Furthermore, there is also a considerable time delay between surgery and symptom improvement.

Recently, destructive procedures to treat Parkinson's disease, such a thalamotomies and paladotomies have been replaced by applying high frequency electrical stimulation to these targets. Deep brain stimulation (DBS) has been found to have distinct advantages over ablation with the major advantage being its reversibility, as well as the option to modify specific stimulation parameters when necessary. Pathological studies further demonstrate that chronic DBS produces little to no tissue damage (Haberler et al. 2000). In theory, DBS can be seen as a potentially safe, effective, flexible and reversible alternative to ablative surgery for treatment resistant depression, if the optimal target can be defined and evaluated.

Functional neuroimaging studies have revealed changes in cortical (frontal, parietal), paralimbic (cingulate, insula) and subcortical (caudate, thalamus) activity following various types of treatments [medication, psychotherapy, sleep deprivation, ECT, repetitive transcranial magnetic stimulation (rTMS), ablative surgery] (Mayberg, 2003). Normalization of frontal abnormalities (both increases and decreases) is the best-replicated finding. Decreases in paralimbic regions, while variable, are also consistently reported. While there is not yet a common pattern that characterizes depression remission across all of the available treatment modalities, medications and all of the available somatic treatments such as ablative surgery, TMS and VNS, changes have been seen in the paralimbic

regions. Specifically, changes have been found in the hippocampus and ventral medial frontal/cingulate areas, having known projections through specific subcaudate tracts (Mayberg et al. 2000).

Regions affected by these white matter interruptions are widespread, as the subcaudate tractotomy is quite large. Specific tracts are less well characterized, but likely involve connections linking orbital frontal, subgenual cingulate, ventral striatum/caudate, thalamus brainstem, hypothalamus and hippocampus/amygdala. The precise optimal target(s) within the subcaudate that mediate antidepressant response is not known at this time. However, imaging studies suggest that disturbances involving more specific connections between the subgenual cingulate and medial frontal, ventral striatum, anterior thalamus, hippocampus, hypothalamus and brainstem may be particularly critical (Seminowicz et al. 2004). Brodmann Area 25WM (BA25WM), also known as the subgenual cingulate region, subgenual white matter, or Cg25, has been shown to be involved in both acute sadness and antidepressant treatment effects; hence indicating its role in modulating mood states (Mayberg et al. 1999). These findings further suggest that DBS may be most effective if these medial pathways are selectively modulated, as this hypothesis has been further verified in a preliminary study in treatment-resistant depressed patients. Mayberg et al. 2005, reported that in a small group of severe refractory depressed patients, DBS induced clinical response in 4 out of 6 patients, with 2 patients achieving full remission. Although these preliminary findings are encouraging, much larger, controlled clinical trials are necessary to show the safety and efficacy of deep brain stimulation of Brodmann Area 25WM.

Deep brain stimulation is considered safe, non-destructive and reversible. The frequency and severity of procedural risks and complications with DBS implantation for depression are expected to be similar to those for Parkinson's Disease and Essential Tremor. An extensive review of Manufacturer and User Facility Device Experience (MAUDE) reports, regarding deep brain stimulation from 1997 to present, has shown no evidence of tissue damage due to excessive electrical stimulation. To date, over 30,000 Deep Brain Stimulation devices have been implanted worldwide. Furthermore, a recent paper by Haberler et al. (2000) concluded that chronic DBS, defined as continuous deep brain stimulaton for up to 70 months, does not cause damage to neural tissue in Parkinson's Disease patients when applied at therapeutic levels.

Unfortunately, there are a limited number of new treatment options for the treatment resistant patient population. Considering the severity of treatment resistant depression and its debilitating effect on patients' and family's lives, Deep Brain Stimulation provides an optimistic opportunity for significant symptom relief and potential quality of life improvement, with minimal risk. Further, this evaluation of DBS' safety and efficacy, gives patients with treatment resistant depression an additional treatment option. The purpose of this proposed clinical study is to evaluate safety and efficacy of subgenual white matter (Brodmann Area 25WM) deep brain stimulation for the treatment of single or recurrent, Major Depressive Disorder, using standard psychiatric rating scales and questionnaires as outcome measures.

2 Objective

2.1 Primary Objectives

To demonstrate the safety and efficacy of deep brain stimulation (DBS) to the subgenual white matter (Brodmann Area 25WM) as an adjunctive treatment for Major Depressive Disorder (MDD), single or recurrent episode.

2.2 Secondary Objectives

To evaluate changes in the following: Hamilton Rating Scale for Depression (HRSD-17), the 30-item Inventory of Depressive Symptomatology (IDS-C30), Quick Inventory of Depressive Symptomatology (QIDS-SR), Young Mania Rating Scale (YMRS), Work and Social Adjustment Scale (WSAS), Quality of Life and safety.

2.3 Primary Variable

Primary Efficacy: Change from Baseline (defined as mean of 3 Montgomery and Asberg Depression Rating Scale (MADRS) scores) to the mean of months 4, 5, and 6 between treatment groups.
The primary endpoint will be defined as at least a 40% reduction in MADRS and no worsening in Global Assessment of Functioning (GAF).

2.4 Secondary Variables

- Change from baseline in GAF over time;
- Change from baseline in the MADRS over time;
- Change from baseline in the Hamilton Rating Scale for Depression - 17 item (HRSD-17) over time;
- Change from baseline in the Inventory of Depressive Symptomatology (IDS-C30) over time;
- Change from baseline in Quick Inventory of Depressive Symptomatology (QIDS-SR) over time;
- Change from baseline in the Work and Social Adjustment Scale (WSAS) over time;
- Change from baseline in Patient Global Impression of Severity over time;
- Change from baseline in Clinician Global Impression of Improvement over time;
- Change from baseline in quality of life over time;
- The incidence of all adverse events (i.e. hospitalization due to worsening depression, suicidal ideation or behavior, medical treatment, and device related events) that occur over study duration.
- Change from baseline in Hamilton Anxiety Rating Scale (HAM-A) over time.

2.5 Other Variables

- Number of patients who have a 40% reduction in Baseline HRSD-17 over time;
- Number of patients who have a 40% reduction in IDS-C30 over time;
- Number of patients who have a 40% reduction in QIDS-SR over time;
- Number of patients in Remission (as defined by a score of ≤ 14 on the IDS-C30) over time;
- Number of patients in Remission (as defined by a score of ≤ 5 on the QIDS-SR) over time;
- Number of patients in Remission (as defined by a score of ≤ 10 on the MADRS) over time;
- Number of patients in Remission (as defined by a score of≤ 7 on the HRSD-17) over time.
- Change from baseline in the Young Mania Rating Scale (YMRS) over time;
- Number of patients with hypomania (defined as present when YMRS ≥ 15.);
- Change in the Neuropsychological Battery test results at 6 and 12 months;
- Change from baseline in the Health and Labor Questionnaire (HLQ) over time;
- Change from baseline in the Columbia Suicide-Severity Rating Scale (C-SSRS) over time

3 Study Design

3.1 Design

This study is designed as a prospective, multi-centered, double-blind, randomized, controlled 12-month pivotal study to evaluate the safety and efficacy of the ANS Libra® Deep Brain Stimulation System for patients with major depressive disorder who have failed at least 4 treatments in the current episode. The primary outcome assessment will occur at 6 months: however, all patients will be followed for 1 year. A total of 201 patients will be randomized from up to 20 sites.

Each potential patient will be pre-screened according to the inclusion/exclusion criteria. A narrative of what study participation entails, will be used to educate potential participants on study requirements. Prior to on-site baseline evaluations, the patient will sign the informed consent. Patients will then undergo 3 baseline evaluations, with each of these evaluations to occur no less than 2 weeks apart from each other. The first 2 baseline visit evaluations will be performed by separate psychiatrists in order to confirm the patient's diagnosis. The patient must score an average ≥ 22 on the MADRS, across 3 evaluations. All patients will be scheduled for surgery, to occur no less than two weeks and no more than 1 month after final baseline evaluation, to implant the ANS Libra® Deep Brain Stimulation system. After device implantation, patients will be randomly assigned to 1 of 2 groups in a 2:1 ratio

(Active Treatment Group & Control Group).

Group 1: DBS Active Treatment Group – implanted with investigational device and activated for stimulation.

Group 2: DBS Control Group – implanted with investigational device, but will not receive active stimulation for the first 6 months of the study. At the end of 6 month visit, these patients will have the investigational device programmed and activated.

After system implant (Week 0), the patient will return to clinic approximately 2 weeks after surgery for evaluation and treatment randomization into either Group 1 or Group 2 (Group 1 = Active Treatment Group; Group 2 = Control Group). Patient will then return to clinic for subsequent evaluations at 2 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, and 1 year post system implantation.

Study Visit Schedule

Timing of visit	**Activities at visit**	**Case Report Forms to be completed** (Appendix C).
Phone Screen	Participant study education Inclusion/Exclusion criteria screening review.	Inclusion/Exclusion Criteria.
Baseline #1 prior to system implantation	Patient signs informed consent; Request/Review - Medical records over last 2 years looking at treatment history and non-compliance issues; Patient screened; Patient completes baseline; **Session videotaped.**	Confirmation of MDD via DSM-IV-TR criteria will occur combined with extensive medical record review; Montgomery and Asberg Depression Rating Scale (MADRS); Demographics and prior history; Medical history; Physician exam; Family history and medications (Antidepressant Treatment History Form - ATHF); Systematic Assessment for Treatment Emergent Events (SAFTEE); Inventory of Depressive Symptomatology (IDS-C30); Hamilton Rating Scale for Depression - 17 item (HRSD-17); Quick Inv. of Depress. Symptom. (QIDS-SR); Subsection for Cluster B of the Structured Clinical Interview for DSM-IV

		Personality Disorders (SCID-II Subsection); Young Mania Rating Scale (YMRS); Work and Social Adjustment Scale (WSAS); Global Assessment of Functioning (GAF); Quality of Life Enjoyment and Satisfaction (QOL); M.I.N.I. Plus; MMSE; Clinical Global Impression of Severity and Improvement (CGI); Patient Global Impression Index (PGI); Health and Labor Questionnaire (HLQ); Hamilton Anxiety Rating Scale (HAM-A); Columbia Suicide-Severity Rating Scale (C-SSRS).
Baseline #2 two weeks after Baseline #1, and prior to system internalization	Patient completes 2nd baseline visit. Evaluations done by a different psychiatrist (evaluator).	Confirmation of MDD via DSM-IV-TR criteria; MADRS; QIDS; SAFTEE; HAM-A; C-SSRS.
Baseline #3 Two weeks after Baseline #2, and prior to system internalization.	Patient completes 3rd baseline visit; MRI scheduled. If the 3 baseline MADRS values are not ≥ 22 the patient will be excluded from re-evaluation for entrance into the study for 6 months.	MADRS; QIDS; SAFTEE; MRI; Neuropsychological Battery (if MADRS values deem patient eligible for study continuation.) HAM-A; C-SSRS.

Day of system internalization (Week 0)	Device implanted according to standard operating procedures.	Surgery Form.
2 weeks after system implant - -Active Group: will have device activated. - Control Group will have device system test performed, but will not get activated.	Randomization; Report any complications;	Office Visit; MADRS; HAM-A; C-SSRS; Programming form.
4 weeks after system internalization	Report any complications; Optimize programming, if necessary.	Office Visit; Programming form; MADRS; IDS-C30; QIDS-SR; SAFTEE; WSAS; GAF; CGI; PGI; HAM-A; C-SSRS.
6 weeks after system internalization	Report any complications; Optimize programming, if necessary.	Office Visit; MADRS; Programming form; QIDS-SR; CGI; PGI; HAM-A; C-SSRS.
8 weeks after system internalization	Report any complications; Optimize programming, if necessary.	Office Visit; Programming form; MADRS; IDS-C30; QIDS-SR; WSAS; GAF; CGI; PGI; HAM-A; C-SSRS.

3 months after system internalization	Report any complications; Optimize programming, if necessary. **Session will be videotaped**	Office Visit; Programming form; MADRS; HRSD-17; IDS-C30; QIDS-SR; SAFTEE; YMRS; QOL; WSAS; GAF; CGI; PGI; HLQ; HAM-A; C-SSRS.
4 months after system internalization	Report any complications; Optimize programming, if necessary.	Office Visit; Programming form; MADRS; IDS-C30; QIDS-SR; WSAS; GAF; CGI; PGI; HAM-A; C-SSRS.
5 months after system internalization	Report any complications; Optimize programming, if necessary.	Office Visit; Programming form; MADRS; IDS-C30; QIDS-SR; WSAS; GAF; CGI; PGI; HAM-A; C-SSRS.
6 months after system internalization	Report any complications; Optimize programming, if necessary; **Session will be videotaped**	Office Visit; Programming form; MADRS; HRSD-17; IDS-C30; QIDS-SR; SAFTEE;

		YMRS; QOL; WSAS; GAF CGI; PGI; HLQ; HAM-A; C-SSRS; Neuropsychological Battery.
7-11 months after system internalization	Report any complications; Optimize programming, if necessary.	Office Visit; MADRS; Programming form; IDS-C30; QIDS-SR; WSAS; GAF; CGI; PGI; HAM-A; C-SSRS; **Month 9 Only:** YMRS; QOL; HLQ; SAFTEE.
12 months after system internalization	Report any complications; Optimize programming, if necessary. **Session will be videotaped**	Office Visit; MADRS; Programming form; HRSD-17; IDS-C30; QIDS-SR; SAFTEE; YMRS; QOL; WSAS; GAF; CGI; PGI; HLQ; HAM-A; C-SSRS; Neuropsychological Battery; Study Exit Form; Long-Term Follow-up consent form.

3.2 Baseline Evaluations

A thorough review of medical records, over at least the previous two years for each patient, will be necessary to review treatment history and any non-compliance to treatment issues. These baseline measurements will be taken after the patient signs the informed consent and complies with all the inclusion/exclusion criteria, prior to device implantation and randomization to treatment. Patient baseline measurements include the Montgomery and Asberg Depression Rating Scale (MADRS); the Hamilton Depression Rating Scale - 17 item (HRSD-17); the Self-Rated Quick Inventory of Depressive Symptomatology (QIDS-SR); Subsection for cluster B personality disorder of the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II); Systematic Assessment for Treatment Emergent Events (SAFTEE); the 30 item Inventory of Depressive Symptomatology (IDS-C30); the Young Mania Rating Scale (YMRS); the Work and Social Adjustment Scale (WSAS); Global Assessment of Function (GAF); the short form Quality of Life Enjoyment and Satisfaction Questionnaire (QOL); Clinical Global Impression of Severity and Improvement (CGI); Patient Global Impression Index (PGI); Health and Labor Questionnaire (HLQ); Hamilton Anxiety Rating Scale (HAM-A) and Columbia Suicide-Severity Rating Scale (C-SSRS). Two different psychiatrists will confirm the diagnosis of MDD via DSM-IV-TR criteria. Previous medical history and psychiatric history will be assessed and recorded including the M.I.N.I. Plus, MMSE, and psychotherapy treatments. A Neuropsychological Battery will be performed after Baseline #3 if patient has met MADRS study inclusion criteria. Portions of these baseline sessions may be videotaped. An initial MRI will occur after Baseline #3 in order to (1) exclude patients presenting with brain abnormalities that might be contributing to severity and treatment resistance of depression or which would not be compatible with the surgery; and (2) to perform surgical lead placement targeting and surgical pre-planning.

3.3 Justification for Study Design

The normal study design to investigate the effect of treatment above and beyond natural history of the condition and the placebo effect is to perform a double blind, randomized controlled study. The present study design fits these criteria. All patients will be implanted with the investigational device bilaterally within Brodmann Area 25WM, according to surgical procedure. The 2-arm study design will allow for a control group to be followed simultaneously with a treatment group. The only difference between these 2 groups will be that 1 group will be receiving active stimulation and the other group will not be receiving active stimulation. We believe that this controlled study design will allow both within patient and between treatment group

comparisons of the effect of DBS on the successful reduction of symptoms from treatment resistant depression.

We will require 3 separate psychiatric baseline evaluations to meet eligibility criteria. Thus, no one person in the study will have the ability to judge if patients are diagnosed properly and meet the baseline scores to be part of this study; hence improving the consistency/reproducibility of the data for the study.

The MADRS was chosen as the primary measurement tool because it has been shown to be unifactorial, hence more sensitive to symptom changes; has been demonstrated to have more individual items that have been shown to be sensitive to change; and is an easy scale to administer.

A statistically significant greater number of patients who meet the response criteria according to MADRS, in the Deep Brain Stimulation group, than in the control group at 6 months, will demonstrate the benefit of Deep Brain Stimulation in the treatment resistant depression patient population. A responder analysis will be performed on this data. The primary endpoint criterion of 40% is a clinically meaningful benefit due to the protracted and disabling nature of this treatment resistant population (Rush et al. 2003; Nahas, 2005).

We believe that this study design will effectively eliminate bias, by addressing the following concerns:

1. The selection criteria for the study will favor placebo non-responders, due to the fact that it naturally selects patients that have undergone multiple therapies with little success;
2. A control group will be used to prove the treatment effect;
3. Active stimulation will not be tested intraoperatively, in order to ensure that patient does not receive any response prior to randomization;
4. The Investigator will be blinded to which treatment the patient will receive in order to minimize bias;
5. The patient will be blinded to which treatment they will receive in order to minimize bias;
6. To help diminish placebo effect over time, all patients will be followed for 12 months and treatment effects will continue to be monitored;
7. All patients will be followed for 12 months post-implant and all willing patients will be followed at 6-month intervals after completing the study.

Finally, a one year study is sufficient to determine safety and efficacy due to the nature of this device and the severity of the patient population. This treatment is not a direct life saving intervention. However, if this therapy is successful it will provide an alternative treatment to those patients who have tried all conventional therapies and failed. In a select group of patients, this

treatment may be able to reduce the suicide rate and provide depressive symptom relief, thus drastically improving their quality of life. In addition, previous device studies of this type that have been undertaken have demonstrated their treatment effect and supported their safety profile by supplying either 6-month, or 1-year of data to obtain PMA approval. We feel this study design supports the collection of valid scientific evidence to support a new device, seeking Pre-Market Approval of this indication. We feel that if this study is successful, DBS will provide physicians with an additional treatment option.

Study Success defined as: Achieving a statistically significant greater number of patients who meet the response criteria as compared to the control group at the 6 month endpoint.

3.4 IPG Implantation

The ANS Libra Deep Brain Stimulation (DBS) System consists of an Implantable Pulse Generator (IPG) designed to be connected to 4 or 8 electrode leads and extensions and programmed by an external programmer. The DBS system for the purposes of this study is to be used for the treatment of severe major depressive disorder. The ANS pulse generator is implanted in a subcutaneous pocket, and receives radio frequency (RF) programming signals by means of the external programmer. The ANS IPG decodes the programmed information and delivers stimulation pulses to a selected combination of output electrodes, on the lead. The Implantation Visit will be classified as “Week 0”.

3.5 Patient Evaluation

All patients will be evaluated 3 times, by at least 2 separate psychiatrists, prior to being considered for device implantation. All patients will be assigned a case manager/counselor to follow the patient for the duration of the study. This case manager will be blinded to the study therapy for the duration of the study.

After system implant (Week 0), the patient will return to clinic approximately 2 weeks after surgery for evaluation and treatment randomization into either Group 1 or Group 2 (Group 1 = Active Treatment Group; Group 2 = Control Group). Patient will then return to clinic for subsequent evaluations at 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, and 1 year post system implantation.

At the end of the 6 month visit, all control group patients will have the option to receive active stimulation and will be followed on a monthly basis until the end of the 1 year study.

4 Test Articles

4.1 System Components

The components of the DBS System to be used in this study include an Implantable Pulse Generator (ANS, Libra and LibraXP DBS IPG), leads (ANS, Libra DBS Lead Kits), extensions, the ANS MTS trial stimulator, the clinician programmer, the patient controller (ANS, QuikLink Controller). The Libra system is comprised of implanted and non-implanted components that include:

- Implantable Pulse Generator (IPG) – generates low-current electrical pulses.
- Lead - contains electrodes to deliver stimulation
- Lead Extension – make the electrical connection between the lead and the generator
- Trial Stimulator - for intraoperative and post operative testing
- Clinician Programmer – for programming the generator
- QuikLink Patient Controller - controls off/on function and amplitude

4.2 Regulatory Status

The ANS Libra DBS system is predicated on the currently approved Genesis neuromodulation system (Approved in US under PMA P010032, Registered in Canada under License No. 67516, CE Marked in Europe and Registered in Australia, and meets ISO 13485), which is indicated for Spinal Cord Stimulation (SCS) and distributed around the world. The ANS device to be used in this study is not currently approved for marketing and distribution in the United States for Deep Brain Stimulation for Major Depressive Disorder. However, the Libra DBS System has received Health Canada approval for investigational testing for treatment-resistant major depressive disorder. The ANS DBS system is categorized in the United States as a class III medical device and the purpose of this clinical trial is to provide safety and efficacy data to support the PMA submission for the ANS Deep Brain Stimulation System.

5 Patient/Subject Selection

5.1 Inclusion Criteria

Patients enrolled in this study must comply with the following inclusion criteria:

1. Men and women (non-pregnant) age is 21-70 years;
2. Diagnosed with non-psychotic major depressive disorder, single or recurrent episode by DSM-IV-TR criteria derived from the MINI;
3. First episode onset before age 45;
4. Current episode ≥ 12 months duration;
5. In the current episode: Documented resistance (i.e. persistence of the major depressive episode) to a minimum of 4 adequate depression treatments from at least 3 different treatment categories (e.g. SSRI's, SNRI's, TCA's, MAO-inhibitors, Mirtazipine, Nefazodone, Trazodone, Bupropion, lithium augmentation, thyroid augmentation, ECT); Adequacy of treatments as defined by a score of at least 3 according to the amended Antidepressant Treatment History Form (ATHF) criteria;
6. In Lifetime: Received a course of psychotherapy for depression;
7. Montgomery Asberg Depression Rating Scale (MADRS) of ≥ 22 at 3 separate baseline visits, rated by 2 separate psychiatrists, Baseline 2 and Baseline 3 MADRS scores cannot be separated by > 6 weeks and cannot improve ≥ 20%;
8. Global Assessment of Function, score <50;
9. Modified mini-mental state examination (MMSE) score ≥24;
10. No change in current antidepressant medication regimen or medication free ≥4 weeks prior to study entry (with exception to sleep, cholesterol, blood pressure, sexual dysfunction, non-migraine headache medication, or medication for other medical reasons not related to depression, in which changes to dose or type will be allowed during course of study);
11. Able to give informed consent in accordance with institutional policies;
12. Able to comply with all testing and follow-up requirements as defined by the study protocol;
13. Must be determined medically stable by surgeon, to undergo deep brain stimulation surgical procedure.
14. Must have platelet count, PT and PTT within normal limits of the laboratory.
15. During last 6 months in the current episode documented treatment under the care of a licensed psychiatrist/psychologist.

5.2 Exclusion Criteria

Patients will be excluded from participation in this study if they meet any one of the following criteria:

1. A diagnosis of a bipolar I or bipolar II disorder by DSM-IV-TR criteria, derived from the MINI;
2. Meets criteria for borderline or antisocial personality disorder in the last 12 months by DSM-IV-TR criteria, derived from the Cluster B Personality Disorders Sections 301.7 – 301.83, and screened via SCID-II at Baseline visit;
3. In the current depressive episode, has been diagnosed with General Anxiety Disorder (GAD) - as defined by the DSM-IV-TR, and GAD is the primary diagnosis;
4. Has an intracranial Central Nervous System (CNS) disease that impairs motor, sensory or cognitive function or that requires intermittent or chronic medication (e.g., Parkinson's Disease, chronic migraine, stroke, Huntington's, head trauma, etc.) with exception to non-migraine headaches;
5. Has been diagnosed with fibromyalgia or has a current condition which requires chronic pain narcotic usage (e.g. morphine, methadone);
6. Has been currently diagnosed with chronic fatigue syndrome;
7. Substantial suicidal risk as defined by (1) MADRS item 10 score of 5 or 6, (2) a current plan and intent, (3) clinician judgment that there is a clear immediate intent for self-harm, (4) more than 3 suicide attempts within the last 12 months;
8. Co-morbid obsessive compulsive disorder, post-traumatic stress disorder, panic disorder, bulimia or anorexia nervosa if previously present, must be in remission for 6 months as defined by DSM-IV-TR criteria, derived from the MINI;
9. Alcohol, medication, or illegal substance dependence or abuse within last 12 months derived from the MINI;
10. Diagnosis of sleep apnea confirmed by a sleep test that is not adequately treated;
11. Advanced cardiovascular disease which renders anesthesia and surgery as unsafe as determined by neurosurgeon;
12. Clinically relevant abnormality (e.g. tumor or growth) on study MRI;
13. Has cardiac pacemaker/defibrillator or other implanted active stimulator;
14. Has a medical condition requiring a repetitive MRI body scan;
15. Requires chemotherapy for the treatment of malignancy or requiring chronic oral or intravenous (immunosuppressive or) steroid therapy;
16. Is unable to comply with study visit schedule and timeline;
17. Past ablative or relevant intracranial surgery;
18. A female lactating or of child bearing potential, with a positive pregnancy test or not using adequate contraception;
19. Lifetime psychotic disorders, schizophrenia, or schizoaffective disorder defined by DSM-IV-TR;

20. Psychotic features in current depressive episode as diagnosed by DSM-IV-TR criteria;
21. Other medical conditions likely to require hospitalization within the next year;
22. Received ECT within 3 months prior to enrollment, or requires ECT for the duration of the study;
23. Has a history of epilepsy or history of status epilepticus;
24. Plans to use diathermy;
25. Has any metallic implants such as aneurysm clips or cochlear implants;
26. Currently participating in another investigational device, drug or surgical trial.

6 Subject Assignment to Treatment and Blinding

Each patient who is willing to consider study participation and who provides informed consent will be evaluated with the inclusion/exclusion criteria for eligibility. Each patient will be enrolled chronologically on a patient screening log and given a screening number until device implantation. The patient will be given a randomization number after device implantation has occurred and the patient has been shown to meet all inclusion criteria and not violate any exclusion criteria. Patients will be block-randomized with a separate randomization number for each study site. Patients will be randomly assigned to a treatment group in a 2:1 ratio, to either:

Group 1: DBS **Active Treatment Group** – Implanted with DBS system and activated for 6 months of DBS.

Group 2: **Control Group** - Implanted with DBS system, device not activated for stimulation for the first 6 months of study.

The patients will be blinded to the functioning of the DBS system. The patient will not be able to tell if they have been randomized to active treatment or to the control group.

The evaluating psychiatrist (Investigator) and/or qualified designee and the case manager will be blinded to the functioning of the DBS system in order to minimize bias. The device will be programmed by one clinician and the information regarding the device will not be given to the evaluating psychiatrist or qualified designee. All efforts will be made to ensure that the evaluating psychiatrist is the same throughout the patient study treatment and follow-up visits, in order to reduce variability in the evaluators scoring. All evaluators will be trained prior to study initiation as well as re-trained on a scheduled basis throughout study duration.

7 Methods and Procedures

7.1 Informed Consent

Written Informed Consent will be obtained from each patient prior to enrollment into the study. All potential patients/subjects will be properly informed as to the purpose of the study and the potential risks and benefits known, or that can be reasonably predicted or expected. The Investigator will retain the original copy of the Informed Consent Form signed by the patient, a duplicate will be provided to the patient and a document signed by the Investigator confirming receipt of patient consent will be returned to the Sponsor. Only the consent form approved by the IRB/IEC will be used. (Appendix A: Sample Informed Consent)

7.2 Screening/Baseline

Study candidates will be screened according to the inclusion/exclusion criteria prior to enrollment in the study. All study participants must provide informed consent. Evaluations will include the following:

- Confirmation of MDD via DSM-IV-TR criteria will occur combined with extensive medical record review by evaluating psychiatrist;
- Montgomery and Asberg Depression Rating Scale (MADRS);
- Demographics and prior history;
- Medical system review;
- Brief physical exam, neurological exam;
- Pregnancy test (if necessary);
- Family history, medication history – antidepressant treatment history form (ATHF - modified);
- MINI Plus;
- HRSD-17;
- SAFTEE;
- Mini Mental State examination (MMSE);
- Subsection for cluster B personality disorder of the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II) ;
- Inventory of Depressive Symptomatology (IDS-C30);
- Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR);
- Work and Social Adjustment Scale (WSAS);
- Short form Quality of Life Enjoyment and Satisfaction Questionnaire (QOL);
- Young Mania Rating Scale (YMRS);
- Clinical Global Impression of Severity and Improvement (CGI);
- Patient Global Impression Index (PGI);
- Health Labor Questionnaire (HLQ);
- Hamilton Anxiety Rating Scale (HAM-A);
- Columbia Suicide-Severity Rating Scale (C-SSRS).

7.2.1 Baseline 2/Baseline 3

A second baseline will be performed no less than 2 weeks and no more than 4 weeks after Baseline #1. Evaluations will include the following:

- Confirmation of MDD via DSM-IV-TR criteria will occur combined with extensive medical record review by evaluator;
- Montgomery and Asberg Depression Rating Scale (MADRS);
- The Quick Inventory of Depressive Symptomatology (QIDS);
- Systematic Assessment for Treatment Emergent Events (SAFTEE-SI);
- Hamilton Anxiety Rating Scale (HAM-A);
- Columbia Suicide-Severity Rating Scale (C-SSRS).

A third baseline will be performed no less than 2 weeks and no more than 6 weeks after Baseline #2. Evaluations will include the following:

- Montgomery and Asberg Depression Rating Scale (MADRS);
- The Quick Inventory of Depressive Symptomatology (QIDS);
- Systematic Assessment for Treatment Emergent Events (SAFTEE-SI);
- Hamilton Anxiety Rating Scale (HAM-A);
- Columbia Suicide-Severity Rating Scale (C-SSRS);
- Neuropsychological Battery – performed only <u>if</u> patient meets eligibility for study participation after scoring ≥ 22 on three baseline MADRS evaluations.
- MRI scan will be performed after patient has meet eligibility requirements (to exclude brain abnormalities, plan for surgery, and targeting);

The patient will also be assigned a case manager to follow each patient's care for the duration of the study.

*If the patient does not have three MADRS values ≥ 22, they will be considered a screen failure and <u>may not</u> be re-evaluated for study participation for a minimum of 6 months.

7.2.2 Outcome measures

<u>Montgomery and Asberg Depression Rating Scale (MADRS)</u>
The Montgomery and Asberg Depression Rating Scale is a 10 item severity scale constructed to be sensitive to change with treatment. It was designed to be sensitive for individual items and is therefore useful for measuring differential profiles of action. Ratings of patients on a 65 item comprehensive psychopathology scale were used to identify the 17 most commonly occurring symptoms in primary depressive illness, and ratings on these 17 items for 64 patients participating in studies of four different antidepressant drugs were used to create a depression scale consisting of

the 10 items which showed the largest changes with treatment and the highest correlation to overall change. (Montgomery & Asberg 1979) An interrater evaluation will also be performed on multiple study visits to increase consistency and reduce variability.

Hamilton Rating Scale for Depression (HRSD-17)
The Hamilton Rating Scale for Depression is a 17-item scale that evaluates depressed mood, vegetative and cognitive symptoms of depression, and comorbid anxiety symptoms. The HRSD-17 was one of the first rating scales developed to quantify the severity of depressive symptomatology. First introduced by Max Hamilton in 1960, it has since become the most widely used and accepted outcome measure for evaluating depression severity. It provides ratings on current DSM-IV symptoms of depression, with the exceptions of hypersomnia, increased appetite, and concentration/indecision. The HRSD-17 was designed to be administered by a trained clinician using a semi-structured clinical interview. The 17-items are rated on either a 5-point (0-4) or a 3 point (0-2) scale.

Inventory of Depressive Symptomatology (IDS-C30)
The construction of the IDS-C30 was intended to remedy deficits in the Hamilton Scale for Depression (HRSD-17) and Montgomery and Asberg (MADRS) depression rating scales by, among others, including all nine symptom domains needed to diagnose a DSM-IV major depressive episode in order to assess symptom remission, improve ability to detect milder levels of symptoms than the HRSD-17, and provide unconfined and more equivalent weighting among items. There are two versions of the IDS with identical items: a clinician rating (IDS-C30) and a self-report (IDS-SR30). Items were selected to represent mood, cognitive, vegetative, anxious, and endogenous symptoms common in depression. Each of the 30 items is rated from 0 to 3, with increasing severity represented by a higher rating. (Rush et al. 1996)

The Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR) is a 16-question shortened self-test, derived from the 30-item IDS, which measures 9 different criterion domains of major depression. Each of the 4 possible answers to each quiz is given an ascending numerical value from 0-3.

Systematic Assessment for Treatment Emergent Events (SAFTEE-SI)
The SAFTEE is a structural clinical interview developed by the National Institute of Mental Health which exams possible treatment-emergent side effects for clinical studies. The SAFTEE-SI looks at specific adverse symptoms for a particular treatment.

The Mini-International Neuropsychiatric Interview (M.I.N.I.) Plus

The MINI is a short structured diagnostic interview, developed jointly by psychiatrists and clinicians in the United States and Europe, for DSM-IV and ICD-10 psychiatric disorders. With an administration time of approximately 15 minutes, it was designed to meet the need for a short but accurate structured psychiatric interview for multi-centered clinical trials and epidemiology studies and to be used as a first step in outcome tracking in non-research clinical settings. The MINI Plus is a more detailed edition of the MINI.

The mini-mental state examination (MMSE) or Folstein test is a brief 30-point questionnaire test that is used to assess cognition. It is commonly used in medicine to screen for dementia. In the time span of about 10 minutes, it samples various functions, including arithmetic, memory and orientation. It was introduced by Folstein *et al* in 1975 and is widely used with small modifications.

Structural Clinical Interview for Personality Disorders (SCID II)

The SCID-II is a semi-structured interview for making DSM-IV Axis II (Personality Disorder) diagnoses and is designed to be administered by a clinician or trained mental health professional. A SCID II takes 1/2 to 1 hour to administer. There are 3 components to the SCID-II. The interview itself covers the 11 DSM-IV Personality Disorders. The SCID-II Personality Questionnaire is available as a screening tool to shorten the time it takes the clinician to administer the SCID-II. After the subject fills out the Personality Questionnaire (which usually takes 20 minutes), the clinician simply circles the numbers to the left of the SCID-II items that correspond to items answered "yes" on the questionnaire. When the SCID-II is administered, the clinician needs only to inquire about the items screened positive on the questionnaire. The assumption is that a subject who responds with a "no" on the questionnaire item would also have answered "no" to the same question had it been read aloud by the interviewer. For this study, only the subsection for Cluster B will be administered.

The Young Mania Rating Scale (YMRS)

The YMRS is an 11-item instrument used to assess the severity of mania in patients with a diagnosis of bipolar disorder. The 11 items are: Elevated Mood, Increased Motor Activity Energy, Sexual Interest, Sleep, Irritability, Speech (Rate and Amount), Language - Thought Disorder, Content, Disruptive - Aggressive Behavior, Appearance, and Insight.
Ratings are based on patient self-reporting, combined with clinician observation (accorded greater score). (Young 1978)

Quality of Life Enjoyment and Satisfaction Questionnaire (QOL)

The short form of the Quality of Life Enjoyment and Satisfaction Questionnaire is a self-report form composed of 16 items each rated on a 5-point scale that indicates the degree of enjoyment or satisfaction experienced during the past week. A total score of items 1 to 14 is computed and expressed as a percentage of the maximum possible score of 70. The 14 items evaluated each subjects' satisfaction with his or her physical health, social relations, ability to function in daily life; ability to get around physically; mood; family relations; sexual drive and interest; ability to work on hobbies, work, leisure time activities; economic status; household activities; living/housing situation; and overall sense of well being. (Rapaport et al. 2005)

Work and Social Adjustment Scale Self Report (WSAS)

The WSAS-SR is used to measure functional impairment attributed to a identified problem (Mundt, 2002). There are 5 questions that are associated with work, home, social leisure, private leisure and ability to form and maintain relationships.

Global Assessment of Functioning (GAF)

The Global Assessment Scale is a hypothetical continuum of mental health illness that looks at psychological, social and occupational functioning. The GAF scale is divided into 10 ranges of functioning in which the clinician picks a single value that best reflects the individual's overall level of functioning. The GAF does not include "impairment in functioning due to physical (or environmental) limitations." (American Psychiatric Association – APA, 1994)

Clinical Global Impression of Severity and Improvement (CGI)

The CGI is used to measure the global impression of a treatment response in a psychiatric patient's illness by a clinician (Guy 1976). Two of three sub-scales are being used to measure severity of the illness and improvement of the illness. Items in the two-subscales being administered are rated on a seven-point scale ranging from "1=normal" to "7=extremely ill" for severity subscale and "1=very much improved" to "7=very much worse" for improvement sub-scale.

Patient Global Impression Index (PGI)

The PGI is used to measure the global impression of a treatment response in a psychiatric patient's illness by the patient. Two sub-scales are being used to measure severity of the illness and improvement of the illness. Items in the two-subscales being administered are rated on a seven-point scale ranging from "1=normal not ill at all" to "7=among the

most extremely ill" for severity sub-scale and "1=very much improved" to "7=very much worse" for improvement sub-scale.

Health and Labor Questionnaire (HLQ)
The HLQ is designed to collect quantitative data on the relation between illness and treatment and work performance. The HLQ data permits the estimation of production losses (costs) of paid and unpaid labor. It contains also an indicator for impediments for paid and unpaid labor, one of the indicators for quality of life. The HLQ is divided into 4 modules to collect data about absence from work, reduced productivity at paid work, unpaid labor production and impediments to paid and unpaid labor. The modular structure permits the omission of questions that are not applicable to the study population. The questionnaire is suitable for self-assessment.

Hamilton Anxiety Rating Scale (HAM-A)
A 14 item test designed to assess the severity of anxiety symptoms. All questions are rated on a 5 point (0-4) scale, with 7 questions on psychic anxiety and 7 questions on somatic anxiety. Total scores range from 0 to 56. Patients with anxiety and panic disorder tend to have a score greater than 20.

Columbia Suicide-Severity Rating Scale (C-SSRS)
The C-SSRS is a semi-structured clinical interview that utilizes a set of prompts and questions to help an interviewer get more complete information on events suggestive of suicidality. This prospective tool aims to standardize terminology and articulate suicidality assessment in a straightforward manner.

7.2.3 Neuropsychological Battery

Neuropsychological Examination: The following neuropsychological tests will be performed and evaluated at or after baseline #3, 6 months, and 1 year visits during the study to assess the safety of Deep Brain Stimulation. The following is a description of all the tests to be performed:

Attention/Working Memory

Wechsler Memory Scale –Working Memory Index Test (Wechsler, 1997)

Letter-Number Sequencing
Examinees are presented with strings of alphanumeric sequences (e.g., 6-B-3-Z) of increasing length (2-8 letter-number pairs). The task

of the examinee is to repeat the letters and then the numbers in alphabetical and numerically ascending order. This test of working memory thus requires re-sequencing of information while holding in memory the original sequence. This task takes 3-5 minutes to complete.

Stroop Color and Word Test (Golden, 1978)
This version of the well-known Stroop test has 3 parts, each consisting of 1 page of 100 stimuli (arranged in 5 columns of 20 items). The first sheet contains the words red, green, and blue, printed in black ink, in random order with the constraint that a word cannot be followed by the same word. The examinee is asked to read the words, and the variable of interest is how many items are completed correctly in 45 sec. On page 2 are 100 "XXXX" printed in either red, green or blue ink, with the constraint that a given item number could not correspond to the same color on the first page, and the same color cannot occur on consecutive items. The examinee is given 45 sec to name the color of the ink in which each stimulus is printed. On the final part, the page consists of the words red, green, and blue, and each word is printed in red, green, or blue ink, but in a manner that the word and color ink are always incongruent. The score is the number of items completed correctly in 45 sec. The whole test takes about 5 minutes.

***Ruff 2 & 7 Selective Attention Test* (Ruff & Allen, 1996)**
This test of sustained and selective attention consists of 20 15-second trials during which patients cross out 2 target stimuli (the numbers 2 and 7) among three rows of either numeric or alphabetic stimuli (each row contains 10 targets and 40 distracters in quasi-random order). The targets embedded among letters are considered "automatic" conditions (because the patient can identify targets simply by the category they belong to), whereas the tasks embedding the targets among numbers are considered "Controlled" conditions requiring effort and working memory since targets and distracters belong to the same stimulus category (numbers). The test evaluates both accuracy (considering errors of omission and commission) and speed. Normative data (based on 360 persons) are available for ages 16-70 years, stratified by education. Test-retest reliability is estimated to be .89 for speed, and .59 to .69 for accuracy on automatic and controlled search tasks (with stability coefficients ranging from .76 to .93). The test is typically completed in 5 minutes.

Executive Functions

Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency Tests

The D-KEFS contains 3 verbal fluency tests assessing timed oral production of items from lexical and semantic categories. In the Letter fluency task the patient is asked to say as many words as possible (excluding proper names and numbers) beginning with a given letter of the alphabet. There are 3 trials, each using a different letter, of 60 seconds each. In the Category Fluency task, the examinee is asked to say as many words as possible belonging to a category (such as animals) in 60 seconds. There are 2 trials using different categories. On the final task (Category Switching), the patient is asked to orally generate consecutive words from 2 alternating categories for 60 seconds. The tasks can be completed in about 8-10 minutes.

The tests are normed on over 2000 individuals, are standardized, are applicable to persons up to 89 years of age, and are co-normed with the WASI. This co-norming feature means that cognitive strengths and weaknesses can be ascertained with confidence given comparability of scores and normative data. Another strength of this instrument is the availability of alternate forms, thus minimizing practice effects (although not eliminating possible familiarity and carry-over effects). Test-retest data are available to facilitate interpretation of score changes over time.

Memory

Hopkins Verbal Learning Test – Revised (HVLT-R; Brandt & Benedict, 2001)

This verbal learning test has six equivalent, alternate forms, making it ideal for repeat administration. It is normed on persons aged 16-92 years and was designed to be tolerated by even significantly impaired individuals. The examinee is provided 3 learning trials to remember an orally presented 12-word list (four nouns from each of 3 semantic categories). Following a 20-25 minute interval, delayed recall and yes/no recognition are assessed. The test takes about 15 minutes excluding the delay interval which is preferably filled with intervening visuospatial tasks. Test-retest reliability is weaker for recognition and retention (.40 and .39; probably limited by skewed
Score distributions), but adequate for recall (.66-.74). Test-retest gains, even when persons were tested as little as 2 weeks apart, were only about 0.5 standard deviations.

Brief Visual Memory Test – Revised (BVMT-R; Benedict, 1997)

Like any of its word list learning analogs (e.g., the HVLT-R), this test involves multiple trial learning followed by delayed recall and recognition trials. However, the stimuli are abstract line drawings rather than words. The patient is shown a set of 6 abstract line drawings (in a 2x3 array) for 10 seconds and is then asked to draw

them in their correct location. This procedure is repeated for a total of 3 learning trials. After 25 minutes, delayed recall and recognition (identifying which 6 of 12 drawings were seen) trials are administered. The brevity of the task and the availability of 6 alternate forms make the test useful for repeated administrations. It is normed for persons aged 18-79 years. Reliability coefficients exceed .90, and test-retest reliability ranges from .60 to .84. Excluding the delay, which is filled with verbal tests, the BVMT-R can be completed in 15 minutes.

Self and Informant Rating of Executive Functions

Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A; Roth et al. 2005)

The self-and informant-report forms consist of 75 items asking the person to report the frequency (never, sometimes, or often) with which certain behaviors have occurred during the month prior to evaluation. The behaviors measured relate to a variety of executive functions (e.g., self-monitoring, emotional control, behavioral inhibition and shifting, planning and organization) and are expressed in 2 indices (Behavioral Regulation Index and Metacognition Index) and an overall summary score (Global Executive Composite). There are also 3 response validity scales. Normative data are available for 1,050 persons for self-report and 1,200 informant reports. The test can be used with adults aged 18-90 years. Test-retest reliability for self-report clinical scores ranged from .82 to .93 over an average re-test interval of about 4 weeks, while informant report test-retest reliability ranged from .91 to .94. Test-retest values were still higher for the summary indexes. Patients and informants usually complete these forms in about 15 minutes.

Testing order:

The above tests should be performed in the following order:

1. HVLT-R immediate recall (3 trials);
2. Ruff 2 & 7;
3. Stroop;
4. Fill rest of 20-25 minute delay with starting the BRIEF;
5. HVLT-R Delayed recall and recognition;
6. BVMT-R Immediate recall (3 trials);
7. DKEFS verbal fluency tests;
8. Letter-Number Sequencing;
9. Continue the BRIEF as needed to fill the BVMT-R delay;
10. BVMT-R Delay recall and recognition;
11. Finish BRIEF.

7.3 DBS System Implantation

The DBS system implant visit should be performed no less than 2 weeks and no more than 1 month after the baseline #3 visit.

Implantation of the DBS system will be performed according to standard surgical procedure for Brodmann Area 25WM (Cg25) DBS implantation.

Pre-Operative Imaging: High resolution, 3D T1 weighted images will be obtained. On or before the day of surgery patients will have a stereotactic frame or appropriate bone fiducials applied using local anesthesia. Additional CT imaging for fusion is optional, as is the use of IV contrast.

Pre-Operative Planning: Standard software (e.g. Framelink, Brainlab, or other) is used to reconstruct the images in axial, coronal, and sagittal views, relative to the AC-PC plane.

The sagittal images will be used first. Surgeon will select an image several millimeters (mm) off midline clearly showing the white and gray matter of the cingulate gyrus. A tentative target point is selected at the center of the subgenual cingulate (Brodmann Area 25WM).

Next, the surgeon will convert to the coronal images perpendicular to the AC-PC plane. The midpoint of the subgenual cingulate gyrus is typically found in the coronal image containing the anterior-most section of the caudate nucleus. Thus the A-P position of the target can be confirmed by scanning a few images anterior and posterior to confirm proximity to this section.

Precise targets can then be selected bilaterally in this same coronal section. A point is selected on each side at the border of the white and grey matter, midway between the superior and inferior banks of the cingulate gyrus. The intended site is approximately 5-7 mm from the midline and 10 mm below the corpus callosum. After targets have been selected, the appropriate frame coordinates can be calculated and used for the stereotactic procedure.

Entry points can also be selected on the stereotactic planner if desired. This practice is variable at different centers. If entry planning is performed it is recommended that an entry site that is slightly anterior to the more typical burr hole used for STN-DBS. This is necessitated by the more anterior nature of this target. Anterior entry (~2cm anterior to the coronal suture) will avoid a difficult approach angle.

DBS Implantation: After sterile preparation of the operative field, burr holes are placed under local or general anesthesia. Again the slightly more anterior entry is recommended. A lateral position of 2-3cm from midline is also recommended. Dura and pia are opened under direct visualization. The

remainder of the operation is performed using an appropriate stereotactic frame or frameless guidance system.

One or more cannulas are inserted to the target coordinate. Microelectrode recording may be performed, at this point, to confirm the location of the grey-white junction within the target area. This procedure is optional.

A DBS electrode will be inserted into the target under fluoroscopic visualization. Once the electrode has been placed in the calculated target intra-operative diagnostic testing will be performed; however, no active deep brain stimulation will be delivered to the patient in order to protect the study blinding process. After confirmation of position the end of the lead is protected and excess lead is coiled in a sterile subgaleal pocket made by blunt dissection. The procedure is then repeated for the contralateral side.

Intraoperative Device Diagnostic Testing: The implanted leads will be tested for proper connectivity as well as impedance; however, no active stimulation will be delivered, so as to not break the blinding of the study.

IPG Implantation: The second stage of the operative procedure involves the implantation of lead extensions and the IPG. This will be performed immediately following the above procedure. The patient is given a general anesthetic and a sterile preparation is performed. The lead ends are accessed either by reopening the scalp incision or by making a smaller incision over the subgaleal pocket. The lead extension is then tunneled subcutaneously to a second incision just below the clavicle (can be left or right depending on patient preference). The extension wire is attached to the DBS leads proximally and to the battery distally. The implantable pulse generator is placed in a subcutaneous pocket that is made below the clavicle. Excess wire is coiled behind the IPG. Once again, a device diagnostic test will occur but no active stimulation will be delivered to the patient at this time.

Lead Localization: The lead will be imaged post-implantation to confirm lead location according to current neurosurgical procedures and/or CT scans. These images must be given to the Sponsor for future analysis.

7.4 Concomitant Treatments

All patients will have the ability to maintain their depression medication regimen as well as regularly scheduled psychotherapy to ensure study and therapy controls are maintained. For the 1-year study, all psychiatric care/decisions must be transferred to the study psychiatrist. For the first 6 months of the study, patients will not be able to add new medications (excluding sleep aids and other meds to manage non-depression related conditions) nor increase current antidepressant medication doses.

Medication additions:
For temporary insomnia, zaleplon, zolpidem, zopiclone, or chloral hydrate (a single dose nightly) or trazodone (< 100 mg) may be used, for a maximum of 14 nights during the study. Lorazepam (< 2 mg/d) may also be administered for treatment emergent anxiety for up to 14 days.

Rescue medications:
The study psychiatrist should first identify a need for a rescue based on his/her clinical judgment of worsening depression. In the event that a patient needs to be "rescued" due to a severe worsening of their depression (defined as patients who score 25% worse than their baseline average on the MADRS or worsening of suicidal ideation), prior to the completion of 6 months in the study, appropriate intervention may be initiated at the principal investigator's discretion considering the protocol-specified guidance. The following guidance should be adhered to when the rescue protocol is initiated:

<u>If a patient is rescued based on a 25% worsening of their MADRS score compared to the average MADRS Scores:</u>

- The patient will be considered a treatment failure.
- The visit will serve as the patient's endpoint data and the patient will be exited from the study. All end-of-study procedures should be performed.
- At the principal investigator discretion, medications may be added or changed as deemed in the best medical interest of the patient.
- Patients who were in either the control group or received active stimulation should enter a separate open-label protocol for long-term follow-up.

<u>If a patient is rescued based on a worsening of suicidal ideation</u>

- A patient who shows imminent suicidal intent but does not attempt suicide will be treated for the acute exacerbation of their symptoms. If the event can be treated with an acute intervention (less than 7 days) then the patient should resume participation in the trial and not be unblinded as to treatment.
- After the acute intervention, the patient must have a MADRS item 10 score of less than 5 to resume participation in the trial.
- After the acute intervention, the patient must resume their previous medication regimen if medications were changed.
- Patient's medications must be stable for a minimum of 7 days prior to an effectiveness visit
- If the patient attempts suicide, or requires a long-term medication change he/she will be considered and followed as a treatment failure.

Patients who were in either the control group or received active stimulation should enter a separate open-label protocol for long-term follow-up.

At any time during the study the patient feels suicidal or in any danger from worsening depressive symptoms, they, or their caretaker should call their study psychiatrist immediately.

7.5 Postoperative Visits

All patients should be called in advanced to remind them of all study visits and to complete the necessary paperwork if applicable. Patients will be assigned a case manager to follow their care for the duration of the study. The patient may schedule visits with the case manager a minimum of every 2 weeks and a maximum of weekly for the study duration. Patients should call the study physician and/or study staff if they are having any complications related to surgery, programming, or related study activities.

Post surgery visit

Patient will return to Neurosurgeon for a postoperative visit approximately 2 weeks post implantation for normal follow up patient care including suture removal and wound evaluation.

7.5.1 Study Visits:

Two weeks after system implant – system diagnostics or programming and activation:

Patients will visit the clinic to have their device tested or programmed and activated (active group) within approximately 2 weeks, after surgery. Patients randomized to the control group will only have device diagnostics performed at this visit. All patients may be seen at any time during the study for device device diagnostics.

For the treatment group, parameters of stimulation will be reassessed with minor adjustments in amplitude made to optimize clinical effects (as measured by the MADRS). Criteria for adjustment will include changes in amplitude if there is either an absence or a loss of improvement since the last adjustment. If a patient is stable or shows evidence of clinical improvement according to the MADRS the settings will be unchanged. If a patient deteriorates following an increase in amplitude or after the introduction of stimulation, the settings will be changed according to the programming plan below. Changes in the specific contact will only be done if there are no behavioral effects at the target contact following adjustments of amplitude.

General Guidelines: Device Programming for Active DBS Stimulation Group:
Contacts: #2, monopolar on each side (in most cases unless post-operative lead placement shows a different contact to be more optimal), will be used in the initial programming session, and amplitude will be adjusted in 2.0 mA increments.
Initial Device Settings: 4.0mA, 130Hz, 91uSec
Relative Change in MADRS from previous rating will dictate changes as follows.

If the **MADRS value is better 2 weeks** after the initial programming session, (better defined as a decrease in MADRS score by ≥ 10% from previous evaluation) **do not change** electrode settings, frequency, or pulse width).

If the MADRS value has decreased by less than 10% 2 weeks after the initial programming session, **Amplitude can be increased by 2.0mA**. If after 4 weeks at this new amplitude setting, the MADRS value has not changed or has not started to decrease, amplitude may be increased by 2mA again.

In the event that the MADRS value has increased by >10% (worsened state), the amplitude should be decreased by 2.0mA. If after **2 weeks,** the MADRS is still unchanged or continues to deteriorate (increased MADRS score); a **new contact** should be selected.

Contact pairs (matched right and left) will be tested consecutively. A change in contacts or addition of contacts will be made if there is either no response or worsening using either higher (8.0mA) or lower (2.0mA) current as described above. If a patient experiences clinical worsening in the context of no history of response to any setting, a careful safety evaluation will occur every 2 weeks. Stimulation will continue at the previous best contacts only if the patient and the investigator conclude that it is safe for the patient to continue in the open stimulation phase of the study.

This visit will include the following:

- MADRS;
- Programming form (for active stim. group);
- Device diagnostics form (for control group);
- HAM-A;
- C-SSRS;
- Office Visit Form.

Week 4 – post-implantation visit

Patient evaluation will take place 4 weeks after system implant. This visit will include the following:

- Office Visit Form;
- MADRS;
- SAFTEE;
- Programming form (by programmer);
- IDS-C30;
- QIDS-SR;
- WSAS;
- GAF
- CGI;
- PGI
- HAM-A;
- C-SSRS.

Week 6 - post-implantation Visit:

Patient evaluation will take place 6 weeks after system implant. This visit will include the following:

- Office Visit Form;
- MADRS;
- Programming form (by programmer);
- QIDS-SR;
- CGI;
- PGI;
- HAM-A;
- C-SSRS.

Week 8 - post-implantation Visit:

Patient evaluation will take place 8 weeks after system implant. This visit will include the following:

- Office Visit Form;
- MADRS;
- Programming form (by programmer);
- IDS-C30;
- QIDS-SR
- WSAS;
- GAF;
- CGI;
- PGI;
- HAM-A;
- C-SSRS.

Month 3 - post-implantation Visit:

Patient evaluation will take place 12 weeks after system implant. This visit will include the following:

- Office Visit Form;
- MADRS;
- Programming form (by programmer);
- HRSD-17;
- IDS-C30;
- QIDS-SR;
- SAFTEE;
- YMRS;
- QOL;
- WSAS;
- GAF;
- CGI;
- PGI;
- HLQ;
- HAM-A;
- C-SSRS.

Months 4 and 5 - post-implantation visits:

Patient evaluation will take place at 16 and 20 weeks after system implant. These visits will include the following:

- Office Visit Form;
- MADRS;
- Programming form (by programmer);
- IDS-C30;
- QIDS-SR;
- WSAS;
- GAF;
- CGI;
- PGI;
- HAM-A;
- C-SSRS.

Month 6 - post- implantation visit:

Patient evaluation will take place 24 weeks after system implant. This visit will include the following:

- Office Visit Form;
- MADRS;
- HRSD-17;
- IDS-C30;
- QIDS-SR;

- SAFTEE;
- YMRS;
- QOL;
- WSAS;
- GAF;
- CGI;
- PGI;
- HLQ;
- HAM-A;
- C-SSRS.
- Neuropsychological Battery (Note: Control Group must have this completed prior to device activation);
- Programming form (by programmer);
- A hand held device will be given to patients at this visit to allow the patient to check their device status (i.e. if the device is “on” or “off”) and indicate battery life.

Months 7, 8, 9, 10 and 11 - post- implantation visits:

Patient evaluation will take place every four weeks after the 6 month visit. This visit will include the following:

- Office Visit Form;
- MADRS;
- Programming form (by programmer);
- IDS-C30;
- QIDS-SR;
- WSAS;
- GAF;
- CGI;
- PGI;
- HAM-A;
- C-SSRS.

At Month 9 the SAFTEE, YMRS, HLQ and QOL will also be administered.

Final Evaluation and exit from the Study

Patient evaluation will take place 52 weeks after the system is implanted. This visit will include the following:

- Office Visit Form;
- MADRS;
- Programming form (by programmer);
- HRSD-17;
- IDS-C30;
- QIDS-SR;
- SAFTEE;
- YMRS;
- QOL;
- WSAS;
- GAF;
- CGI;
- PGI;
- HLQ;
- HAM-A;
- C-SSRS;
- Neuropsychological Battery;
- Study Exit form.

7.5.2 Control Group (Non-Active Stimulation):

At the end of the 6 month visit, patients will be given the option to have device programmed and activated for DBS. Patient will then be followed monthly, until the end of the 52 week study.

7.6 Long-Term Follow-Up

All patients will be encouraged to enroll in a long-term follow-up study under a separate protocol sponsored by ANS to monitor the continued efficacy and safety of this system. Efficacy assessments and device related adverse events will be collected on all willing participants at specific intervals after they exit the currently proposed study. A separate study protocol and patient informed consent will be signed for this long term follow up study.

All study patients may have access to the device at no cost for battery replacement and or revision(s) until the device is commercially available in the United States. The patients/physicians must make a request to the study sponsor to have the device shipped to the appropriate location.

8 Adverse Events (AEs)

8.1 AE Definitions

An ADVERSE EVENT is “Any change, undesired, noxious or pathological in a patient or subject illustrated by signs, symptoms and /or laboratory changes that occur during a clinical trial, whether or not considered drug/treatment related.”

A SERIOUS/SEVERE AE is where the event is/causes:
Life threatening or fatal
Requires or prolongs hospitalization
The patient to be disabled

A DEVICE RELATED AE is an anticipated (those events listed in section 8.4) or unanticipated (those events that occur that are not listed in section 8.4) event that occurs that is considered device related. A device-related event is one that the Investigator feels that the device (i.e. IPG, extension or lead) contributed in any way to the adverse event occurring. A stimulation-related event is one that resolves when stimulation is turned off or turned down.

A NON SERIOUS AE is an event other than one described above.

8.2 AE Recording

All Adverse Events volunteered by the Subjects/Patients or elicited by the Investigator must be recorded on the AE forms provided. All serious/severe AEs must be recorded whether or not considered device/treatment related. All device related complications that occur during the study duration and/or malfunctions of study device should be recorded on the AE forms provided. Device complications are defined as those complications relating directly to the functioning of the stimulation system (i.e. IPG, extension or lead).

8.3 Reporting AEs

Throughout the course of the proposed study, all serious/severe adverse events and device related adverse events would be recorded and monitored by the Sponsor and the Investigator. Every effort will be made to remain alert to possible adverse experiences and unexpected findings. If adverse experiences occur, the first concern will be the safety of the subject. Appropriate medical intervention will be made. All completed suicides and suicide attempts (defined by the Columbia Suicide Severity Rating Scale (CSSRS) $\geq$ 3) must be reported to the Sponsor immediately **(less than 10 days)** upon discovery. Once the Sponsor is notified of these events, the Sponsor will report these events to the FDA within 10 days.

Individual reports of device related complications will be documented and reported appropriately. The investigator must report all serious AEs to the Sponsor immediately upon discovery by telephone and forward the completed AE form as soon as it is available. The Investigator must also promptly report the resolution to all reported serious or device related AEs.

8.4 Anticipated Adverse Events and Complications

Implantation of a deep brain stimulation lead is a surgical procedure that may expose the patient to the risks of post-operative pain, stress, or discomfort, intracranial hemorrhage, subcutaneous hemorrhage, intracranial infarctions, venous air embolism (air entering the veins), venous infarctions, symptomatic neumocephalus (intracranial air causing confusion requiring an extra day stay in the hospital), seizure or convulsions, seroma, infection, aphasia, paralysis, stroke, death, cerebrospinal fluid leakage or abnormality. An additional neurosurgical procedure may be necessary to manage one of the above complications or to replace a fractured lead or to replace the pulse generator

The anticipated adverse events associated with the use of this device may include the following:

- Neuropathy;
- Neuralgia;
- Headache;
- Asthenia, hemiplegia or hemiparesis;
- Cognitive impairment, including confusion, abnormal thinking, hallucinations, alteration of mentation, amnesia, delusions, or dementia;
- Infection;
- Fever;
- Disequilibrium;
- Ataxia;
- Myoclonus;
- Hearing and visual disturbance;
- Paresis;
- Dystonia;
- Attention deficit;
- Dysarthria;
- Sleep disturbance;
- Suicide or Suicide attempt;
- Increase in drug side effects;
- Autonomic instability (change in vital signs);
- Urinary incontinence;
- Worsening depression symptoms (will not be considered an AE);
- Anxiety;
- Ruminativeness;
- Hypomania;

- Mania;
- Panic attacks;
- Obsessive compulsive disorder (OCD) symptoms;
- Psychosis;
- Seizure;
- Apathy;
- Eye disorder;
- Sweating;
- Diarrhea;
- Sensory deficit;
- Drowsiness;
- Difficulty breathing;
- Increased salivation;
- Nausea and/or vomiting;
- Rapid heart rate;
- Pneumonia;
- Skin disorder;
- Edema including periorbital;
- Syncope;
- Persistent pain or redness at the IPG site or the surgery site/extension;
- Pulling sensation along extension site;
- Allergic or rejection response to implanted materials;
- General erosion or local skin erosion over the pulse generator (IPG), burr hole cap, and/or extension;
- Undesirable changes in stimulation possibly related to cellular changes in tissue around the electrodes, changes in the electrode position, or loose electrical connections and/or lead fracture;
- Initial jolt or tingling during stimulation;
- Paresthesia;
- Loss of therapeutic benefit as a result of change in electrode positions, lead fracture, loose electrical connections, DBS system battery failure, DBS system malfunction, or inadvertent turning off of device;
- Lead fracture;
- Lead migration;
- System dislodgement;
- DBS battery failure;
- DBS system malfunction.

8.5 AE Classification

Each adverse event will be classified by the Investigator and reported to the Sponsor using the Adverse Event Form of the patient's Case Report Form.

9 Data Analysis and Statistical Plan

9.1 Statistical Plan

The study design for this investigation is a prospective, double-blind, randomized, and controlled study. The primary objective is to demonstrate the safety and efficacy of using subgenual white matter (Brodmann Area 25WM) deep brain stimulation as an adjunctive treatment for Major Depressive Disorder, single or recurrent episode.

9.2 Sample Size

Data in an uncontrolled pilot study of Deep Brain Stimulation showed that greater than 40% of the patients improved with a minimum of a 40% reduction in MADRS score following 6 months of deep brain stimulation. For this study, the population response rate among patients treated with deep brain stimulation is assumed to be 40%. If the population response rate in the placebo group is assumed to be 18.5% then 159 patients randomized 2:1 (106 in the deep brain stimulation group and 53 in the placebo group) will provide 80% power to reject the primary effectiveness null hypothesis. Sample size calculations were performed using the inequality of proportions option in PASS 2005 and the Z test pooled. To allow for a dropout rate as high as 20%, the sample size will be increased to 201 patients (134 in the deep brain stimulation group and 67 in the placebo group).

9.3 Datasets

The primary analysis of effectiveness will be intent to treat and will include all randomized patients. Analyses of safety will include all patients who are implanted.

9.4 Primary Effectiveness Analysis

The primary effectiveness variable is change from baseline (mean of Baselines 1, 2, and 3) to the mean of Months 4, 5 and 6 in the MADRS. Patients who are missing one or two of the assessments at Months 4, 5 or 6 will have the available visits used. The primary endpoint is a clinical response defined as a 40% or greater reduction from baseline in the MADRS plus no worsening in Global Assessment of Functioning. Patients missing the MADRS for Months 4, 5 and 6 will be considered as non-responders. The primary hypothesis is as follows:

$H_O: \Pi_{DBS} = \Pi_{control}$
vs.
$H_A: \Pi_{DBS} \neq \Pi_{control}$,

where Π_{DBS} and $\Pi_{control}$ are the population response rates in the Deep Brain Stimulation and control groups, respectively. This hypothesis will be tested

by a logistic regression that includes the effects of treatment group, study site, level of treatment resistance as a continuous variable (as defined by ATHF criteria), and baseline MADRS, and will be tested as a two-sided test at the 5% level of significance. Study sites with fewer than three patients in either treatment group will be pooled.

A number of exploratory analyses are planned for the primary endpoint and are described in a separate Statistical Analysis Plan.

9.5 Secondary Effectiveness Analyses

The following secondary endpoints will be compared between the treatment and control groups, in the order that they will be tested :

1. Change from baseline to Month 6 in GAF
2. Change from baseline to Month 6 in Patient and Clinician Global Impression of Severity
3. Change from baseline to Month 6 in Patient and Clinician Global Impression of Improvement
4. A comparison of the active and control groups at month 6 on the Short form Quality of Life Enjoyment and Satisfaction Questionnaire (QOL)
5. Change from baseline to Month 6 in the Inventory of Depressive Symptomatology (IDS-C30)
6. Change from baseline to Month 6 in the Quick Inventory of Depressive Symptomatology (QIDS-SR)
7. Change from baseline to Months 6 in the Work and Social Adjustment Scale (WSAS)
8. Change from baseline to Month 6 in the Hamilton Rating Scale for Depression - 17 item (HRSD-17)
9. A 50% or greater reduction from baseline in the MADRS plus no worsening in Global Assessment of Functioning and no attempted suicide at 6 months
10. The proportion of subjects in the active as compared to the control group at the end of month 6 who had a 50% or greater reduction in MADRS score from baseline
11. A 50% or greater reduction from baseline in the HRSD-17 at 6 months
12. A 40% or greater reduction from baseline in the MADRS at 6 months
13. A remitter analysis will be performed with remitter defined as HAM-D score $\leq$ 7 at 6 months
14. The proportion of subjects in the active as compared to the control group at the end of month 6 who are remitters defined as MADRS score <10

The first eight secondary endpoints are continuous variables based on quantitative scales. Each of these variables will be analyzed based on the multiple imputation procedure and pooling of study sites described under the secondary analyses of the primary variable. An analysis of covariance that

includes the effects of treatment group, study site, and the corresponding baseline measure will be used to analyze each variable.

The last six secondary endpoints will be analyzed first in the same manner as described for the primary endpoint and then after the multiple imputation procedure described for the primary endpoint.

The secondary endpoints will be tested in the order they are presented above using a step down procedure to maintain an overall error of 5%. This step down procedure will only be performed if the primary endpoint is statistically significant and only descriptive information will be provided if the primary endpoint is not statistically significant. If the primary endpoint is statistically significant ($p<0.05$) then the first secondary endpoint will be tested at a significance level of 5%. If that is significant, the second secondary endpoint will be tested at a significance level of 5%. This procedure will continue until an endpoint is found to be nonsignificant ($p>0.05$), or all 14 secondary endpoints are found to be significant.

The above imputation procedure described for the primary endpoint will be used for all secondary endpoints to create a complete dataset of values over the entire course of the study. A mixed effects repeated measures analysis will then be used to estimate the time course of mean changes from baseline. This will be used as supportive information only..

9.6 Other Analyses

The ability of patients to correctly guess their assigned treatment will be done by comparing the patients' perceived treatment with the actual treatment and estimating kappa statistics. An estimated kappa statistic >0.60 will be deemed substantial strength of agreement[35]. In addition, to assess whether the patients' perceived treatment is related to disease improvement, rather than stimulation effects, patients' perceived treatment will be compared with whether or not they reached the primary endpoint and kappa statistics will also be estimated. Other analyses will be performed according to the Statistical Analysis Plan.

9.7 Safety Analyses

9.7.1 Primary Safety Analysis

The primary safety analysis will include a descriptive analysis of all adverse events during the controlled phase, comparing active stimulation with the placebo group. Adverse events with sufficient incidence will be compared between treatment groups by a two-sided Fisher's Exact Test at the 5% level of significance. In addition, all adverse events among patients treated with active stimulation during either the controlled phase or the open label phase will be summarized along with their exact two-sided 95% confidence interval.

A total of 134 patients receiving active stimulation during the controlled phase will provide a 74% chance of observing at least one patient with an adverse event rate of 1%. Moreover, a total of 201 patients exposed to active stimulation during either the controlled phase or the open label phase will provide an 87% chance of observing at least one patient with an adverse event rate of 1%.

9.7.2 Other Analyses of Safety

An additional safety evaluation will be performed on the Neuropsychological battery. The Neuropsychological battery will be completed at baseline, Month 6 and Month 12. Changes from baseline at Month 6 will be compared between treatment groups by an analysis of covariance that includes the effects of treatment group, study center, and corresponding baseline value. P-values will be reported only as summary statistics and no inference of statistical significance will be made from these data. Changes from baseline to Month 12 will be presented as summary statistics for all patients from both original treatment groups combined. Only available data will be used in these analyses with no imputation of missing data.

The numbers of patients with Columbia Suicide-Severity Rating Scale (C-SSRS) scores >3 will be tabulated by treatment group for each study visit throughout the blind and open label phases, and for both treatment groups combined in the open label phase.

9.8 Stopping Rule for Futility

The futility analysis will be done when 75 to 100 patients have achieved the primary endpoint by either completing their Month-6 visit or have terminated from the trial prior to their Month 4 visit. No more than 125 patients will be enrolled into the trial until the results of the futility analysis have been completed and reviewed by FDA.

The futility analysis will be performed using the average of the revised alternative hypothesis (H_A) and the observed interim results. With the current sample size of 201 patients, the alternative hypothesis becomes a 40% response rate for patients on stimulation and a 20.7% response rate among patients in the control group because these population proportions provide 80% power to reject the primary hypothesis. The futility analysis will be performed under the assumption that the remaining patients will be drawn from populations with response rates that are the average of H_A and the interim results. Based on these revised population proportions, 5000 sets of simulation results among the remaining approximately 84 stimulation patients and 42 control group patients will be run. Each set of simulated results will be added to the observed results and a two- sided Fisher' Exact

p-value will be calculated. The probability of a successful outcome of the study is then the proportion of these p-values that are <0.05. If the probability of a successful study outcome is <10% the study will be stopped for futility.

10 Withdrawal of Subjects from Study

Subjects may be discontinued from the study for non treatment-related reasons only when no other option is possible. Reasons for discontinuation include, but are not necessarily limited to:

- Voluntary withdrawal from the study by the subject;
- Subject has moved from the area and is determined to be lost-to-follow-up;
- Investigator may discontinue the Subject's participation in the study for reasons including, but not limited to: subject noncompliance, unwillingness or inability to cooperate with study requirements (therapy regimen, follow-up visits, study determination, etc...).

The reason for discontinuation will be recorded on the appropriate case report form.

Prior to discontinuing a subject, every effort should be made to contact the subject in an effort either to get the subject back into compliance with the protocol, or to obtain as much follow-up data as possible. If a subject decides to discontinue from the study, the subject shall have the option of having the system surgically removed followed by normal psychiatric care. Once the patient exits the study, the device will be turned off (no matter what the randomized treatment was assigned). The device can only be reactivated by the study psychiatrist after the patient enters a separate open-label protocol for long-term follow-up. The patient must sign a separate informed consent and must satisfy the inclusion criteria of the long-term follow up study prior to being enrolled. The study psychiatrist must also deem the subject fit to begin or continue with stimulation.

11 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be appointed to review all SAE data and ensure the appropriate follow up actions necessary. Keeping in mind the safety of patients the status of the study will be evaluated based on a risk to benefit ratio. The Board will create a guidance document prior to the first patient being implanted. This guidance document will indicate the frequency of DSMB meeting, stopping rules and other pertinent information to guide study review.

12 Modification of Protocol

Any amendments to this protocol must be prepared by the study monitor and approved by ANS, the Investigator and the local authority (FDA/IRB/IEC) before implementation.

13 Discontinuation of Study

ANS reserves the right to discontinue any study for administrative reasons at any time, such as but not limited to, a decision to discontinue further clinical investigations with the test article, improper conduct of the study by the Investigator, inability to obtain the number of patients required by the protocol, etc. Reimbursements for reasonable expenses will be made if such action is necessary.

This study may be terminated by the DSMB if an unacceptable number of intracranial hemorrhages or an unacceptable number of completed suicides or suicide attempts is reached without an appropriate explanation. Guidance regarding event evaluation is provided in the DSMB Plan

Study enrollment will be suspended if the following criterion is met until the Data Safety Monitoring Board and FDA can review the safety and effectiveness data to determine whether the study should be halted, modified, or continued.

- If the lower bound of the two-sided 95% confidence interval (based on the normal approximation) for the rate of completed suicides in the combined patient population exceeds 2% at any point during the study.

This study may be terminated if the number of the following events is reached without an appropriate explanation by the 6 month primary endpoint:

- If greater than 24 patients experience an intracranial hemorrhage. This would assume that during the study at the specified interval the rate of intracranial hemorrhage would exceed 12% then the study would be terminated.

14 Administrative Requirements and Quality Assurance

14.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

Before the study can begin the Investigator must provide the Sponsor with a copy of the approval notice for the protocol and informed consent forms, signed by the appropriate committee chairperson.

14.2 Clinical Supplies

The Investigator agrees to keep all test articles in a secure location with restricted access. The Investigator will maintain an inventory of test article receipt and distribution. The Sponsor will provide an itemized inventory of all supplies dispatched. The Investigator or appropriate designee will provide written confirmation of receipt. Investigational devices and device accessories required for maintenance of the implanted devices will be made available to all patients enrolled in this study, at the request of the study Investigator, during the period the patient has completed study participation and prior to PMA approval.

14.3 Reporting and Recording of Data

All study data will be recorded on electronic Case Record Forms (eCRF). Electronic data capture (EDC) will also be utilized to monitor, correct, and store the collected data.

14.4 Monitoring

The Investigator will permit the Study Monitor to visit the Investigational Site at regular intervals to review all the CRFs, study related adjunctive data, and study management. These reviews are for the purpose of verifying the adherence to the protocol and the completeness and exactness of the data being entered as required by Federal Regulations. The Study Monitor must be kept informed of all issues pertinent to the study. The Study Monitor will be available to discuss by telephone questions regarding adverse events, removal of patients/subjects from the study, conduct of the study or any other questions that should arise. At the final monitoring visit the Study Monitor must resolve any outstanding data deficiencies and retrieve all used and unused test articles.

14.5 On-site Audits

The various National Regulatory Authorities (including the United States Food and Drug Administration) in the person of a scientifically trained and properly authorized employee of the department, may request access to all study records, including source documents, for inspection and copying. Similar auditing procedures may also be conducted by a representative of the Sponsor.

14.6 Record Storage and Retention

Federal law and GCP requires that a copy of all study records (e.g., Informed Consent documents, source documents, study records, etc.) which support CRFs of this study, must be retained in the files of the responsible Investigator for a minimum of two years following notification by ANS that all Investigations (not merely the Investigators portion) are completed, terminated, or discontinued, or that the Food and Drug Administration has approved the submission.

If the Principal Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept responsibility. ANS must be notified in writing of the name and address of the new custodian.

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16 Appendices

16.1 Appendix A: Product Labeling

16.2 Appendix B: Sample Informed Consent

16.3 Appendix C: Case Report Forms (CRFs)

16.4 Appendix D: Study Visit Schedule

16.1 Appendix A: Product Labeling

Libra™

Deep Brain Stimulation System

MAJOR DEPRESSIVE DISORDER STUDY

CAUTION: Investigational device limited by federal (United States) law to investigational use.

Clinician's Manual

ANS
A St. Jude Medical Company

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SYMBOLS AND DEFINITIONS

The following symbols are used in this documents and on some of the products and packaging:

Denotes that the user should pay special attention to avoid serious consequences. This document presents the symbol, the word WARNING or CAUTION, and a brief explanation of the seriousness of the situation.

A warning alerts the user to a situation which, if not avoided, could result in (1) death or serious injury, (2) serious or adverse reactions, or (3) safety hazards.

A caution alerts the user to a situation which, if not avoided, may result in (1) minor or moderate injury or (2) damage to the equipment or other property.

This symbol advises the reader to consult this document for important safety-related information.

Denotes device contains a type BF applied part to protect you from shock. The device is internally powered and is intended for continuous operation.

Denotes single use only

Denotes expiration date

Denotes date of manufacture

Denotes temperature limits for storage conditions

Denotes humidity limits

Denotes pressure limits

Denotes ethylene oxide gas sterilization

Denotes do not use if the product sterilization barrier or its packaging is compromised

Denotes catalog number

Denotes manufacturer

Denotes content, the number of items contained in the package

Denotes code that uniquely identifies an inventory item

Denotes serial number

Denotes batch code

Rx only Denotes for prescription use only

Indicates that the Libra Deep Brain Stimulation System is listed by the Canadian Standards Association (CSA) International as certified.

ABOUT THIS MANUAL

This manual provides information about the Advanced Neuromodulation Systems, Inc.™ (ANS™) Libra™ Clinician Programmer (model 6850), and Libra (model 6608) and Libra*XP*™ (model 6644) implantable pulse generators. For information about other components of the Libra Deep Brain Stimulation (DBS) System, see the manuals packaged with those products.

BRIEF SYSTEM DESCRIPTION

The ANS Libra DBS System consists of an implantable 8-channel Libra or dual 4-channel Libra*XP* neurostimulator, known as an implantable pulse generator (IPG). The IPG is used in conjunction with leads and extensions of various lengths and is programmed by an external programmer. This system is designed to deliver electrical stimulation, in various combinations of amplitude, pulse width, and frequency, to specific targets in the brain. The IPG, lead, and extension comprise the implantable components of the Libra DBS System. The Libra Clinician Programmer and QuikLink™ Controller support the operation of the IPG.

INVESTIGATIONAL INDICATIONS

The ANS Libra DBS system is intended for clinical investigation purposes only. The system is being investigated for the management of patients with Major Depressive Disorder, single or recurrent episode, with deep brain stimulation.

CONTRAINDICATIONS

Implantation of an ANS Libra DBS System is contraindicated for use by patients who are unable to operate the system. It is also contraindicated for use with

- **Pacemakers**—Patients with demand-type cardiac pacemakers should not be implanted with a DBS system.
- **Magnetic Resonance Imaging (MRI)**—Do not use a full body radio-frequency (RF) coil or other extremity coils on patients implanted with a deep brain stimulation system. Because energy from MRI can be transferred through the implanted system, the potential for heat generation at the location of the electrodes exists. This isolated temperature rise may cause tissue damage at the location of the implanted electrodes, possibly resulting in severe injury or death. Injury can occur during MRI treatment whether the deep brain stimulation system is turned on or off. All patients are advised to inform their health care professional that they should not be exposed to MRI. In the instance that MRI must be performed, precisely follow the guidelines provided in Appendix E.

⚠ WARNINGS

Other System Components—Refer to the individual system component manuals for additional warnings and precautions related to those devices.

Diathermy—Do not use short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy (all now referred to as diathermy) on patients implanted with a deep brain stimulation system. Energy from diathermy can be transferred through the implanted system and can cause tissue damage at the location of the implanted electrodes, resulting in severe injury or death. Diathermy is further prohibited because it may also damage the deep brain stimulation system components. This damage could result in loss of therapy, requiring additional surgery for system replacement. Injury or damage can occur during diathermy treatment whether the deep brain stimulation system is turned on or off.

Poor Surgical Risks—Deep brain stimulation systems should not be implanted in patients who are poor surgical risks or patients with multiple illnesses or active general infections.

Implanted Defibrillators—Deep brain stimulation systems may adversely affect the programming and operation of implanted cardioverter defibrillators.

Explosive or Flammable Gases—Do not use programming devices in an environment where explosive or flammable gas vapors are present. The operation of programming devices could cause these vapors to ignite, resulting in severe burns, injury, or death.

Theft Detectors and Metal Screening Devices—Certain types of antitheft devices, such as those used at entrances and exits of department stores, libraries, and other public establishments, and/or airport security screening devices may affect stimulation. It is recommended that patients use caution when approaching such a device and request assistance to bypass the device. If they must proceed through the device, patients should move through the device quickly and check the stimulator after passing through to verify if it is turned on or off.

Operation of Machinery and Equipment—Patients should not operate potentially dangerous machinery, power tools, or vehicles or engage in any activity that would be potentially unsafe if their symptoms were to return unexpectedly.

Device Components—The use of non-ANS components with this system may result in damage to the system and increased risk to the patient.

Case Damage—If the IPG case is pierced or ruptured, severe burns could result from exposure to the battery chemicals.

Anticoagulants—Physicians should use extreme care with lead implantation in patients with a heightened risk of intracranial hemorrhage. Physicians should also consider underlying factors, such as previous neurological injury or prescribed medications (anticoagulants), that may predispose a patient to the risk of bleeding.

High Charge Density—A potential risk of tissue damage exists with stimulation parameter settings of high amplitudes and wide pulse widths. Higher amplitude and pulse width settings required to achieve therapy may indicate a system problem or less than optimal lead placement.

If the stimulation parameters exceed the charge density limit of 30 $\mu C/cm^2$, a warning will appear on the Clinician's Programmer. Parameter values exceeding the charge density limit should only be programmed with due consideration of the warnings concerning charge densities. Charge density can be reduced by lowering the stimulation amplitude or pulse width.

PRECAUTIONS

General Precautions

Surgeon Training—Implanting physicians should be experienced in stereotactic and functional neurosurgery.

Physician Training—Clinicians should undergo device programming training and be experienced in the diagnosis and treatment of the indication for which the DBS components are being used.

Patient Selection—It is extremely important to select patients appropriately for deep brain stimulation.

Infection—It is important to follow proper infection control procedures. Infections related to system implantation might require that the device be explanted.

Implantation of Two IPGs—If two IPGs are implanted, ensure that at least 8 inches (20 cm) separates the implanted IPGs to minimize the possibility of interference during programming. Verify programmed parameters in both devices at the end of each programming session.

High Stimulation Outputs—Stimulation at high outputs may cause unpleasant sensations or motor disturbances or may render the patient incapable of controlling the stimulator. If unpleasant sensations occur, the device should be turned off immediately.

Handling, Implantation, Sterilization, Storage, and Explantation

Single-Use Device—The implanted components of the Libra DBS System are intended for a single use only. Do not resterilize or reimplant an explanted component for any reason.

Expiration Date—Do not implant a system component if the use-before date has expired.

Care and Handling of Components—Use extreme care when handling system components prior to implantation. Excessive heat, excessive traction, excessive bending, excessive twisting, or the use of sharp instruments may damage and cause failure of the components.

Package and Component Damage—Do not implant a device if the sterile package or its components shows signs of damage, if the sterile seal is ruptured, or if contamination is suspected for any reason. Return the components to ANS for evaluation.

Exposure to Body Fluids or Saline—If the metal contacts on the proximal end of the lead or extension are exposed to body fluids or saline prior to connection, corrosion can occur. If exposure occurs, clean the metal contacts with sterile deionized water or sterile water (not saline) and dry completely prior to lead connection and implantation.

System Testing—The system should always be tested after implantation and before the patient leaves the surgery suite to ensure correct operation.

Component Disposal—Return all explanted components to ANS for safe disposal.

Hospital and Medical Environments

High Output Ultrasonics and Lithotripsy—The use of high output ultrasonic devices, such as an electrohydraulic lithotriptor, may cause damage to the electronic circuitry of an IPG. If lithotripsy must be used, do not focus the energy near the IPG.

Ultrasonic Scanning Equipment—The use of ultrasonic scanning equipment may cause mechanical damage to an implanted deep brain stimulation system if used directly over the implanted device.

External Defibrillators—The safety of discharging an external defibrillator on patients with implanted deep brain stimulation system components has not been established.

Therapeutic Radiation—Therapeutic radiation may damage the electronic circuitry of an implanted deep brain stimulation system, although no testing has been done and no definite information on radiation effects is available. Sources of therapeutic radiation include therapeutic x-rays, cobalt machines, and linear accelerators. If radiation therapy is required, the area over the IPG should be shielded with lead.

Electrosurgery Devices—Electrosurgery devices should not be used in close proximity to an implanted deep brain stimulation system. Contact between an active electrode and an IPG, lead, or extension can cause direct stimulation of the tissue at the electrode site and cause severe injury to the patient. If the use of electrocautery is necessary, turn the IPG off.

Psychotherapeutic Procedures—The safety of electromagnetic psychotherapeutic procedures (such as electroshock therapy and transcranial magnetic stimulation) in patients implanted with DBS system components has not been established.

Home and Occupational Environments

Electromagnetic Interference (EMI)—Certain commercial electrical equipment (e.g., arc welders, induction furnaces, and resistance welders), communication equipment (e.g., microwave transmitters, linear power amplifiers, and high power amateur transmitters), and high voltage power lines may generate sufficient EMI to interfere with the deep brain stimulation system operation if approached too closely.

Household Appliances—Household appliances that contain magnets (e.g., refrigerators, freezers, stereo speakers, mobile telephones, cordless telephones, standard wired telephones, AM/FM radios, and some power tools) may unintentionally cause the deep brain stimulation system to turn on or turn off.

Patient Activities/Environmental Precautions—Patients should take reasonable care to avoid devices that generate strong electromagnetic interference (EMI), which may cause the deep brain stimulation system to unintentionally turn on or off. Patients should also avoid any activities that would be potentially unsafe if their symptoms were to return unexpectedly.

Therapeutic Magnets—Patients should be advised to not use therapeutic magnets. Therapeutic magnets (e.g., magnets used in pillows, mattress pads, back belts, knee braces, wrist bands, and insoles) may unintentionally cause the deep brain stimulation system to turn on or off.

Mobile Phones—The effect of mobile phones on DBS systems is unknown; patients should avoid placing cellular phones directly over the device.

ANTICIPATED ADVERSE EVENTS AND COMPLICATIONS

The implantation of a deep brain stimulation system involves risk. In addition to those risks commonly associated with surgery, implantation of a DBS system may expose the patient to the risks of post-operative pain, stress, or discomfort, intracranial hemorrhage, subcutaneous hemorrhage, intracranial infractions, symptomatic neumocephalus (intracranial air causing confusion requiring an extra day stay in the hospital), seizure or convulsions, seroma, infection, aphasia, paralysis, stroke, death, cerebrospinal fluid leakage or abnormality. An additional neurosurgical procedure may be necessary to manage one of the above complications.

DBS Complications—may occur leading in some cases to surgical revision or explantation of the system. DBS complications include, but are not limited to the following:

- Neuropathy;
- Neuralgia;
- Headache;
- Asthenia, hemiplegia or hemiparesis;
- Cognitive impairment, including confusion, abnormal thinking, hallucinations, alteration of mentation, amnesia, delusions, or dementia;
- Cerebrospinal fluid abnormality;
- Disequilibrium;
- Ataxia;
- Myoclonus;
- Hearing and visual disturbance;
- Paresis;
- Dystonia;
- Attention deficit;
- Dysarthria;
- Sleep disturbance;
- Suicide or Suicide attempt;
- Increase in drug side effects;
- Autonomic instability (change in vital signs);
- Urinary incontinence;
- Worsening depression symptoms;
- Anxiety;
- Ruminativeness;
- Hypomania;
- Mania;
- Panic attacks;
- Obsessive compulsive disorder (OCD) symptoms;
- Psychosis;
- Seizure;
- Apathy;
- Eye disorder;
- Sweating;
- Diarrhea;
- Sensory deficit;
- Drowsiness;
- Difficulty breathing;
- Increased salivation;
- Nausea and/or vomiting;
- Rapid heart rate;
- Pneumonia;
- Skin disorder;
- Edema including periorbital;
- Syncope;
- Persistent pain or redness at the IPG site or the surgery site/extension;
- Pulling sensation along extension site;
- Allergic or rejection response to implanted materials;
- General erosion or local skin erosion over the pulse generator (IPG), burr hole cap, and/or extension;
- Undesirable changes in stimulation possibly related to cellular changes in tissue around the electrodes, changes in the electrode position, or loose electrical connections and/or lead fracture;
- Initial jolt or tingling during stimulation;
- Paresthesia;
- Loss of therapeutic benefit as a result of change in electrode positions, lead fracture, loose electrical connections, DBS system battery failure, DBS system malfunction, or inadvertent turning off of device;
- Lead fracture;
- Lead migration;
- System dislodgement;
- DBS battery failure;
- DBS system malfunction.

SYSTEM DESCRIPTION

A Libra DBS System consists of four primary components: IPG (neurostimulator), lead(s), extension(s), and programmer.

IPG

The Libra IPG is designed to be connected to one DBS extension. The Libra*XP* IPG is designed to be connected to two DBS extensions. The IPGs are powered by a hermetically sealed battery within a titanium case and use microelectronic circuitry to generate constant current electrical stimulation.

The IPG is insulated on all sides except the side with the markings. This allows the IPG case to be used as an anode for monopolar stimulation. Ensure that the marked side is implanted facing up and away from muscle.

The Libra IPG contains a radiopaque identification tag. The identification tag is visible inside the IPG header block using standard x-ray procedures. The tag contains a code: "ANS" identifies ANS as the manufacturer; "P" or "R" identifies the device as a Libra IPG Model 6608 or Libra*XP* Model 6644; and the two numbers following the "P" denote the year of manufacture (see Figure 1).

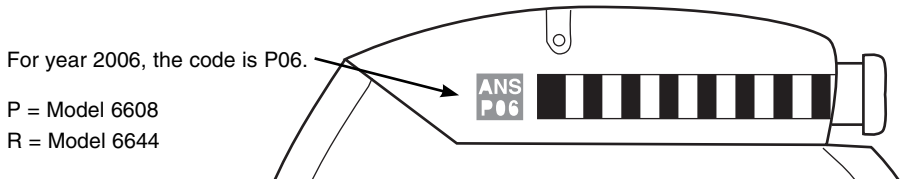


FIGURE 1

Leads and Extensions

ANS DBS leads consist of electrodes on the distal end, connected by individually insulated wires to contact bands on the proximal end. The proximal end has a nonoperational metal band (the most distal band) that serves as an insertion handle. The insulated wires are covered by a biocompatible polymer. ANS DBS leads are designed for introduction into the brain using standard stereotactic neurosurgery techniques.

The DBS extension is designed to connect the lead to the IPG. One end of the extension is designed to receive the proximal end of the lead, and the opposite end of the extension is designed for insertion and connection with the IPG.

Consult the Lead and Extension manual for more information and directions for use of these devices.

Programmer

The Libra Clinician Programmer controls the creation and adjustment of all programming parameters. The programmer uses radio-frequency signals to communicate with the IPG.

Sterilization Information

Sterile components in this kit have been sterilized using ethylene oxide (EtO) gas before shipment and are supplied in sterile packaging to permit direct introduction into the operative field. An expiration date (or 'use-before date') is marked on the label of each package.

⚠ **CAUTION:** ANS implantable components are intended for single use only. Do not resterilize.

SUGGESTED IMPLANT GUIDELINES

The implanting surgeon should carefully review the following suggested guidelines for implantation of a Libra system.

CONNECTING THE EXTENSION TO THE IPG

1. If needed, clean the proximal end of the extension with sterile, deionized or distilled water and dry it completely. Use clean gloves and ensure that all body fluids and saline residue are cleaned from the proximal end of the extension. This is important to prevent future corrosion and potential failure of the system.

> ⚠ **CAUTION:** Exposure of the internal IPG contacts to body fluid or saline can affect stimulation. If this occurs, clean the contacts with sterile, deionized or distilled water (**not saline**) and dry completely prior to extension connection and subsequent implantation.

2. Slide a connector strain relief on to the proximal end of the extension, being careful not to sharply bend the extension (see Figure 2).

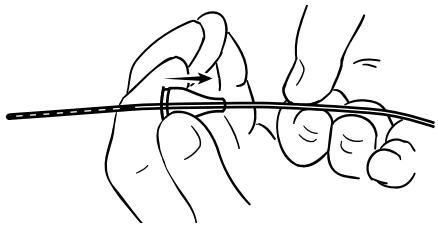


FIGURE 2

3. Carefully slide the proximal end of the extension into the IPG header until it stops (see Figure 3).

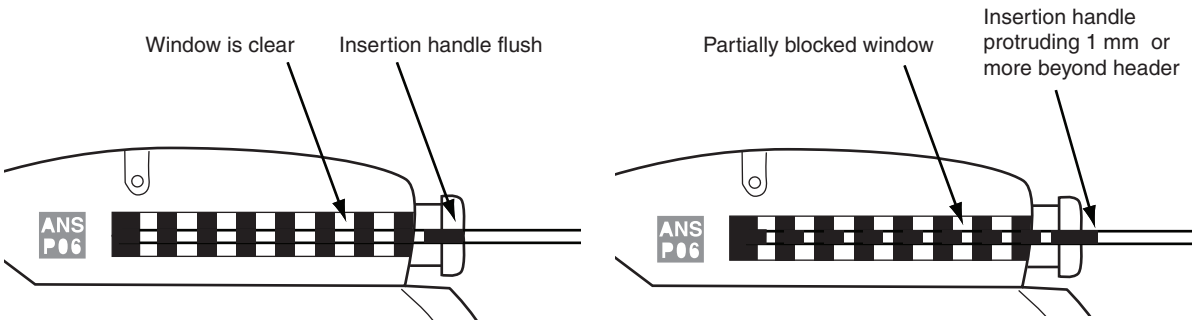


FIGURE 3

4. Use the torque wrench to tighten the setscrew clockwise until the torque wrench clicks (see Figure 4).

NOTE: After the torque wrench is removed, check the septum to ensure it has closed. If the septum is not closed, gently reseat the septum flaps.

⚠ **CAUTION:** Use only the torque wrench included in the extension kit, IPG kit, or torque wrench kit (Model 1101). If you need to loosen the setscrew, turn the setscrew (in quarter turns counterclockwise) only as far as necessary to remove the extension from the IPG header. Retracting the setscrew too far could cause damage to the septum.

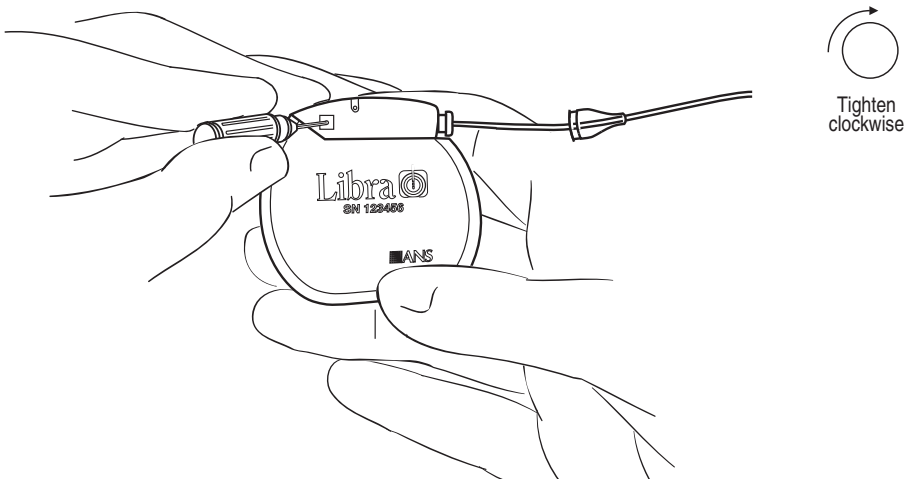


FIGURE 4

5. Slide the connector strain relief into position over the O-ring at the proximal end of the IPG (see Figure 5). Tie a 2-0 nonabsorbable suture around the connector strain relief.

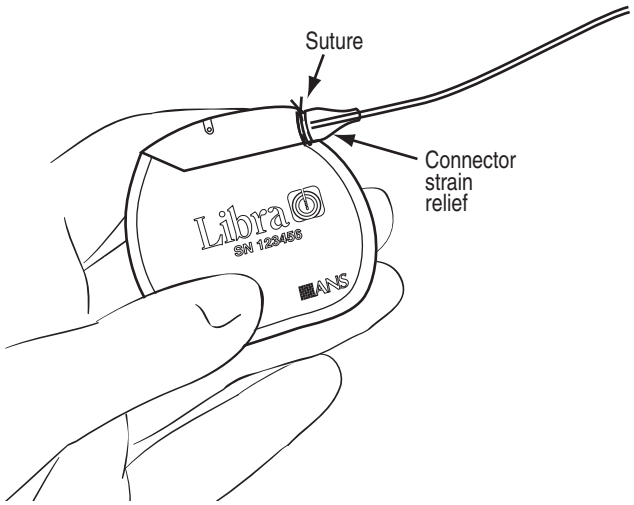


FIGURE 5

IPG Placement

1. Carefully place the IPG in a subcutaneous pocket, at a depth not to exceed 4 cm (1.5 inches), with the logo side facing toward the skin surface.

   NOTE: The logo side of the IPG is uninsulated to enable monopolar stimulation. Implanting the IPG backwards may increase undesired muscle stimulation.

2. Carefully coil any excess extension in loops no smaller than 2.5 cm (1 inch) in diameter and place them behind the IPG (see Figure 6). The loop(s) are intended to provide strain relief for the lead, extension, and IPG connections.

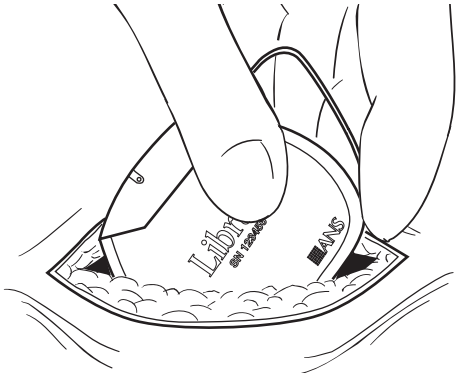


FIGURE 6

3. To stabilize the IPG within the pocket and prevent movement, pass a suture through the hole at the top of the IPG header and secure it to the connective tissue.

4. Before closing, verify that the system is operational by placing the wand from the Libra Clinician Programmer (6850) in a sterile bag and positioning the wand over the IPG site.

   NOTE: If a communication error occurs during programming, reposition the wand **farther** away from the IPG.

5. Close the IPG pocket incision. The IPG in the pocket should be positioned away from the pocket incision suture line (see Figure 7).

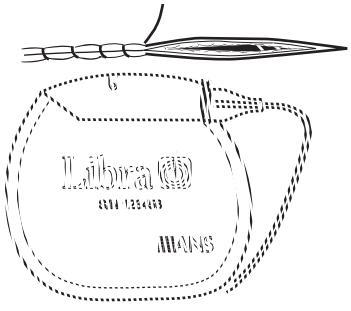


FIGURE 7

6. Complete the patient registration information and identification card, and give the identification card to the patient.

IPG Replacement

1. After ensuring that the IPG is turned off, open the IPG pocket per normal surgical procedure, and carefully remove the IPG from the pocket.

> ⚠ **CAUTION:** Exercise extreme caution when using sharp instruments and electrocautery around the extension.

2. Carefully remove the suture from the strain relief, being careful to not damage the extension (see Figure 5).
3. Insert an ANS torque wrench into the IPG header septum and loosen the setscrew by turning it counterclockwise in quarter turns.
4. Gently retract the extension from the IPG header. Clean and dry all contacts on the extension, ensuring they are free of fluid and tissue.

   NOTE: If an extension needs to be replaced, do the following:
   1. Make an incision above the extension connector assembly and disconnect the extension from the lead.
   2. Sever the distal end of the extension just proximal to the extension connector assembly.
   3. Carefully pull the extension out through the IPG pocket.
5. Place a new strain relief over the extension.
6. Insert the extension into the new IPG.
7. Tighten the setscrew clockwise until the torque wrench clicks.
8. Remove the torque wrench and ensure the septum is closed.
9. Slide the connector strain relief into position over the O-ring at the proximal end of the IPG. Tie a 2/0 non-absorbable suture over the strain relief.
10. Place the new IPG into the pocket, at a depth not to exceed 4 cm (1.5 inches) with the logo side facing outward away from the muscle layer.
11. Carefully coil any excess extension in loops no smaller than 2.5 cm (1 inch) in diameter and place them behind the IPG.
12. To stabilize the IPG within the pocket and minimize movement, pass a suture through the hole at the top of the IPG header and secure it to the connective tissue.
13. Before closing, verify that the system is operational by placing the wand from the Libra Clinician Programmer (6850) in a sterile bag and positioning the wand over the IPG site.
14. Close the IPG pocket incision.
15. Complete the patient registration and identification card, and give the identification card to the patient.
16. Return any explanted components to ANS. Refer to "Explanted Component Disposal" for more information.

EXPLANTED COMPONENT DISPOSAL

Explanted products should be returned to ANS for proper disposal. Returned product must be decontaminated and placed in a container with a biohazard label. Please include an explanation on the "Returned Product Information Report" that is packaged with the IPG. Contact ANS Customer Service to obtain suitable containers and biohazard labels.

Return explanted products to

Advanced Neuromodulation Systems, Inc.
6901 Preston Road
Plano, TX 75024

CLINICIAN PROGRAMMER

OVERVIEW

The Libra Clinician Programmer (Model 6850) is an external device that is used to program the stimulation parameters of Libra neurostimulators via radio frequency telemetry. The major parts of the Clinician Programmer are shown in the following illustration.

The general flow of the programmer operation is as follows:

- the programmer provides a series of choices arranged in a loop. There are two types of choices: parameters (which have a value that can be adjusted) and actions (which cause an action to occur).
- and buttons are used to move forward and backward between the choices.
- the and buttons are used to change the value of the highlighted choice.
- the button is used to initiate or select the highlighted choice.
- the and buttons are used only for very infrequent, special actions.

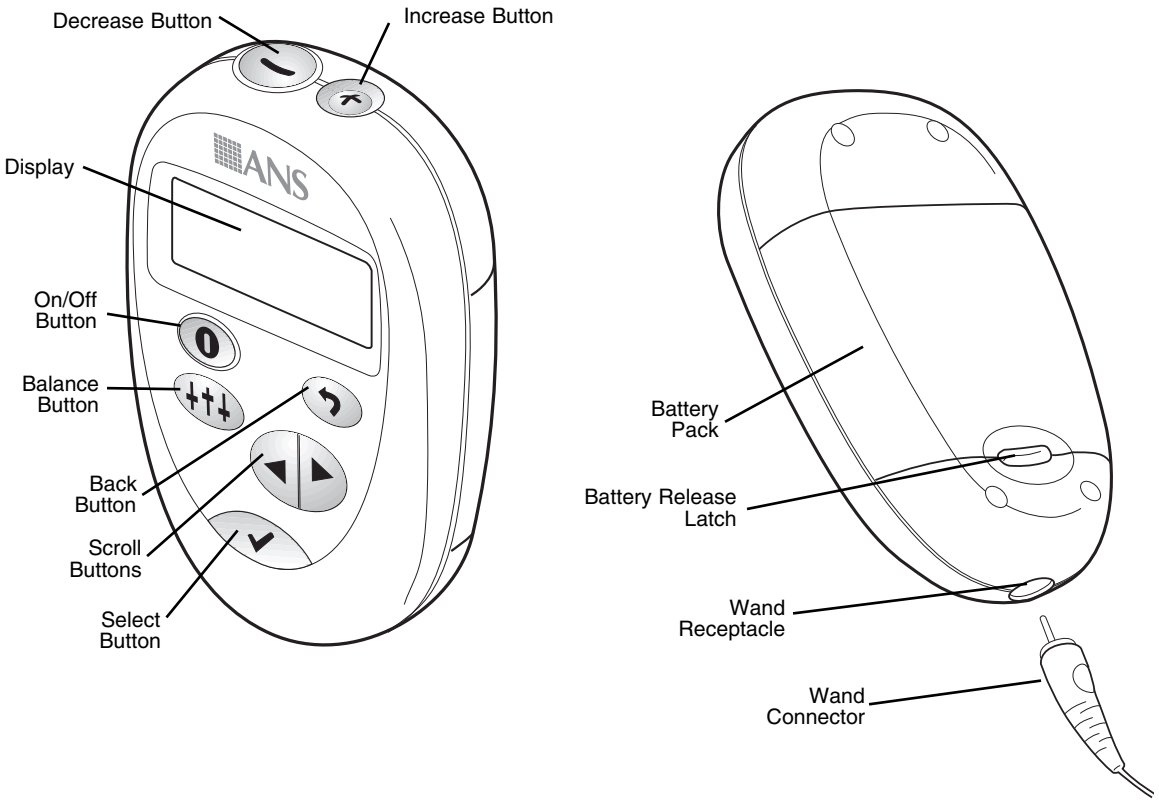


FIGURE 8

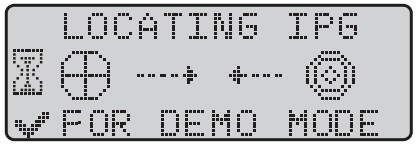
DEMO MODE

A demo mode is available in the clinician programmer. Demo mode is intended as a training tool to practice using the programmer prior to using it during an actual programming session. All of the major functions of the programmer are simulated in demo mode.

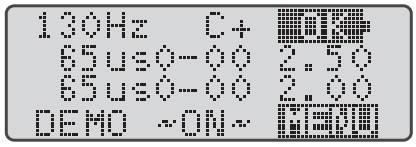
NOTE: Demo mode simulates programming a Libra*XP* (6644).

To enter demo mode

1. Place the programmer wand at least 8 inches away from all neurostimulators.
2. Press the red button to turn the programmer on.
3. Press the green button when the following screen appears.



4. The Home screen (shown below) will appear when you have entered demo mode. Follow the directions in The Home Screen section of this manual to enter programming mode, and the directions in the Programming Mode section to practice programming.



To exit demo mode

1. Return to the Home screen by
   - using the scroll buttons to highlight EXIT then pressing the green button.
   - then highlighting SAVE AND EXIT and pressing the green button.
2. From the Home screen, press the red button to turn the programmer off.

BASIC OPERATION

This section provides an overview of the most commonly used features of the programmer. For more details, see the *Programming Mode* and *Amplitude Adjustment Mode* sections of this manual.

Turning Stimulation Off

To turn stimulation off

1. Press the red  button to turn the programmer on.
2. Place the wand over the neurostimulator.
3. Wait for the Home screen to appear.
4. Use the scroll  button to highlight STOP in the lower right corner.
5. Press the green  button. The stimulation output indicator will change from ~ON~ to ~OFF.

Turning Stimulation On

To turn stimulation on

1. Press the red  button to turn the programmer on.
2. Place the wand over the neurostimulator.
3. Wait for the Home screen to appear.
4. Use the scroll  button to highlight START in the lower right corner.

   NOTE: The START option will not appear if the programmer detects a problem with the stimulation program. Instead, the programmer will only give the MENU option, so that the problem can be fixed by reprogramming the neurostimulator.
5. Press the green  button. The stimulation output indicator will change from ~OFF to ~ON~, and the RAMP symbol will flash as stimulation increases from zero to the programmed amplitude.

Typical Programming Session

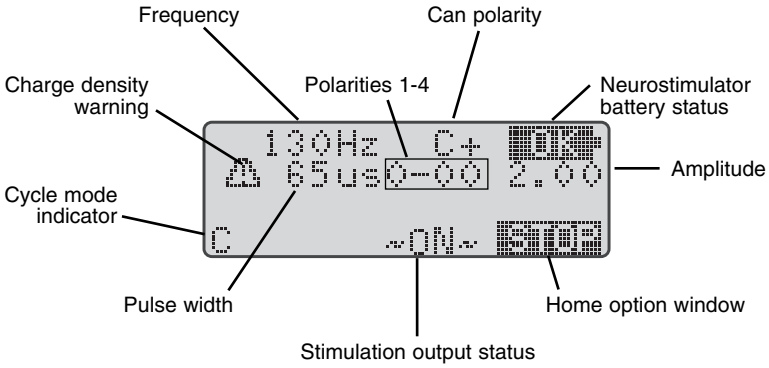
This section provides an overview of the steps for a basic programming session in which the neurostimulator parameters will be adjusted. See the *Programming Mode* section of this manual for more information about the full functionality of the system.

To:	Do the following:
1. Turn the programmer on	Press the red  button.
2. Establish telemetry with the neurostimulator	Place the wand over the neurostimulator.
3. Check the neurostimulator battery status and stimulation parameters	Read the information on the Home screen. See the Home screen section of this manual to interpret the information on the screen.
4. Start a programming session	Use the scroll buttons to highlight "MENU" in the lower right corner, then press the green  button. With the "P" highlighted, press the green  button. A message will appear, and stimulation will turn off.
5. Turn stimulation back on	There are two ways to turn stimulation back on: **Choice 1**: Highlight JUMPTO and press the green  button. Stimulation will immediately turn on at the amplitude it was at prior to starting the programming session. **Choice 2**: Highlight AMP and press the  button. Stimulation will increase from zero in increments of STEP. In this way, stimulation can be turned on gradually.
6. Change parameters	Use the scroll  buttons to move between choices and highlight the desired parameter. The choices span several screens. If you continue to scroll in the same direction you will eventually move through all screens. When the desired parameter is highlighted, use the  buttons to change the value of the parameter.
7. Initiate actions	Use the scroll  buttons to highlight the desired action. Press the green  button to initiate the action.
8. End the programming session	Highlight EXIT, then press the green  button. Press the green  button again when "SAVE AND EXIT' is highlighted. Stimulation will then be ramped on and the Home screen will be displayed.
9. Turn the programmer off	Press the red  button.

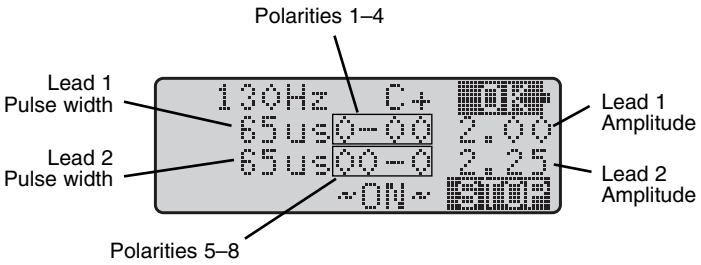
The Home Screen

When the Clinician Programmer is off and the red ⏻ button is pressed, a series of self-tests are started. These tests take approximately 5 seconds and are designed to ensure that the programmer is functioning properly. Next, the programmer attempts to establish communication with the neurostimulator. If it is able to establish communication, it will display the Home screen.

The Home screen (shown below) is displayed whenever the Programmer is turned on and successfully establishes communication with the neurostimulator. This screen provides a summary of the stimulation parameters, stimulation on/off status, and neurostimulator battery status.



Libra
Stimulation Output Status Option Window



Libra*XP*

Use the scroll buttons to change the function displayed in the option window in the lower right corner, then use the green button to select that action. The option window choices are shown below. The programmer hides (does not offer) choices that are incompatible with the current stimulation program and neurostimulator status. The choices are arranged in a loop, so that, continuing to scroll in the same direction will ultimately bring you back around to the first choice.

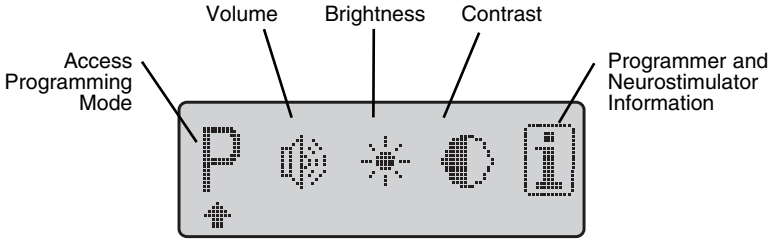
START Turns stimulation on

STOP Turns stimulation off

AMP Enters amplitude adjustment mode

MENU Provides access to programming mode and programmer preferences

When MENU is selected the following screen will be displayed. Use the scroll buttons to move the selector arrow until it is positioned under the desired action, then press the green button.

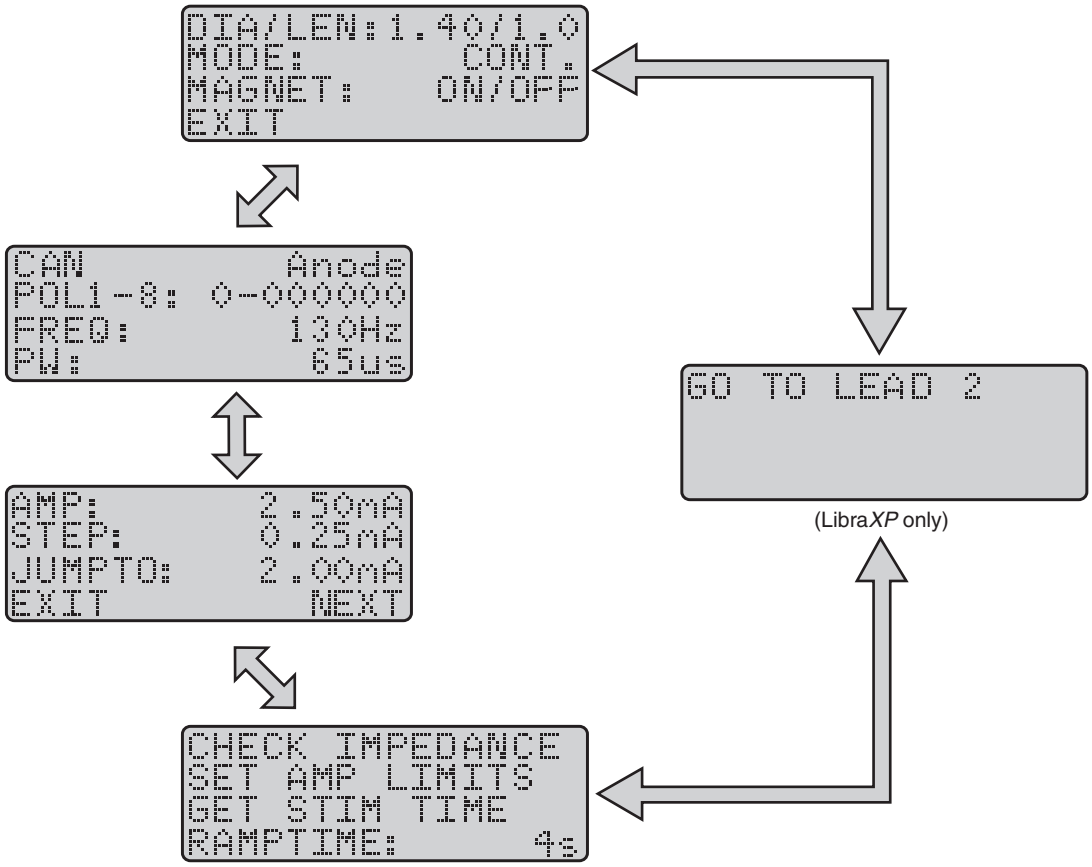


Selecting P provides access to the programming mode. Selecting i provides information about the programmer and the neurostimulator. The other icons adjust the sound volume, screen brightness and screen contrast on the programmer. Pressing the button returns to the Home screen.

PROGRAMMING MODE

Programming mode is used to change the parameters of the stimulation program, and to interrogate the neurostimulator for certain diagnostic information. Programming mode provides a series of choices (parameters and actions) arranged in a loop that spans multiple screens. The scroll buttons are used to move forward and backward between the choices. Scrolling forward at the bottom of one screen moves the cursor to the top of the next screen. Likewise, scrolling backward at the top of one screen moves to the bottom of the prior screen. The sequence of the choices is shown below.

NOTE: LibraXP offers the choice to GO TO LEAD 1 (POL1-4) or GO TO LEAD 2 (POL5-8) upon entry into programming mode.



There are two types of choices in programming mode: actions and parameters. The following pages provide a description of the action and parameter choices available within programming mode.

AMP

Use this to set the amplitude of the stimulation generated by the neurostimulator.

Highlighting this line and pressing:

(+) increases AMP by an amount equal to STEP

(−) decreases AMP by an amount equal to STEP

This line shows the amplitude of the stimulation being generated by the neurostimulator, and allows it to be changed. When AMP is zero, it will display OFF. Stimulation amplitude can be adjusted in the following ways:

- Highlight the AMP line and press (+) or (−) to increase or decrease amplitude by an amount equal to STEP
- Press the red (I) button to turn amplitude off.
- Highlight JUMPTO, and then press (✓) to change amplitude to the value shown on the JUMPTO line.

  NOTE: The ⚠ on the AMP or PW lines means that the charge density is above 30 μC/cm^2 at the current AMP and PW settings.

> ⚠ **WARNING:** A potential risk of tissue damage exists with stimulation parameter settings of high amplitudes and wide pulse widths. High amplitude and pulse width settings required to achieve therapy may indicate a system problem or sub-optimal lead placement.

CAN

Use this to set the polarity of the neurostimulator (can) case.

Highlighting this line and pressing:

(+) toggles the can polarity between ANODE and OFF

(−) toggles the can polarity between ANODE and OFF

The neurostimulator case can be programmed to be either: ANODE (a positive electrode, for monopolar stimulation), or OFF (not part of the stimulation circuit, for bipolar stimulation). Keep in mind the following when adjusting CAN:

- AMP will be turned off whenever CAN is changed
- AMP limits will be disabled whenever CAN is changed
- When CAN is set to ANODE, none of the electrodes on the lead can be set to anode. When CAN is changed to ANODE all electrodes on the lead set to anode will be automatically switched OFF.
- *LibraXP*: Both leads must have the same CAN setting. The CAN parameter can only be changed when programming lead 1. When programming lead 2, ANODE or OFF will be shown in brackets "[ ]" indicating that it cannot be changed.

CHECK IMPEDANCE

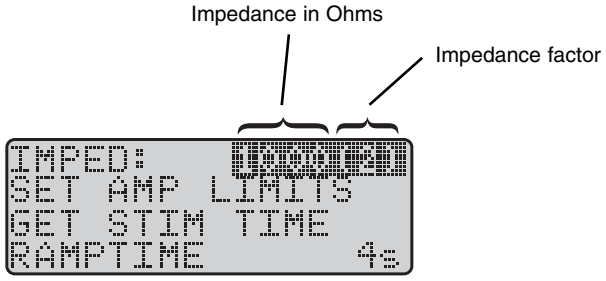
Use this to obtain an estimate of the impedance of the system with the current stimulation parameters and electrode configuration. Also use this to obtain the impedance factor to calculate device longevity.

Highlighting this line and pressing:

✔ starts a sequence that measures the system impedance

Impedance measurements can be helpful for troubleshooting problems, or estimating device longevity. See the *Troubleshooting* section of this manual for information on interpreting impedance measurements and Appendix C and D for information on calculating device longevity.

Before an impedance measurement can be taken, the programmer waits for the neurostimulator impedance measurement circuitry to stabilize. The programmer automatically calculates the required stabilization time, and displays a countdown on its screen. At any time after the stabilization time, position the wand over the neurostimulator and press the green ✔ button to obtain the impedance measurement.



NOTE: It is only necessary to hold the wand over the neurostimulator when the green ✔ button is pressed. It is NOT necessary to hold the wand over the neurostimulator while the programmer is counting down.

NOTE: The stabilization time can be reduced by increasing AMP, FREQ or PW.

DIA/LEN *(ELECTRODE DIAMETER AND LENGTH)*

Use this to specify the dimensions (diameter and length) of the electrodes on the lead.

Highlighting this line and pressing:

⊕ moves between the electrode diameter and length choices

⊖ moves between the electrode diameter and length choices

The programmer uses the electrode dimensions to calculate the average charge density, and displays a warning when it exceeds 30 μC/cm^2. Each time the programmer is turned on, it resets this parameter to the smallest electrode dimensions. See the manual packaged with the DBS lead to determine the lead dimensions.

EXIT

Use this to exit programming mode and return to the Home screen.

Highlighting this line and pressing:

 exits programming mode and provides the choice to save or discard the changes made to the program

After finishing programming the neurostimulator, you must select EXIT to leave programming mode. Otherwise, the programmer will not turn off, and it will periodically beep to remind you to EXIT programming mode.

After selecting EXIT, you will be given the option to keep or discard the program changes you have just made. In certain circumstances when amplitude limits are enabled, you will also be prompted to adjust/confirm the amplitude limits.

⚠ **CAUTION:** Always EXIT programming mode and turn the programmer off and back on before attempting to program a different IPG. Failing to do so, can abruptly change stimulation parameters in the second IPG.

FREQ

Use this to set the stimulation frequency.

Highlighting this line and pressing:

 increases the stimulation frequency in increments of 10 Hz

 decreases the stimulation frequency in increments of 2 Hz

This line shows the frequency of the stimulation currently being generated by the neurostimulator, and allows it to be changed. FREQ (frequency) is the number of stimulation pulses delivered each second. Keep in mind the following points when adjusting FREQ:

- The highest frequencies may not be programmed with long pulse widths. The maximum frequencies are:

	Max. FREQ for:	
	1 Lead	**2 Leads**
PW ≤ 248 µsec	240 Hz	200 Hz
PW > 248 µsec	220 Hz	180 Hz

- *LibraXP*: Both leads must have the same FREQ setting. FREQ can only be changed when programming lead 1. When programming lead 2, the FREQ parameter value will be shown in brackets "[ ]" indicating that it cannot be changed.

GET STIM TIME

Use this to get information about stimulator use.

Highlighting this line and pressing:

 reports the current values of TOTALDAYS and STIMDAYS

TOTALDAYS is the number of days since the neurostimulator was manufactured—whether or not stimulation output is on.

STIMDAYS is the number of days that stimulation was actually turned on. For example, if stimulation was turned on for 12 hours per day for 48 hours, then STIMDAYS counts this as one day, while TOTALDAYS counts it as two.

STIMDAYS and TOTALDAYS can be useful for troubleshooting and assessing patient compliance. See the *Troubleshooting* section of this manual for details.

GO TO LEAD 1 / GO TO LEAD 2 *(LIBRAXP ONLY)*

Use this to move to (and program) the other lead on Libra*XP* neurostimulators.

Highlighting this line and pressing:

 turns lead 1 stimulation off, and retrieves the stimulation parameters of lead 2 (and vice versa when going from lead 2 to lead 1)

When entering programming mode, a prompt will appear allowing you to select which lead to program. Stimulation output from the other lead is turned off while you program this lead, and vice versa.

JUMPTO

Use this to immediately turn stimulation on at the amplitude shown on this line.

Highlighting this line and pressing:

 immediately changes AMP to the amplitude displayed on the JUMPTO line

JUMPTO provides an alternate, shortcut method of adjusting the stimulation amplitude. Some of the uses for this feature may include:

- The JUMPTO line displays the value that the stimulation amplitude was at when the programming session was started, thereby providing a continuous reminder of the last programmed stimulation amplitude.
- The programmer automatically turns stimulation off when a programming session is started. JUMPTO provides a fast way to turn stimulation back on. This may be useful for patients that are sensitive to stimulation being turned off, but are tolerant of stimulation being quickly turned on.

⚠ **CAUTION:** Some patients may be startled by abruptly turning on stimulation. Use the AMP line to gradually turn on stimulation in patients who are sensitive to abruptly turning on stimulation.

MAGNET

Use this to set how the neurostimulator will respond if it senses a magnet.

Highlighting this line and pressing:

 toggles magnet mode between OFF and ON/OFF

 toggles magnet mode between OFF and ON/OFF

The neurostimulator contains a sensor that detects the presence of a strong magnet. It can be programmed to respond to a magnet in two different ways:

- OFF: The neurostimulator will turn stimulation output OFF the first time it detects a magnet. Stimulation cannot be turned back on with the magnet.
- ON/OFF: The neurostimulator will toggle stimulation output between ON and OFF each time it detects a magnet.

MODE

Use this to set the stimulation mode.

Highlighting this line and pressing:

✓ enters the stimulation mode adjustment screen

The neurostimulator has two stimulation modes: continuous and cycle.

- *Continuous mode* produces stimulation until the neurostimulator is turned off via a magnet, programmer or QuikLink.
- *Cycle mode* produces stimulation in a repeating cycle of a defined *on time* followed by a defined *off time*. The Home screen will display a "C" in the lower left corner when the neurostimulator is in cycle mode.

After entering the mode adjustment screen, use the ⊕ / ⊖ buttons to toggle between CONT (continuous) and CYCLE modes. When CYCLE is selected use the scroll buttons and ⊕ / ⊖ buttons to adjust the H (hours), M (minutes) and S (seconds) cycle on and cycle off times in the stimulation mode adjustment screen. When finished, highlight DONE and press ✓ to leave stimulation mode adjustment screen.

POL

Use this to set the polarity of the electrodes on the lead.

Highlighting this line and pressing:

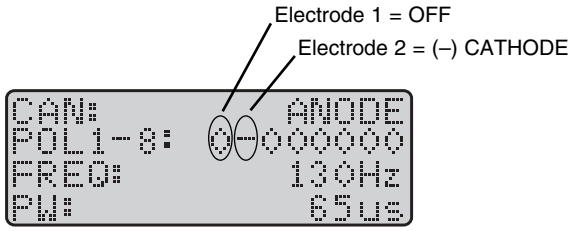
⊕ when CAN is OFF, changes the polarity of the electrode from 0 (OFF) to + (anode) to – (cathode)

⊕ when CAN is ANODE, changes the polarity of the electrode from 0 (OFF) to – (cathode)

⊖ when CAN is OFF, changes the polarity of the electrode from 0 (OFF), to – (cathode) to + (anode)

⊖ when CAN is ANODE, changes the polarity of the electrode from 0 (OFF), to – (cathode)

The electrodes on ANS leads are numbered 1 through "X", with the most distal electrode designated electrode #1. The programmer supports programming Libra neurostimulators with a single lead with up to 8 electrodes, and Libra*XP* neurostimulators with two leads with 4 electrodes each.



PW

Use this to set the pulse width of the stimulation produced by the neurostimulator.

Highlighting this line and pressing:

 increases the width of the stimulation pulse by 13 microseconds

 decreases the width of the stimulation pulse by 13 microseconds

This line shows the pulse width of the stimulation currently being generated by the neurostimulator, and allows it to be changed. The longest pulse widths may not be programmed with the highest frequencies (see FREQ for details).

RAMPTIME

Use this to set how long stimulation will take to ramp up to the programmed amplitude when the neurostimulator is turned on.

Highlighting this line and pressing:

 moves to the next longer ramp time

 moves to the next shorter ramp time

Some patients may find it more comfortable to have stimulation gradually ramp up when the neurostimulator is turned on, as opposed to jumping directly to the programmed amplitude. This line allows you to set how quickly stimulation is increased when the neurostimulator is turned on. The ramp time choices are 0, 2, 4, 8, 15, 30, 45, and 60 seconds. Both leads on a Libra*XP* use the same ramp time.

> **NOTE**: RAMPTIME is not used in programming mode. In programming mode, amplitude changes are made as fast as practicable.

SET AMP LIMITS

Use this to enable and set the values of the amplitude limits, or disable amplitude limits.

Highlighting this line and pressing:

 enters the amplitude limits configuration screen

Libra neurostimulators give you the option to allow your patients to adjust their stimulation within your prescribed amplitude limits using their controller. This feature is enabled from the amplitude limits configuration screen by changing MIN or MAX so that they are not equal to AMP. Amplitude limits are disabled by setting MIN and MAX equal to AMP. When finished, highlight DONE and press  to leave stimulation mode adjustment screen.

- MAX is the maximum amplitude to which patients will be able to increase their stimulation amplitude.
- MIN is the minimum amplitude (other than OFF) to which patients will be able to decrease their stimulation amplitude.
- STEP is the increment by which stimulation amplitude will be adjusted each time the increase amplitude or decrease amplitude button is pressed.

Each time the increase amplitude or decrease amplitude button is pressed, stimulation amplitude is adjusted by an amount equal to STEP. This allows you to control both the range (from MIN to MAX) and the number of amplitude choices that you prescribe. Some patients may find it easier to have only a few choices whereas others may need the fine-tuning that can be provided with more, smaller increments.

> **NOTE:** STEP should be adjusted before entering the amplitude limits configuration screen. Adjusting STEP afterward may cause MIN and/or MAX to reset.
>
> **NOTE:** STEP, MIN and MAX should be set just prior to exiting programming mode. Upon exiting programming mode, the programmer will automatically prompt you to change MIN if it is no longer less than or equal to AMP, or MAX if it is no longer less than or equal to AMP.

STEP

Use this to set the increment by which AMP will be adjusted both in programming mode, and in amplitude adjustment mode.

Highlighting this line and pressing:


increase STEP by 0.05mA


decrease STEP by 0.05mA

This line shows the increment by which the stimulation amplitude will be increased or decreased when the AMP line is highlighted and the  or  button is pressed. This allows you to change how stimulation is stepped up. A larger step size can be used to quickly make large amplitude changes, and a smaller step size allows fine tuning of the amplitude.

This parameter is also used to set the increment by which amplitude will be increased or decreased when using amplitude limits. Keep in mind the following points when using STEP for amplitude limits:

- STEP can be increased to reduce the number of amplitude steps offered to a patient. This may make it easier for patients to use and understand.
- *LibraXP*: The STEP value for lead 1 can be different than the STEP value for lead 2.

AMPLITUDE ADJUSTMENT MODE

Amplitude adjustment mode is accessible from the Home screen when amplitude limits have been enabled. See *SET AMP LIMITS* for information on enabling amplitude adjustment mode. See the *Home screen* section for information on accessing amplitude adjustment mode.

In this mode, the ⊕ and ⊖ buttons can be used to adjust stimulation amplitude in the same way that a patient provided with a QuikLink controller would do so.

Adjusting amplitude via amplitude adjustment mode is slightly different than doing so through programming mode, which may provide you with additional flexibility. Specifically:

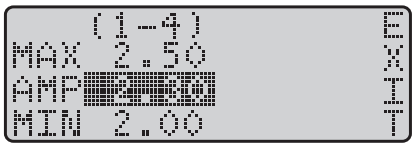
- Programming mode must be used to enable and configure amplitude limits, and to set all parameters. Amplitude adjustment mode only allows amplitude to be adjusted.
- Stimulation is turned off when entering programming mode, but not when entering amplitude adjustment mode.
- *LibraXP*: In amplitude adjustment mode, amplitude can be adjusted while stimulation is being delivered to both leads, whereas in programming mode it cannot.

Highlighting an AMP value and pressing:

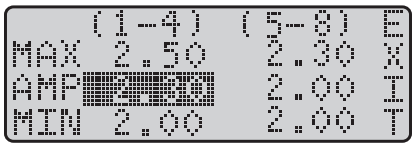
⊕ increases stimulation amplitude by an amount equal to STEP

⊖ decreases stimulation amplitude by an amount equal to STEP

Highlighting EXIT and pressing ✔ returns to the Home Screen.



Libra, Model 6608



LibraXP, Model 6644

CLEANING THE PROGRAMMER

Clean the programmer by wiping off the outer surface using a moist cloth and a small amount of mild soap. Do not submerge the controller in liquids or use a cloth that is saturated. Do not use alcohol, cleaning solutions, or solvents to cleanthe programmer.

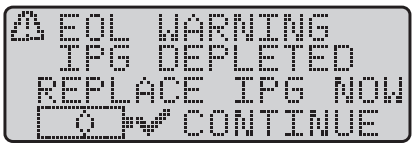
TROUBLESHOOTING

Daily Change in Stimulation Sensation

The Libra and Libra*XP* IPGs perform a battery diagnostic every 24 hours, which momentarily interrupts stimulation. If a patient reports a sensation that occurs at the same time every day, he or she is most likely sensing the battery diagnostic. For help reprogramming the IPG to alleviate this sensation, contact ANS Customer Service at +1-972-309-8000.

Neurostimulator Battery Warnings

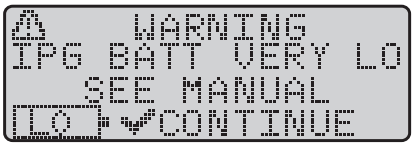
Libra neurostimulators contain circuitry to detect when their battery voltage has fallen below a preset "low battery" level, and when it has fallen below a preset "battery depleted" level. When this occurs, the programmer will display the corresponding warning.



IPG Battery Depleted Warning (EOL – End of Life)

When the "EOL warning" is displayed, the neurostimulator battery is depleted and stimulation may stop abruptly without further warning.

> ⚠ **WARNING: Schedule neurostimulator replacement surgery NOW.**
>
> The EOL Warning indicates that the neurostimulator battery is depleted and stimulation can abruptly stop at any time without further warning. Consider the effects that an abrupt cessation of stimulation and return of the underlying symptoms would have on this patient, and as appropriate, place the patient under continuous monitoring until surgery and/or make plans to manage the underlying symptoms.



IPG Battery Very Low Warning

When the "IPG Battery Very Low" warning appears, do the following

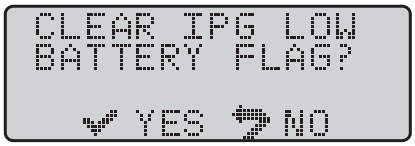
1. Enter programming mode.
2. Use GET STIM TIME to obtain the value of STIMDAYS. Write down this value.
3. Use CHECK IMPEDANCE to obtain the current value of the impedance factor.
4. Use APPENDIX C or D to calculate the estimated device longevity at the current stimulation parameters.
5. If STIMDAYS and the calculated longevity are approximately equal, then schedule replacement IPG surgery. Otherwise, call ANS Customer Service for assistance in determining whether or not to clear the IPG low battery flag.

Clearing an IPG Low Battery Flag

In certain situations, particularly when using low stimulation parameters and/or regularly turning the neurostimulator off, a neurostimulator may prematurely trigger a battery warning. This is caused by a battery passivation layer that will dissipate after the neurostimulator is used more. The neurostimulator is fully functional, and the battery has its full specified capacity. This situation may recur multiple times with the same neurostimulator.

To clear a low battery flag proceed as follows

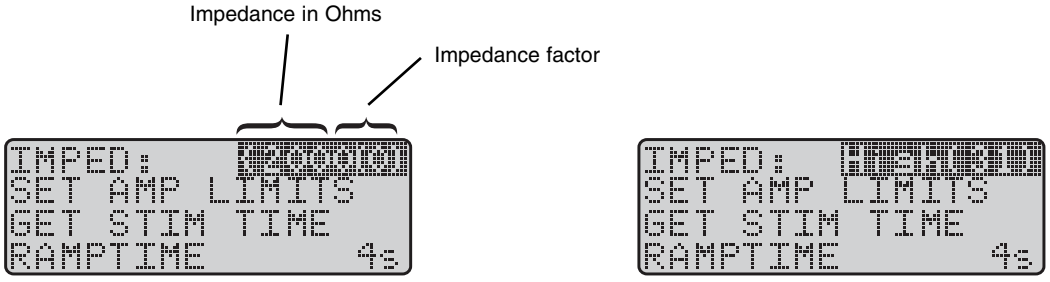
1. While the low battery warning is displayed on the screen, press the button, then the button.
2. When the following screen appears, press the button.



3. Instruct the patient to use their controller to check the battery status regularly and contact you if the low battery warning reappears. The low battery flag may need to be cleared more than once.

Impedance Measurements

Impedance measurements can be helpful for troubleshooting problems, or estimating device longevity. To obtain an impedance measurement, enter programming mode and use the CHECK IMPEDANCE action. After the impedance measurement is taken, the screen will appear as shown below. The impedance in ohms is displayed followed by the impedance factor in parentheses.



Keep in mind the following when interpreting impedance measurements:

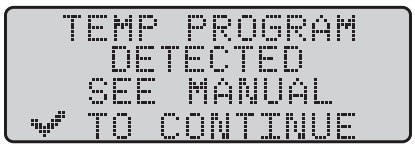
- **When the impedance factor is zero**: A zero impedance factor indicates that the neurostimulator output is very low. When the patient is receiving effective stimulation at this output, the device longevity will be very good (use Appendix C or D to calculate longevity). However, because the neurostimulator output is very low, it is not possible to obtain a definitive impedance measurement—only an estimate of the maximum value. For this reason, the impedance reading is always reported as being "< xxxx" (less than xxxxΩ) when the impedance factor is zero.

  NOTE: If the patient can tolerate it, AMP can be temporarily increased to the point that the impedance factor becomes non-zero, and thereby obtain a better impedance estimate. This value of the impedance factor should **not** be used for estimating longevity.

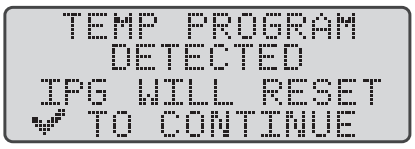
- **Erratic sequential impedance measurements**: Sequential impedance measurements taken at the same stimulation parameters should be consistent (±1 impedance factor). If you obtain very different impedance measurements at the same stimulation parameters, this may indicate a system problem. Contact ANS customer service for assistance.

- **HIGH impedance readings**: There are two situations in which the impedance will be reported as "HIGH." One is when the impedance is over 3000 Ohms. The other is when the impedance factor is 31. Impedance factor 31 indicates that the neurostimulator cannot deliver the required current. This may indicate that there is an open circuit. Contact ANS customer service for assistance.

TEMP PROGRAM



Libra, Model 6608



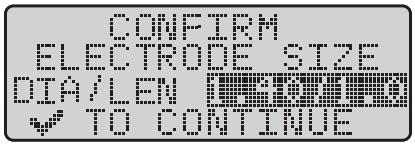
LibraXP, Model 6644

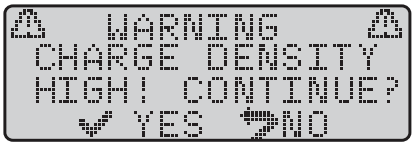
The temp program message indicates that the stimulation program was not correctly saved at the end of the prior programming session. When the programmer detects a temp program, it will not allow the neurostimulator to be turned on. Instead, the only option the programmer gives is to enter programming mode so that the stimulation parameters can be adjusted as necessary, and the program properly saved.

> **NOTE:** For Libra neurostimulators (Model 6608), the temp program stimulation parameters are retained when entering programming mode. So, if the patient was getting acceptable results from the temp program, then you can simply enter programming mode, and then immediately EXIT to properly save the program and correct this situation.
>
> For Libra*XP* neurostimulators (Model 6644), the program stimulation parameters are reset to factory defaults and stimulation is turned off. Enter programming mode and reprogram the IPG.

HIGH CHARGE DENSITY

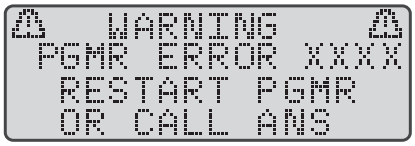
The programmer automatically checks every amplitude and pulse width increase request to determine if it will cause the maximum average charge density to be exceeded. If so, the programmer first asks you to confirm the electrode size (diameter and length). Then, if after the electrode size is confirmed, the charge density is too high, it displays the charge density warning shown below.



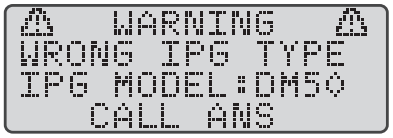


Selecting YES sends the requested increase to the neurostimulator and allows you to exceed the maximum recommended charge density. While the charge density is being exceeded, a warning symbol will appear next on the AMP and PW lines, and on the Home screen. Selecting NO cancels the requested increase.

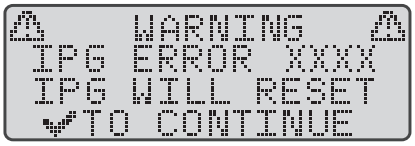
OTHER ERROR AND WARNING MESSAGES



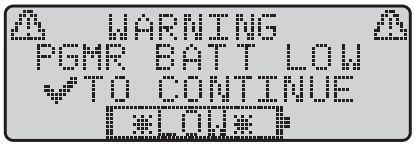
This message appears if the programmer detects a problem with its circuitry or software. Try restarting the programmer and replacing the batteries. If that fails, call ANS Customer Service to arrange service.



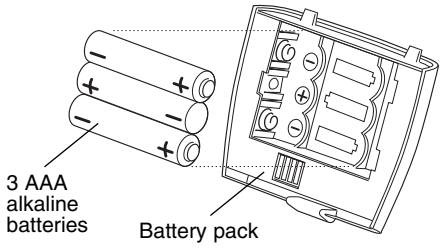
This message appears if the programmer detects an ANS neurostimulator that cannot be programmed with this model programmer. Call ANS Customer Service for instructions.



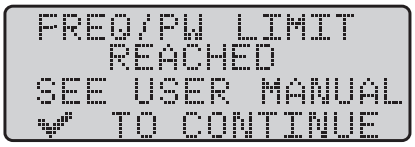
This message appears if the programmer detects an error in the neurostimulator or stimulation program. When this happens the neurostimulator is reset to its factory settings and turned off. Use the programmer to reprogram the neurostimulator and call ANS Customer Service for assistance as required.



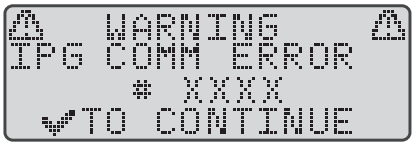
This message appears when the programmer detects that its batteries are low. Remove the battery pack from the back of the programmer and replace the batteries with 3 new AAA batteries as shown below.



NOTE: ANS recommends that you do not use rechargeable batteries. They may display an inaccurate battery capacity when you check your programmer's batteries. They will not affect a check of your IPG's battery capacity.



This message appears when the frequency or pulse width requested would exceed the capabilities of the IPG. (See Freq for details.) Decrease frequency so that pulse width can be increased, or vice versa.



This error occurs when the programmer was unsuccessful in its attempt to communicate with the neurostimulator. It may be possible to correct this by repositioning the wand over the neurostimulator, or moving away from sources of electromagnetic interference.

> **NOTE:** If the COMM error occurs while you are in programming mode, you will be taken to the Home screen and required to re-enter programming mode. In addition, the Libra*XP* will lose the changes made since the program was last saved.

CUSTOMER SERVICE INFORMATION

For help with an ANS product, including technical service or repairs, contact Customer Service using the following information:

Advanced Neuromodulation Systems
6901 Preston Road
Plano, TX 75024
USA

+1-972-309-8000
+1-972-309-8150 Fax

RETURNED MERCHANDISE POLICY

All returns must be accompanied by a Return Merchandise Authorization (RMA) number, which is available by contacting ANS Customer Service at 972-309-8000. Customer Service can only issue RMAs after receiving the original purchase order number, invoice date, and serial number information for the product.

REGISTRATION AND PATIENT IDENTIFICATION CARD

At time of implantation, the registration form included in the product's packaging should be completed and returned to ANS. This registration process will activate the system warranty and allow tracking of the product.

LIMITED WARRANTY

I. General Warning

A. Advanced Neuromodulation Systems, Inc. Libra Deep Brain Stimulation (DBS) Systems are comprised of implantable components, programmers, controllers, and patient accessories. The patient accessories may include a magnet. The implantable components include leads, lead kits, IPGs, IPG kits, extensions, and accessories. Upon being implanted, these components must withstand exposure to an extremely hostile and unpredictable environment in the human body. The implanted components may fail during or following implantation into the body for any one or a number of reasons, including, but not limited to, medical complications, body rejection phenomena, lead breakage, or improper handling, implantation, or use, or insulation breach.

B. Advanced Neuromodulation Systems, Inc. makes no representations or warranties that failure or cessation of function of any component, or the system, will not occur, that the body will not react adversely to implantation, or that medical complications will not develop.

II. LIMITED WARRANTY

A. LIMITATION OF WARRANTY

1. Advanced Neuromodulation Systems, Inc., 6901 Preston Road, Plano, TX 75024, warrants the Advanced Neuromodulation Systems, Inc.'s Libra DBS System to be free from defects in material or workmanship within one year from the date of implantation or ownership, subject to the terms and conditions contained in this warranty. Only patient-customers who receive an Advanced Neuromodulation Systems, Inc. Libra DBS System and return a properly completed warranty registration card to Advanced Neuromodulation Systems, Inc. within 60 days from the date of surgery may enforce this limited warranty.

2. THIS WRITTEN LIMITED WARRANTY CONTAINS THE FINAL, COMPLETE AND EXCLUSIVE STATEMENT OF WARRANTY TERMS FOR ADVANCED NEUROMODULATION SYSTEMS, INC. LIBRA DBS SYSTEMS, AND IT APPLIES IN LIEU OF ANY OTHER WARRANTY, EXPRESS OR IMPLIED. ADVANCED NEUROMODULATION SYSTEMS, INC. DISCLAIMS ALL IMPLIED WARRANTIES, INCLUDING THE WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE. NO PERSON IS AUTHORIZED TO MAKE ANY OTHER GUARANTEES, WARRANTIES OR REPRESENTATIONS ON BEHALF OF ADVANCED NEUROMODULATION SYSTEMS, INC. This limitation may not apply to you because some states and countries prohibit the limitation or exclusion of implied warranties. You may have other rights under state law not specifically addressed in this limited warranty.

B. THIS LIMITED WARRANTY FOR THE LIBRA DBS SYSTEM DOES NOT APPLY TO

1. Any damage caused by misuse, neglect, accident, modification, improper application, or from other than normal and ordinary use.

2. Any damage caused by any repair or attempted repair by anyone other than an authorized Advanced Neuromodulation Systems, Inc.-trained technician.

3. Any damage resulting from failure to clean or use in accordance with the Operating Instructions and/or Services Manual furnished by Advanced Neuromodulation Systems, Inc.

C. LIMITATION OF DAMAGES

ADVANCED NEUROMODULATION SYSTEMS, INC. DISCLAIMS LIABILITY FOR ANY DIRECT, INDIRECT, INCIDENTAL, OR CONSEQUENTIAL DAMAGE ARISING OUT OF, OR IN CONNECTION WITH, THE USE OR PERFORMANCE OF THE SYSTEM, WHETHER SUCH CLAIM IS BASED ON CONTRACT, TORT, WARRANTY, OR OTHERWISE. This limitation of liability applies to all warranty claims. No waiver or amendment of this limited warranty shall be valid unless in writing signed by Advanced Neuromodulation Systems, Inc. Some states, and countries, do not allow the exclusion or limitation of incidental or consequential damages, so the above limitation may not apply to you.

III. IMPLANTABLE COMPONENTS

A. Subject to Sections I and II and paragraph III(B) of this Limited Warranty, if any of the implantable components should fail to function due to a defect in material or workmanship during the warranty period, Advanced Neuromodulation Systems, Inc. will, at its option:

1. Replace the implantable component with an equivalent, or functionally equivalent, implantable component at no charge to the patient-consumer; or

2. Issue a credit to the patient-consumer for a replacement Advanced Neuromodulation System, Inc. implantable component, the credit being equal to the net invoice price for the replaced implantable component.

B. For repair, replacement, or credit under this limited warranty

1. The implantable component must be implanted prior to the expiration date indicated on the component's packaging, and

2. If the implantable component is explanted, the patient-consumer, his or her authorized representative, physician or hospital, must return the component to Advanced Neuromodulation Systems, Inc. The patient-consumer, or his or her authorized representative, must, at his or her own expense, mail or ship the product together with a Return Merchandise Authorization number obtained from Customer Service to Advanced Neuromodulation Systems, Inc. within 30 days after explantation. If the implantable component is not explanted, the component's serial number or lot number must be provided within 30 days after discovery of the defect.

3. Upon Advanced Neuromodulation Systems, Inc.'s receipt of the product, the returned implantable component shall become the exclusive property of Advanced Neuromodulation Systems, Inc.

IV. PROGRAMMERS, CONTROLLERS, AND PATIENT ACCESSORIES

A. Subject to Sections I, II, and paragraph IV(B) of this Limited Warranty, if any Libra DBS System programmer, controller, or patient accessory fails to function due to a defect in material or workmanship during the warranty period, Advanced Neuromodulation Systems, Inc. will, at its option

1. Repair any defective part of the programmer, controller, or accessory at no charge to the patient-consumer; or

2. Replace the programmer, controller, or accessory with an equivalent, or functionally equivalent, programmer, controller, or accessory at no charge to the patient-consumer; or

3. Issue a credit to the patient-consumer for a replacement Advanced Neuromodulation Systems, Inc. programmer, controller, or accessory in an amount equal to the net invoice price for the defective programmer, controller, or accessory.

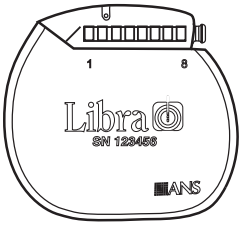
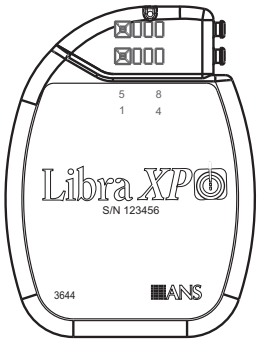
B. For repair, replacement or credit under this limited warranty:

1. The patient-consumer, or his or her authorized representative, must, at his or her own expense, mail or ship the product together with a Return Merchandise Authorization number obtained from customer service to Advanced Neuromodulation Systems, Inc. within 30 days after discovery of the defect.

2. Upon Advanced Neuromodulation Systems, Inc.'s receipt of the product, the returned component shall become the exclusive property of Advanced Neuromodulation Systems, Inc.

APPENDIX A: IPG SPECIFICATIONS AND KIT COMPONENTS

IPG SPECIFICATIONS

Model No:	**6608**	**6644**
		
	Libra	**Libra*XP***
Height:	1.96 in. (50 mm)	2.98 in. (76 mm)
Width:	2.11 in. (54 mm)	2.27 in. (58 mm)
Thickness:	0.54 in. (14 mm)	0.54 in. (14 mm)
Weight:	1.8 oz. (53 g)	2.93 oz. (83 g)
Volume:	1.75 $in.^3$ (29 cm^3)	2.99 $in.^3$ (49 cm^3)
Power Source:	Lithium Thionyl Chloride Cell	
Storage Temperature:	-10°C (14°F) and 55°C (131°F)	
Storage Humidity:	10% to 90%	
Storage Pressure:	70-150 kPa (10.2-21.8 psi)	
Connector Strength:	Exceeds EN45502-1 Requirements	

OPERATIONAL SPECIFICATIONS

Libra

Parameter	**Range**	**Steps**
Pulse Width	52–507 µs	13 µs
Frequency	2–240 Hz	2 Hz
Amplitude	0–12.75 mA	0.05–.75 mA

LibraXP

Parameter	**Range**	**Steps**
Pulse Width	52–507 µs	13 µs
Frequency	2–200 Hz	2 Hz
Amplitude	0–12.75 mA	0.05–.75 mA

KIT COMPONENTS

Each model #6608 kit includes the following:

1 each 8-Channel Libra IPG
2 each Connector Strain Reliefs
1 each Torque Wrench
1 each Port Plug
1 each Registration Form
1 each Clinician's Manual
1 each Temporary Identification Card

Each model #6644 kit includes the following:

1 each Dual 4-Channel Libra*XP* IPG
2 each Connector Strain Reliefs
1 each Torque Wrench
2 each Port Plugs
1 each Registration Form
1 each Clinician's Manual
1 each Temporary Identification Card

APPENDIX B: LIBRA CLINICIAN PROGRAMMER SPECIFICATIONS AND KIT COMPONENTS

SPECIFICATIONS

Dimensions:	6.8 cm (2.7") x 10.77 cm (4.2") x 2.6 cm (1")
Weight:	128 grams (4.6 oz.)
Storage Temperature:	-20°C to + 60°C (-4°F to + 140°F)
Storage Humidity:	10% to 90%
Storage Pressure:	70-150 kPa (10.2-21.8 psi)
Operating Temperature:	10ºC to 40º C (50ºF to 104ºF)
Operating Humidity:	30% to 70%
Operating Pressure:	70-106 kPa (10.2-15.4 psi)

Each model #6850 kit includes the following:

- 1 each Libra Clinician Programmer
- 1 each Battery Pack
- 3 each AAA Batteries
- 1 each Programming Wand
- 1 each Magnet
- 1 each Carrying Case
- 1 each Manual

FCC statement (FCC ID: PX 2001). This neurostimulation equipment has been tested and found to comply with the limits for a Class B digital device, pursuant to part 15 of the FCC Rules, if this programmer does interfere with other equipment, which can be determined by turning the programmer off and then on again, either: reorient or relocate the equipment; or increase the separation between the programmer and the equipment.

NOTE: Changes or modifications to this product not authorized by ANS could void the FCC certification and negate your authority to operate this product.

APPENDIX C: BATTERY LONGEVITY FOR LIBRA

The battery life of the IPG depends on the parameters you have selected, the impedance that the current encounters in the neurostimulation circuit, and the hours per day it is used. To optimize the Libra IPG battery life for patients who require programming parameters resulting in Impedance Factors equal to or greater than one (1), try reducing the amplitude slightly and increasing the pulse width. Doing so may lower the impedance factor and reduce battery drain. This Appendix provides the information necessary to calculate the initial estimated life of the Libra IPG. These estimates are based on the selected stimulation parameters and will account for the electrode impedance.

LIBRA DBS SYSTEM LONGEVITY CALCULATION

To estimate the battery life of an implanted Libra DBS System, perform the following calculations:

NOTE: Please contact ANS to determine the longevity for any reading with an impedance factor greater than 8 or for any frequency above 200 Hz.

Step One **-** Determine **Value 1** using the Libra Clinician Programmer and the following chart.

Impedance Factor	Value 1
0	1
1	1.76
2	1.72
3	1.73
4	1.78
5	1.84
6	1.92
7	2.01
8	2.10

Step Two **-** Use **Value 1** and the parameters currently set on the patient's Libra DBS System to solve the following equation:

_____ x _____ x _____ x _____ = _____ = **A**
Pulse Width **Frequency** **Amplitude** **Value 1**

Step Three **-** Determine **Value 2** by matching the patient's **Frequency** to the **Impedance Factor** using the following chart:

Value 2 Calculation			
	Impedance Factor		
Frequency	**0**	**1–4**	**5–8**
2–50	0	3,200	3,600
52–100	0	6,400	7,000
102–150	0	9,600	10,500
152–200	0	12,500	13,500

Value 2 = _____ = **B**

Step Four - Determine **Value 3** using the Libra Clinician Programmer and the following chart:

Impedance Factor	Value 3
0	203
1	205
2	213
3	221
4	231
5	242
6	253
7	265
8	278

Value 3 = _____

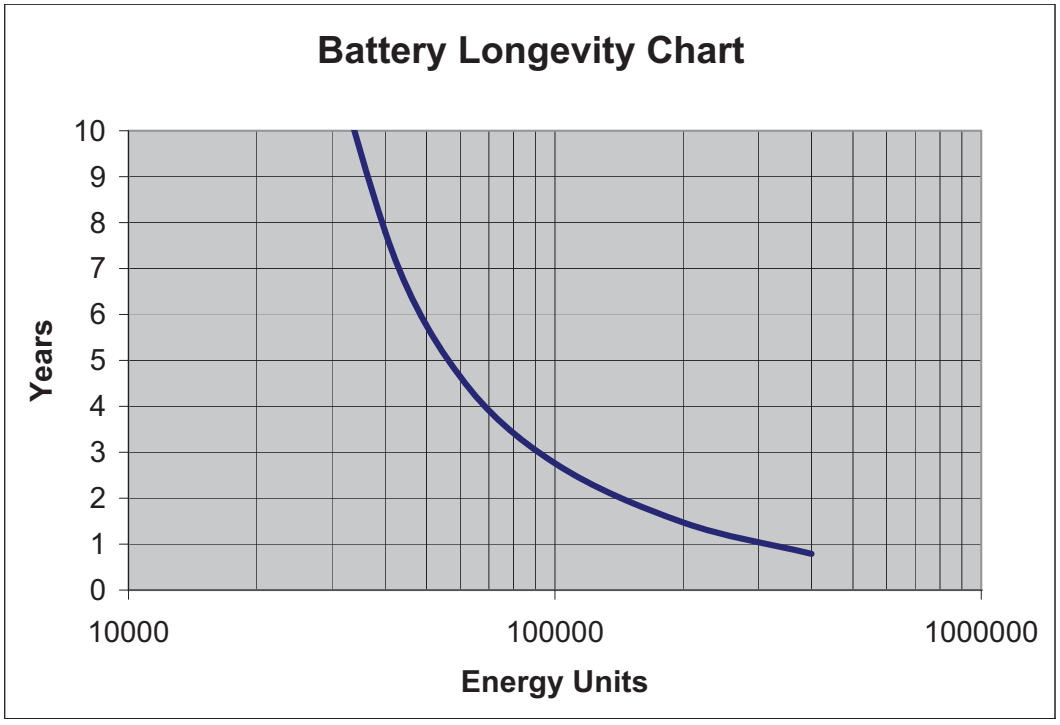
Step Five - Solve the following equation:

$$\frac{\text{_____}}{\textbf{(Pulse Width + 200)}} \times \frac{\text{_____}}{\textbf{Frequency}} \times \frac{\text{_____}}{\textbf{Value 3}} = \frac{\text{_____}}{\textbf{1,000}} = \textbf{C}$$

Step Six - Use results **A**, **B**, and **C** from the previous steps to find the total energy units.

$$\frac{\text{_____}}{\textbf{A}} + \frac{\text{_____}}{\textbf{B}} + \frac{\text{_____}}{\textbf{C}} + \frac{15{,}000}{\textbf{Constant}} = \text{TOTAL ENERGY UNITS} = \text{_____}$$

Step Seven - Using the **Total Energy Units** from Step Six, find the corresponding energy units along the x-axis of the Libra Battery Longevity Chart, follow the vertical line up until it intersects with the longevity curve, and then follow the horizontal line over to the y-axis to find the estimated longevity (years).



NOTE: The battery longevity chart above is a logarithmic chart. Each vertical line to the left of the center line labeled "100,000" is equal to 10,000 energy units. Each vertical line to the right of the center line labeled "100,000" is equal to 100,000 energy units.

APPENDIX D: BATTERY LONGEVITY FOR LIBRA*XP*

BATTERY LONGEVITY—LIBRA*XP* IPG

The battery life of the IPG depends on the parameters you have selected, the impedance that the current encounters in the neurostimulation circuit, and the hours per day it is used. To optimize the LibraXP IPG battery life for patients who require programming parameters that result in Impedance Factors equal to 1 or greater, try reducing the amplitude slightly and increasing the pulse width to compensate. This may result in a lowing the impedance factor and reducing battery drain. This appendix provides the information necessary to calculate the initial estimated life of a Libra*XP* IPG. These estimates are based on the selected stimulation parameters and account for electrode impedance.

LIBRA SYSTEM LONGEVITY CALCULATION

To estimate the battery life of an implanted Libra*XP* IPG, perform the following calculations:

> **NOTE:** Please contact ANS to determine the longevity for any reading with an impedance factor greater than 8 or for any frequency above 190 Hz.

Step One - Determine **Value-1** using the Libra Clinician Programmer and the following chart:

Impedance Factor	**Value-1**
0	1
1	1.76
2	1.72
3	1.73
4	1.78
5	1.84
6	1.92
7	2.01
8	2.10

Step Two - Use **Value-1** and the parameters currently set on the patient's Libra DBS System to solve the following equation:

_____ x _____ x _____ x _____ = _____ = **A1**
Pulse Width (Stim Set 1) **Frequency** **Amplitude (Stim Set 1)** **Value-1**

_____ x _____ x _____ x _____ = _____ = **A2**
Pulse Width (Stim Set 2) **Frequency** **Amplitude (Stim Set 2)** **Value-1**

A1_____ + **A2**_____ = **A** _____

> **NOTE:** If only one side is implanted and turned on, the value for the other side will be zero.

Step Three - Determine **Value-2** by matching the patient's **Frequency** to the **Impedance Factor** (see page 34) using the following chart:

Value-2 Calculation			
	Impedance Factor		
Frequency	**0**	**1-4**	**5-8**
2–50	0	3,200	3,600
52–100	0	6,400	7,000
102–150	0	9,600	10,500
152–190	0	12,500	13,500

Value-2 = _____ = B

Step Four - Determine **Value-3** using the Libra Clinician Programmer and the following chart:

Impedance Factor	**Value-3**
0	203
1	205
2	213
3	221
4	231
5	242
6	253
7	265
8	278

Value-3 = _____

Step Five - Solve the following equation:

_____ x _____ x _____ = _____ = **C1**
(Pulse Width [Stim Set 1] + 200) **Frequency** **Value-3** **1,000**

_____ x _____ x _____ = _____ = **C2**
(Pulse Width [Stim Set 2] + 200) **Frequency** **Value-3** **1,000**

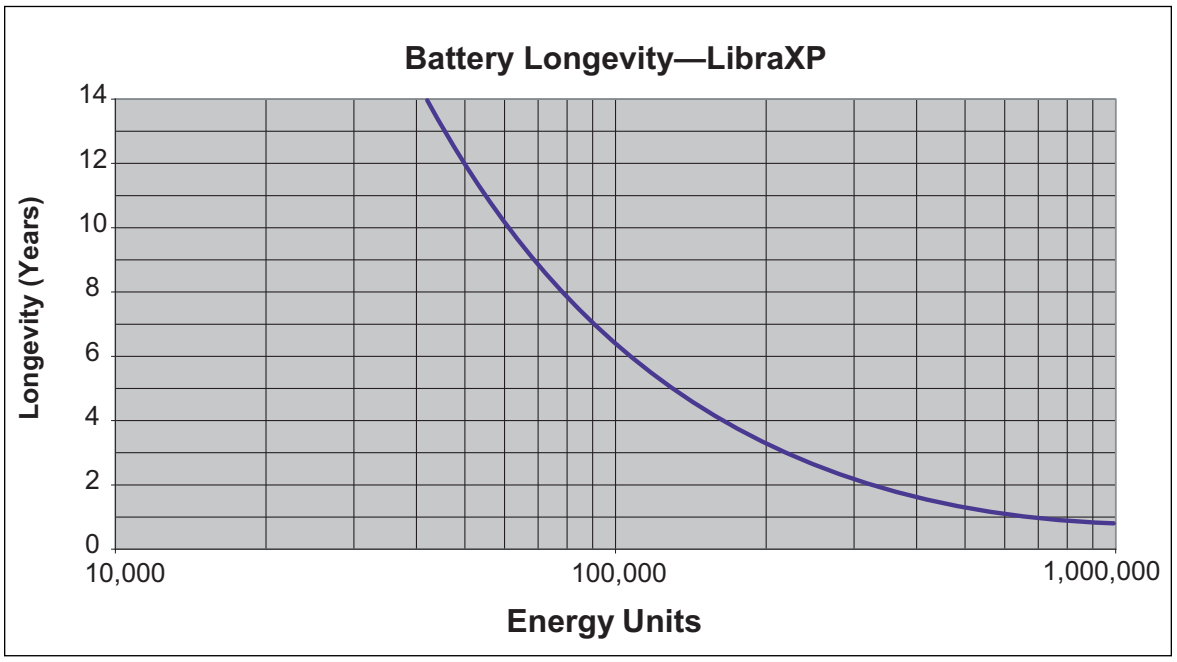
C1_____ + **C2**_____ = **C** _____

NOTE: If only one side is implanted and turned on, the value for the other side will be zero.

Step Six - Use results **A**, **B**, and **C** from the previous steps to find the total energy units.

$$\underset{\textbf{A}}{\_\_\_\_\_} + \underset{\textbf{B}}{\_\_\_\_\_} + \underset{\textbf{C}}{\_\_\_\_\_} + \frac{15{,}000}{\textbf{Constant}} = \_\_\_\_\_ = \text{TOTAL ENERGY UNITS}$$

Step Seven - Using the **Total Energy Units** from Step Six, find the corresponding energy units along the x-axis of the LibraXP Battery Longevity Chart, follow the vertical line up until it intersects with the longevity curve, and then follow the horizontal line over to the y-axis to find the estimated longevity.



NOTE: The Battery Longevity Chart above is a logarithmic chart. Each vertical line to the left of the center line labeled "100,000" is equal to 10,000 energy units. Each vertical line to the right of the center line labeled "100,000" is equal to 100,000 energy units.

APPENDIX E: LIBRA SYSTEM AND MRI SAFETY FOR THE LIBRA IPG

MRI ASTM Guidelines

Risks

MRI machines have the potential to induce deflection, torque, and heating of implanted medical devices. Additionally, implanted medical devices can interfere with the MRI to create artifacts in the resulting image. ASTM Test Standards have been developed to quantify these effects in order to evaluate the safety concerns involving MRI scans on patients with an implanted medical device.

Testing and Results

Testing was conducted on the Libra DBS Systems (Libra and Libra*XP* IPGs) to determine the affect of the MRI environment on the implanted system. The induced mechanical forces, torque and deflection, were evaluated under worst-case conditions in a 1.5T MRI magnet. The MRI scanner, the software used, and the parameters under which the scans were conducted are inherent to the results of any testing. The following testing was performed using a 1.5T GE Medical Systems LX Echospeed System with 9.0 software. The system's magnet was a superconducting, cylindrical self-shielded, LCC magnet (CX-K4) manufactured by GE Medical Systems. The MRI environment induced no mechanical forces on the leads or extensions used with the Libra DBS System. This is explained by the lack of magnetic materials in the lead and extension. The Libra and Libra*XP* IPGs experienced mechanical forces less than the maximum torque and deflection on the device due to gravity. The maximum mechanical force due to gravity is considered to be a conservative criteria by the ASTM standards.

Quantitative analysis of RF heating on the Libra DBS Systems was conducted *in vitro* using a 16-rung, quadrature birdcage, transmit/receive headcoil (GE Medical Systems, Model 46-282118G2). Although this testing following the applicable ASTM standard showed minimal heating at higher SAR levels, the maximum recommended SAR level of 0.4 W/kg should be followed for clinical MRI scanning of patients with implanted medical devices. All scanning should be limited to a head-only, transmit and receive head coil in a 1.5T MR System. Configurations were tested with one loop approximately 3–4 cm in diameter at the burr hole site and 1–1.5 loops approximately 4–4.5 cm in diameter beneath the IPG.

For the Libra IPG: At a Specific Absorption Rate (SAR) of 3.1 W/kg, the maximum temperature rise was 4.6 degrees Celsius when testing a unilateral implant; at an SAR of 1.7 W/kg, the maximum temperature rise was 2.5 degrees Celsius for a unilateral implant. At an SAR of 3.1 W/kg, the maximum temperature rise was 6.2 degrees Celsius when testing a bilateral implant; at an SAR of 1.7 W/kg, the maximum temperature rise was 2.4 degrees Celsius for a bilateral implant.

For the dual header Libra*XP* IPG: At an SAR of 3.1 W/kg, the maximum temperature rise was 3.8 degrees Celsius when testing a unilateral implant. For a bilateral configuration with the extensions less than 0.25 cm apart, the maximum heating at an SAR of 1.6 W/kg was 4 degrees Celsius at the left tip electrode and 2.9 degrees Celsius at the right tip electrode.

Artifact testing was conducted on the Libra DBS Systems to determine the extent of image distortion. Image distortion occurs within 1.0 cm of the lead, 2.8 cm of the extension, 10.4 cm of the Libra IPG, and 12.7 cm of the Libra*XP* IPG. These distortion areas should be used as a guideline to anticipate image disruption due to the implanted device. Implanted devices are unlikely to impair the diagnostic use of MR imaging when the area of interest is beyond the distortion area listed for the specific device. Artifact testing was conducted at worst-case conditions and followed the applicable ASTM standard.

MRI Safety Guidelines

Implant Recommendations

- The Libra DBS Systems should be implanted as close to the centerline of the patient as possible. Avoid unnecessary offset of the IPG and extensions. Safety testing was conducted with the lead tip within 0.5 cm, the extension within 5.7 cm, and the IPG center within 9 cm of the centerline.
- Placing a loop in the lead and beneath the IPG allows for strain relief of the system at the connection points. Heating tests were conducted with a loop approximately 3–4 cm in diameter at the burr hole and one and a half loops approximately 4–4.5 cm in diameter beneath the IPG.
- Avoid implanting the IPG in the mid to lower torso of the patient and avoid unnecessary offset of the system. Safety testing was conducted with the IPG in the upper torso, 28 cm below the landmark and within 9 cm of the centerline.
- Avoid separation of the extensions when using a Libra*XP* IPG for bilateral stimulation. Separation of the extensions increases the distance of one extension along the y-axis away from the centerline of the magnet when scanning a patient in the upright, supine position.

Pre-scan Preparation

An appropriate health care professional with access to a Libra Clinician Programmer should be available to assist and prepare the patient's device for the MRI procedure as described below:

- The patient should be in the supine position when in the magnet to bring the implant as close to the centerline of the magnet as possible.
- If the IPG has already been implanted, record the patient's current therapeutic settings, set the IPG's amplitude to 0 mA, set the Magnet mode to Off, and turn the IPG output to Off.
- Instruct the patient to alert the MRI system operator of any problems (heating, shocks, vision impairment, etc.) so the operator can terminate the MRI if needed.

  CAUTION: Due to the risk of localized heating that may result in tissue damage, an MRI procedure should not be performed on a patient with a Libra DBS System that is suspected to have a broken lead or extension wire. If a broken lead or extension wire is suspected, an x-ray should be obtained prior to an MRI to verify the presence of the broken wire. Additionally, the test procedure detailed in Appendix I may be run on the Libra DBS System to test for an open circuit due to broken lead or extension wires.

MRI Scanner Parameters and Settings

- Use only MRI systems operating at a static magnetic field strength of 1.5 Tesla.
- Use only a transmit and receive type RF head coil to minimize the exposure of the Libra DBS System to the MRI RF fields. Do not use a whole body RF coil, a head coil that extends over the chest area, a head coil that is not both a transmit and receive type RF coil.
- Select imaging parameters to perform MRI at a specific absorption rate (SAR) that does not exceed 0.4W/kg in the head.
- Carefully perform continuous verbal and visual monitoring of the patient throughout the MRI procedure.
- Discontinue the MRI if the patient experiences any pain or discomfort or if you suspect heating or other problems with the implanted components.

Post-scan Evaluation

- Verify that the IPG is functional.
- Reprogram the stimulation parameters to pre-MRI values, if necessary.

ANS

A St. Jude Medical Company

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Plano, Texas 75024, USA
+1-972-309-8000
+1-972-309-8150 Fax
sjmneuro.com

37-1128-01C
JAN 11

16.2 Appendix B: Sample Informed Consent

SUBJECT INFORMATION AND CONSENT FORM

NAME OF RESEARCH STUDY: A clinical evaluation for the management of patients with Major Depressive Disorder, single or recurrent episode, with deep brain stimulation.

SPONSOR: Advanced Neuromodulation Systems, Inc. (ANS)
6901 Preston Rd.
Plano, TX 75024

PRINCIPAL INVESTIGATOR:

RESEARCH STUDY ADDRESS:

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or procedures that you do not clearly understand.

You are being asked to take part in a research study. However, before you agree to take part in this study, please read this consent form. Please ask as many questions as you need to be sure you understand the possible risks and benefits.

It is important for you to understand that, if you participate in the study, you are required to transfer your psychiatric care to the study psychiatrist for the length of the study. The study psychiatrists will need to be able to have access to a sufficient amount of your psychiatric medical history in order to verify eligibility for the study.

This consent form contains important facts to help you decide if it is in your best interest to take part in this study. If you have any questions that are not answered in this consent form, one of the research staff will be happy to give you further information.

Introduction

You are being asked to participate in a one year research study of a new surgical procedure to treat severe depression. The procedure is called Deep Brain Stimulation (DBS). This procedure requires an operation on your brain to place DBS electrodes. The DBS system used in this study (trade name Libra® Deep Brain Stimulation System from Advanced Neuromodulation Systems) is not approved by the Food and Drug Administration (FDA) for clinical use and is considered a "significant risk" device. This system has been approved by the FDA for use in this experiment.

The DBS electrodes will provide electrical stimulation to a part of your brain called the subgenual cingulated cortex or Brodmann Area 25 (cg25). You are being asked to participate in the study because you have a severe form of depression that has not responded to several standard treatments.

The goal of the present study is to evaluate the safety and efficacy of DBS (stimulating Brodmann 25) in the treatment of severe depression. DBS refers to the electrical stimulation of structures deep within the brain. Brodmann Area 25 is a part of your brain about the size of a

sugar cube near the front and middle of your brain thought to control mood. DBS is not currently approved to treat severe depression. You will be one of 201 people, from up to 20 sites, who take part in this study.

The study doctor in charge of this study or a member of the study staff has discussed with you the requirements for participation in this study. It is important that you are completely truthful with the study doctor and staff about your health history. You should not participate in this study if you do not meet all qualifications.

CRITERIA FOR PARTICIPATION

To participate in this study you must be currently depressed. You must be a male or female between the ages of 21-70. You must have failed several treatments for depression. If you are currently taking antidepressant medications, you must have been on these medications at the same doses for the 4 weeks prior to enrolling in the study and the first six months of the study (unless side effects require a decrease in dose). You must currently be receiving care from a psychiatrist. You must be willing to transfer your psychiatric care to the study psychiatrist for the length of the study. You must also be willing to sign a written release of information to allow the study team to share information with your psychiatrist about your participation in this study and for your psychiatrist to share information with us.

You cannot participate in this study if it is not safe for you to have general anesthesia required for surgery. You cannot participate if you are currently suicidal or have had more than 3 serious attempts in the past 12 months. You cannot participate if you have been diagnosed with fibromyalgia, chronic fatigue disorder, a history of major psychotic episodes, chronic pain disorders requiring certain medication, substance abuse or dependence in last 12 months (e.g. alcohol, medication, cocaine, marijuana), neurological disorder that impairs motor, sensory or cognitive functions, bipolar I or II disorder, and other types of psychiatric disorders. You cannot participate if you have a diagnosis of sleep apnea that is not currently treated. You cannot participate if you are pregnant or planning to become pregnant during the study. You cannot participate if you have a cardiac pacemaker or other implanted electrical device. You cannot participate in this study if you have had electroconvulsive therapy (ECT) in the last three months or will require ECT for the duration of this study. You cannot participate if you have a history of epilepsy or status epilepticus. You cannot participate if you plan to use diathermy at any time during the study. You cannot participate if you have any metallic implants such as aneurysm clips in the vicinity of Brodmann Area 25 or cochlear implants your study doctor feels may interfere with the implant of the ANS device. You cannot participate in this study if you are currently participating or plan to participate in another investigational device, drug or surgical study. You also may not participate in this study if you have any medical conditions requiring an MRI; Conditions that require chemotherapy for the treatment of a malignancy or requiring chronic oral or intravenous steroid therapy; Females lactating or of child bearing potential, with a positive pregnancy test or not using adequate birth control; and/or a medical condition requiring hospitalization in the next year.

Procedures

Screening Visits
After enrolling in the study, you will have three screening visits in order to determine your eligibility to be in this study. There will be at least two weeks between each visit.

During the first screening visit, your doctor will determine whether you are eligible for the study. This visit will include recording your current condition and symptom. The first screening visit will take about four hours to complete. At this visit, the following procedures will occur:

- You will be asked about your medical and family history, current health problems and medications;
- You will have a physical exam;
- If you are female, you may be asked to provide a urine sample for a pregnancy test;
- You will be asked to complete several questionnaires regarding your mood and your quality of life;
- The study psychiatrist will ask you questions about your mood, functioning, physical symptoms and quality of life.

Some of your answers will be videotaped.

During the second screening visit, the doctor will ask you several questions about your mood and symptoms. You will also be asked to complete some questionnaires. This visit will take about 60 minutes.

The third screening visit will occur at least two weeks before surgery. During this visit, the doctor will ask you several questions about your mood and symptoms. If you qualify for the study after answering the questions, you will meet with the neurosurgeon that will explain the procedure, and perform an exam to make sure you can have surgery. You will schedule a time for several tests on your memory and cognitive function (how your thought processes are working). You may also schedule a Magnetic Resonance Imaging (MRI) scan before the surgery. This is a picture of your brain, which will allow the neurosurgeon to rule out any problems. You will not feel any pain as part of this scan. Because of the number of these tests, this visit could take up to four hours.

Medications
You may continue to take antidepressant and other medications during this study. However, you must stay on the same medications at the same doses during the four weeks prior to enrolling into the study and during the 6 months following surgery (excluding sleep aids and other meds to manage non-depression related conditions).

Neurosurgical Exam
You will meet with the neurosurgeon who will explain the planned surgical procedure. The neurosurgeon will perform a detailed physical examination. A small amount of blood (about 30-40 milliliters or 3-4 tablespoons) will be drawn. The neurosurgeon will review your blood and urine tests to make sure that you are medically able to undergo brain surgery. You will sign a separate surgical consent just prior to the operation.

Surgery

You will be admitted to the hospital on the morning of the surgery. A MRI scan will be obtained and used in the operating room to place the surgical frame and the DBS electrodes.

DBS system includes:

- Two **leads**, which consists of insulated wires with four electrodes at the end
- Two **extensions**, which connects the lead to the power source
- **Implantable Pulse Generator (IPG),** which is the power source.

The IPG is a metal "can" about 2 inches in diameter and about ½ inch thick that is inserted like a pacemaker under the skin. It contains a small battery and produces the electrical impulses needed for stimulation. Battery life varies for each patient, depending on the type and intensity of stimulation needed for good symptom relief. For patients using electrical stimulation to treat disabling tremor and chronic pain, battery life has typically been three to five years when used continuously. When it is time to replace the battery, minor surgery is required to remove the used IPG and insert a new one.

In the operating room, local anesthesia will be used to numb your scalp, an incision measuring approximately 2 inches long will be made on each side of your head, and then two holes will be placed in the top of your skull (one on each side of your head) to obtain access to your brain. The neurosurgeon will then insert two small electrodes into your brain. The electrodes contain special contacts attached to tiny wires that come out of the holes made in your skull.

Immediately after insertion of the electrodes, you will have a second procedure (approximately 45 minutes under general anesthesia) to connect the electrodes to the extension cable that is tunneled under the skin behind your ear, and this is then connected to the IPG which will be placed below your collarbone, just under your skin. Following surgery, you will have an image taken to make sure that the electrodes are in the right place.

Randomization

There will be 2 groups in the study. The group you are assigned to will be chosen by chance (like flipping a coin). This will happen only after the surgery is completed. At that time, you will be randomly assigned to treatment Group A or Group B. You have a 67% chance (2 out of 3) of being in Group A. You have a 33% chance (1 out of 3) of being in Group B. If you are randomly assigned to Group A your doctor will turn your DBS system on. If you are randomly assigned to Group B your DBS system will not be turned on until 6 months after your system has been fully implanted.

Neither you nor the study doctor will know which group you are in.

Follow-up visits

After the system implant, the study period will last approximately 12 months.
You will return to the neurosurgeon's office within 2 weeks after surgery to check your wounds and healing process. You will also need to return to the study psychiatrist's office 14 times for study related visits, which will occur 2 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months and 1 year after your

Patient Initials _____

system has been fully implanted. You will receive a phone call a few days before each visit, to remind you of your upcoming appointment. You will also be assigned a case manager from the study psychiatrist's office who will keep in contact with you throughout the length of the study.

Case Manager Visits
You will have scheduled visits with your case manager a minimum of every two weeks to a maximum of weekly for the length of the study. The case manager will follow your care for the duration of the study.

Post-operative follow up visit (within weeks after surgery)
This visit will occur within two weeks after surgery at the neurosurgeon's office. The following procedures will occur:

- Your neurosurgeon will ask if you have had any complications since surgery
- Your neurosurgeon will check your wounds for any sign of infection, to possibly remove sutures and to make sure you are healing properly.

Weeks 2, 4, 6 and 8, and Months 3, 4, 5, 7, 8, 9, 10 and 11 Visits
At these visits, the following procedures will occur:

- You will be asked if you have had any complications since your last visit
- The doctor will ask you several questions about your mood, in order to assess your level of depression
- You will be asked to complete a questionnaire to assess your mood and quality of life
- This visit will include programming on your system, if necessary, to optimize your system.

The visit will take about 60 minutes. Some of your answers at 3 month visit will be videotaped.

6 Month Visit
This visit will include the following procedures:

- You will be asked if you have had any complications since your last visit
- You will have a psychiatric evaluation. The doctor will ask you several questions about your mood and symptoms. This is in order to assess your level of depression
- You will be asked to complete a questionnaire to assess your mood and quality of life
- Your visit will include programming to optimize your system, if necessary
- You will also have several tests on your memory and cognitive function (how your thought processes are working)

This visit will take about four hours. Some of your answers will be videotaped.

12-Month Visit
This visit will include the following procedures:

- You will be asked if you have had any complications since your last visit
- You will have a psychiatric evaluation. The doctor will ask you several questions about your mood and symptoms. This is in order to assess your level of depression
- You will be asked to complete a questionnaire to assess your mood and quality of life
- Your visit will include programming to optimize your system, if necessary
- You will also have several tests on your memory and cognitive function (how your thought processes are working)

This visit will take about four hours.

Patient Initials _____

At the end of this study, you will be asked to participate in a long-term study. The study staff will tell you more about that study at that time. You will be given a separate informed consent form for that study.

Risks and Discomforts

This study is designed to test a new treatment for your depression. There may be some risks, discomforts, or side effects that are not yet known.

Risk of Surgery

As with any surgery, there are risks involved from the surgery and/or the anesthesia. Your doctor will discuss these with you. The risk of serious complications from surgical placement of the electrodes is estimated at 8-10%. This is based on known risks of similar surgery done in different brain targets for the treatment of Parkinson's disease and other conditions. The most serious risk of surgery is bleeding into the brain (7-8%). Bleeding into the brain can lead to death or stroke that may result in permanent neurological deficits (8-9%), including weakness, paralysis, seizures or convulsions, difficulty speaking, impaired thinking and loss of feeling. The risk of death with the general anesthesia for implantation of the pacemaker is small. Damage to brain tissue might also be experienced. There is also a possibility of bleeding under the skin of your scalp. You may experience pain, discomfort and/or swelling at the sites of the incisions in the head and chest, and at the sites where the pins of the stereotactic frame go. These problems generally go away within 1 week. You can also have air entering the veins or brain which can cause damage. Air entering the brain may cause confusion leading to an extra day stay in the hospital. Cerebrospinal fluid or fluid around the brain may leak or be found to be abnormal during the surgery. An additional surgery may be necessary to manage some complications.

Risk of DBS Treatment

While using the device several complications can occur. Occasionally, you might experience headache, disequilibrium (unbalance feeling), paresis (partial loss of limb movement), sleep disturbance, and sensory deficit. Less common complications would include neuralgia (painful feeling of nerves), cognitive impairments (confusion, abnormal thinking, hallucinations, alteration of mentation, amnesia, delusions or dementia), ataxia (loss of coordination of legs or trunk muscles), hearing and visual disturbance, apathy, eye disorder, drowsiness, difficulty breathing, increased salivation, rapid heart rate, pneumonia, edema including periorbital (swelling), and syncope (fainting). Some rare complications include neuropathy (problems with nerves) and myoclonus (jerking or twitching movements). Other complications that might occur during the study include fever, attention deficit, dysarthria (slowed or slurred speech), suicide or suicide attempt, increase in drug side effects, autonomic instability (change in vital signs), urinary incontinence, worsening depression symptoms, anxiety, ruminativeness, hypomania, mania, panic attacks, obsessive compulsive disorder (OCD) symptoms, psychosis, sweating, diarrhea, and nausea and/or vomiting.

Risk of Device

It is also possible that an implanted electrode or IPG may move, break or become dislodged. There is also the chance of allergic reaction to the device. Care must be taken to see that implanted devices do not become infected. This could cause an infection not only in the area of the implanted device, but an infection that involves the whole body. Such an infection would require treatment with antibiotics and possibly surgery to remove the stimulation system. The risk of infection or malfunction of the DBS device and/or IPG is about 10.6%. It may be

necessary to remove the DBS device. Reasons for removing the device include damage to device or infection that does not respond to antibiotics. If your depression does not improve over time or you experience a worsening in your clinical condition, the investigators will discuss with you the options of removing the device. Removal of the device has a very low risk of serious complications but they are the same as those associated with surgical implantations of the device (see above). The loss of therapeutic response, tingling sensation, initial jolt or tingling during start of the device, undesirable changes in stimulation, or wearing away of skin over IPG site, burr hole cap or extensions, persistent pain or redness at IPG site or extension may result as a complication related to the device.

At a Neurological Devices Advisory Panel held in March 2000, data was presented that found that during a study of Parkinson's disease patients receiving deep brain stimulator implantations (in a different part of the brain), 139 of 159 patients experienced one or more adverse events. Serious adverse events were experienced by 52.2% of patients including 6.3% of patients who experienced hemiparalysis or hemiparesis in the one study. The rate of any adverse event was about 88%. In that study the system was implanted into either the globus pallidus or the subthalamic nucleus, which are two different locations in the brain. In 2002, the device was approved by the FDA for "bilateral stimulation of the internal globus pallidus (Gpi) or the subthalamic nucleus (STN) as an adjunctive therapy in reducing some of the symptoms of advanced, levodopa-responsive Parkinson's disease that are not adequately controlled with medication." The device used in the study reported was made by a different manufacturer but is similar to the ANS device you will be receiving. It cannot be determined at this time whether the risks will be more, less or the same as those reported at the panel meeting. If you have any questions regarding the risks that could occur, please discuss your concerns with your implanting physician.

You may require additional neurosurgical procedures to manage one of the complications listed above, or to replace a fractured lead. You may also require further surgical procedures to replace the IPG device when the battery expires.

<u>Additional risks of having a DBS system</u>:

You should not be exposed to diathermy (deep heating) treatments that are sometimes used for muscle relaxation. Energy from diathermy can be transferred through the implanted system and can cause tissue damage at the location of the implanted electrodes, resulting in severe injury or death. Please be aware that you should always inform your health care providers that you have an implanted DBS system and should not be exposed to any type of diathermy.

You should not be exposed to repeat Magnetic Resonance Imaging (MRI). MRIs have the potential to induce repositioning, rotation, and heating in implanted medical devices. Exposure to MRI with an implanted DBS system may also cause permanent neurological damage or even death. If you need regular MRI to monitor another medical condition, you cannot participate in this study.

The risks of performing electroconvulsive therapy (ECT) with DBS are not known, but may include serious neurological injury or death. You should not have ECT with an implanted DBS system whether the device is active (ON) or inactive (OFF). If your depression worsens and you choose to have ECT after the first 6 month period or withdrawal from the study we will discuss

with you whether the DBS device should be removed beforehand. In addition, you should not receive rTMS or MST therapy with an implanted DBS system.

The long-term effects of DBS for depression are not known. There may be side effects or risks that are not yet known. You will be monitored carefully to determine if you are experiencing a reaction to DBS.

Reproductive Risks
If you are a female of childbearing potential, you will be asked to take a urine pregnancy test to ensure you are currently not pregnant. You will also be required to use proper birth control methods for the duration of the study. Women who are currently nursing a child are not allowed to take part in this study.

Safeguards

If you agree to participate in this study, you must report all of your past and present diseases to the Investigator. Any allergies you have must also be reported.

Potential Benefit

Deep brain stimulation has the potential to improve your depression. However, it cannot be guaranteed that the treatment you receive will be more effective than classical antidepressant treatments. This study may help future patients suffering from major depression. You may not directly benefit from participating in this study.

Alternatives to Being in this Study

If you are not to be able to have an implant or if you choose not to undergo the surgical procedure to implant the system, you will have the chance to discuss other treatment options with your doctor. There may be other medications or forms of psychotherapy that may help you. Electro-convulsive therapy (ECT) is another alternative that has been used to treat depression that is unresponsive to conventional treatments. There is also an FDA approved potential surgical alternative treatment called vagus nerve stimulation. Another option will be to continue your current method of treatment. You should discuss other treatment alternatives with your psychiatrist before choosing to participate in this study.

Confidentiality

We will protect information about you and your taking part in this research study to the best of our ability. If information about this study is published, your name will not be given. However, the U.S. Food and Drug Administration (FDA), the _____ Institutional Review Board (IRB), your doctors and designated representatives of the study sponsor, Advanced Neuromodulation Systems, Inc. (ANS), may sometimes look at the medical records and study information of those who take part in this study. Representatives of ANS may be given permission to be present during the surgical procedure.

A court of law could order medical records shown to other people, but that is unlikely. However, absolute confidentiality cannot be guaranteed.

Payment for Medical Care for Injury Related to this Study

Complications or any unexpected events are possible in any research study. Advanced Neuromodulation Systems, Inc. (ANS) will pay for emergency treatment for any injury or adverse condition that appears while you are involved in the study that is not covered by your insurance company. The injury or adverse condition must have occurred as a direct result of treatment that was being administered in accordance with the study protocol. Payment for non-emergency treatment is not available. Payment for lost wages, disability or discomfort is not available. You do not give up any of your rights by signing this form.

Cost of Being in the Study

The charges for implanting the DBS system and for the follow up visits required by the study protocol will be covered by the study sponsor. You will not be billed for any of the procedure or device costs required by the study. The sponsor will also cover your expenses for any tests performed for study purposes.

You will be compensated for your travel costs and for your time involved in the study. You will receive $50 for each of the eighteen study visits completed and parking vouchers to cover travel-related expenses. If you decide to drop out of the study before you have completed the 12-month study visit, your payment will be prorated. You would then be paid for the visits that you completed during your time taking part in the study. MODIFY AS NEEDED TO DETAIL HOW PAYMENT WILL BE PROCESSED

Post-study Care

At the end of the 12 month study period or if you exit the study prior to the end of the 12 month study period, you will continue to be followed by your study psychiatrist so he/she can program your DBS system. ANS will cover the customary costs associated with these visits up to a maximum of 4 programming visits a year and will cover surgical costs and expenses for care directly related to the DBS system, such as costs associated with removing or replacing the device. This coverage will continue until the DBS system is approved by the FDA for the treatment of major depressive disorder, ANS discontinues this study or the FDA denies approval of the DBS system, whichever occurs first. Once one of the preceding events takes place, you will be notified by the study doctor or his/her staff. Post study care is limited to reasonable and necessary care and does not include any non-device related care or other psychiatric care such as hospitalizations, counseling, psychiatric visits, etc. Please discuss all plans and questions regarding your ongoing care with your study physician.

Whom to Contact with Questions

If you should experience an adverse event, or have a study related question please contact immediately: **_____at (XXX) XXX-XXXX or after hours at (XXX)XXX-XXXX.**

If you are considering suicide right now, please immediately call **911** or the National Suicide Prevention Hotline at **1-800-273-TALK (8255)**. The National Suicide Prevention Hotline is a 24-hour, toll-free suicide prevention service available to anyone in suicide crisis. Alternatively, please contact your study doctor _____ or staff _____ immediately at **(XXX) XXX-XXXX** or after hours at **(XXX) XXX-XXXX**.

If you have any questions or concerns about your rights regarding research in human subjects please contact**. The_____ Institutional Review Board at (XXX) XXX-XXXX or after hours at (XXX) XXX-XXXX**

Voluntary Participation/Withdrawal from Study

Your participation in this study is strictly voluntary and will not prejudice you from future relations with your psychiatrist, or Advanced Neuromodulation Systems. If you decide to participate, you are free to stop participating at any time. If you decided to withdraw, notify your study psychiatrist. This will allow your study psychiatrist to tell you if there are any potential medical risks of withdrawal. If you withdraw from this study your device will be turned off and you will have two options. The first option is to have the DBS system removed. The second option is to enroll in a long-term follow up study. To be eligible to enroll in the long term follow up study, you must have your DBS system implanted for 6 months. You must also understand that your study psychiatrist or Advanced Neuromodulation Systems may stop the project or your participation in it at any time.

You will be kept informed of any significant findings throughout this study that may affect your willingness to continue to participate.

Authorization

The protocol has been explained to me along with the possible discomforts, inconveniences, and risks of the study. I understand that if I refuse to participate or withdraw at any time, my treatment will not be affected in any way. I have had an adequate chance to ask questions and I know I may ask questions at any time during the study. I do not waive any rights I would otherwise have by signing this form.

_____
Printed name of Patient or Responsible Party

_____ _____
Signature of Patient or Responsible Party Date

_____
Printed name of Witness

_____ _____
Signature of Witness Date

_____
Printed name of Investigator

_____ _____
Signature of Investigator Date

I WILL BE GIVEN A SIGNED COPY OF THIS INFORMED CONSENT

16.3 Appendix C: Case Report Forms (CRFs)

Informed Consent Process

ICF Date: ____/____/_____ ICF Time: ____: ____AM/PM

ICF IRB Approved: ____/____/_____

ICF Copy to Patient ☐ Yes ☐ No
If No, specify why:_____

California Bill of Rights ☐ Yes ☐ NO ☐ NA

If No, specify why:_____

If yes, Date ____/____/_____ Time: ____: ____AM/PM

Copy to Patient ☐ NA ☐ Yes ☐ No If No, specify why:_____

NOTES:

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Inclusion Criteria

YES

- ☐ Men and women (non-pregnant) age 21-70;
- ☐ Diagnosed with non-psychotic major depressive disorder, single or recurrent episode by DSM-IV-TR criteria derived from the MINI;
- ☐ First episode onset before age 45;
- ☐ Current episode > 12 months duration;
- ☐ In the current episode: Documented resistance (i.e. persistence of the major depressive episode) to a minimum of 4 adequate depression treatments from at least 3 different treatment categories (e.g. SSRI's, SNRI's, TCA's, MAO-inhibitors, Mirtazipine, Nefazodone, Trazodone, Bupropion, lithium augmentation, thyroid augmentation, ECT); Adequacy of treatments as defined by a score of at least 3 according to the amended Antidepressant Treatment History Form (ATHF) criteria;
- ☐ In Lifetime: Received a course of psychotherapy for depression;
- ☐ Montgomery Asberg Depression Rating Scale (MADRS) of ≥ 22 at 3 separate baseline visits, rated by 2 separate psychiatrists, Baseline 2 and Baseline 3 MADRS scores cannot be separated by > 6 weeks and cannot improve ≥ 20%;
- ☐ Global Assessment of Function, score <50;
- ☐ Modified mini-mental state examination (MMSE) score >24;
- ☐ No change in current antidepressant medication regimen or medication free ≥4 weeks prior to study entry (with exception to sleep, cholesterol, blood pressure, sexual dysfunction, non-migraine headache medication, or medication for other medical reasons not related to depression, in which changes to dose or type will be allowed during course of study);
- ☐ Able to give informed consent in accordance with institutional policies;
    - o Date signed: ____/____/_____
- ☐ Able to comply with all testing and follow-up requirements as defined by the study protocol;
- ☐ Must be determined medically stable by surgeon, to undergo deep brain stimulation surgical procedure.
- ☐ Must have platelet count, PT and PTT within normal limits of the laboratory.
- ☐ During last 6 months in the current episode documented treatment under the care of a licensed psychiatrist/psychologist.

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Exclusion Criteria

NO

- ☐ A diagnosis of a bipolar I or bipolar II disorder by DSM-IV-TR criteria, derived from the MINI;
- ☐ Meets criteria for borderline or antisocial personality disorder in the last 12 months by DSM-IV-TR criteria, derived from the Cluster B Personality Disorders Sections 301.7 – 301.83, and screened via SCID-II at Baseline visit;
- ☐ In the current depressive episode, has been diagnosed with General Anxiety Disorder (GAD) - as defined by the DSM-IV-TR, and GAD is the primary diagnosis;
- ☐ Has an intracranial Central Nervous System (CNS) disease that impairs motor, sensory or cognitive function or that requires intermittent or chronic medication (e.g., Parkinson's Disease, chronic migraine, stroke, Huntington's, head trauma, etc.) with exception to non-migraine headaches;
- ☐ Has been diagnosed with fibromyalgia or has a current condition which requires chronic pain narcotic usage (e.g. morphine, methadone);
- ☐ Has been currently diagnosed with chronic fatigue syndrome;
- ☐ Substantial suicidal risk as defined by (1) MADRS item 10 score of 5 or 6, (2) a current plan and intent, (3) clinician judgment that there is a clear immediate intent for self-harm, (4) more than 3 suicide attempts within the last 12 months;
- ☐ Co-morbid obsessive compulsive disorder, post-traumatic stress disorder, panic disorder, bulimia or anorexia nervosa if previously present, must be in remission for 6 months as defined by DSM-IV-TR criteria, derived from the MINI;
- ☐ Alcohol, medication, or illegal substance dependence or abuse within last 12 months derived from the MINI;
- ☐ Diagnosis of sleep apnea confirmed by a sleep test that is not adequately treated;
- ☐ Advanced cardiovascular disease which renders anesthesia and surgery as unsafe as determined by neurosurgeon;
- ☐ Clinically relevant abnormality (e.g. tumor or growth) on study MRI;
- ☐ Has cardiac pacemaker/defibrillator or other implanted active stimulator;
- ☐ Has a medical condition requiring a repetitive MRI body scan;
- ☐ Requires chemotherapy for the treatment of malignancy or requiring chronic oral or intravenous (immunosuppressive or) steroid therapy;
- ☐ Is unable to comply with study visit schedule and timeline;
- ☐ Past ablative or relevant intracranial surgery;

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Exclusion Criteria

NO

- ☐ A female lactating or of child bearing potential, with a positive pregnancy test or not using adequate contraception;
- ☐ Lifetime psychotic disorders, schizophrenia, or schizoaffective disorder defined by DSM-IV-TR;
- ☐ Psychotic features in current depressive episode as diagnosed by DSM-IV-TR criteria;
- ☐ Other medical conditions likely to require hospitalization within the next year;
- ☐ Received ECT within 3 months prior to enrollment, or requires ECT for the duration of the study;
- ☐ Has a history of epilepsy or history of status epilepticus;
- ☐ Plans to use diathermy;
- ☐ Has any metallic implants such as aneurysm clips or cochlear implants;
- ☐ Currently participating in another investigational device, drug or surgical trial.

I have reviewed the above criteria and this patient is qualified to participate in the study:

Investigator Signature _____

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

DEMOGRAPHICS

Date of Birth:	**Gender:**	Height:	**Race:**
☐☐ ☐☐ ☐☐☐☐	☐ Male		☐ Caucasian ☐ African American
Month Day Year	☐ Female	____ft. __ in	☐ Hispanic ☐ Asian
			☐ Other _____

LIVING STATUS

What is the subject's marital status?	☐ Single ☐ Married ☐ Divorced ☐ Separated ☐ Other:_____
What is the subject's current living situation?	☐ Lives alone ☐ Lives with spouse/partner and/or children ☐ Lives with other family ☐ Lives in boarding home ☐ Hospitalized ☐ Other:_____

INSURANCE INFORMATION

What is the subject's current insurance status?	☐ Private Insurance ☐ Self Pay ☐ Medicaid ☐ Medicare ☐ Other _____

PSYCHIATRIC HISTORY

Age of onset of MDD:	_____ **years of age**
Number of lifetime episodes:	_____ **number of episodes**
Date of onset of current episode:	_____/____/_____ (mm/dd/yyyy)
Is the subject of the melancholic subtype?	☐ YES ☐ NO
Has the subject ever had an electroconvulsive therapy (ECT)?	☐ Full Course ☐ Partial Course ☐ Never had ECT ↓ ***If partial, why?*** _____ ***Last treatment date:*** ____/____/_____ **(mm/dd/yy)**
Has subject ever been hospitalized for an MDD episode?	☐ Current ☐ Lifetime ☐ Both Lifetime/Current ☐ Never hospitalized for MDD
Has the subject attempted suicide in the last:	☐ Never attempted
Past 12 Months	☐ YES ☐ NO Number of times _____
> 12 months, but < 2 years	☐ YES ☐ NO Number of times _____
> 2 years, but <3 years	☐ YES ☐ NO Number of times _____

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

PSYCHIATRIC HISTORY CONTINUED	
Does the subject have a family history of mood disorders?	☐ YES ☐ NO
If yes, which family members had the mood disorders?	☐ 1st Degree (immediate family) ☐ Other ☐ Both

Indicate the type of psychotherapy the subject has participated in:			
Cognitive Behavioral Therapy	**Current** ☐ Yes ☐ No	☐ Successful ☐ Unsuccessful	Duration in months: _____
	Past ☐ Yes ☐ No	☐ Successful ☐ Unsuccessful	Duration in months: _____
Group Therapy	**Current** ☐ Yes ☐ No	☐ Successful ☐ Unsuccessful	Duration in months: _____
	Past ☐ Yes ☐ No	☐ Successful ☐ Unsuccessful	Duration in months: _____
Interpersonal Therapy	**Current** ☐ Yes ☐ No	☐ Successful ☐ Unsuccessful	Duration in months: _____
	Past ☐ Yes ☐ No	☐ Successful ☐ Unsuccessful	Duration in months: _____
Psychodynamic Therapy	**Current** ☐ Yes ☐ No	☐ Successful ☐ Unsuccessful	Duration in months: _____
	Past ☐ Yes ☐ No	☐ Successful ☐ Unsuccessful	Duration in months: _____
Supportive	**Current** ☐ Yes ☐ No	☐ Successful ☐ Unsuccessful	Duration in months: _____
	Past ☐ Yes ☐ No	☐ Successful ☐ Unsuccessful	Duration in months: _____
Other: _____	**Current** ☐ Yes ☐ No	☐ Successful ☐ Unsuccessful	Duration in months: _____
	Past ☐ Yes ☐ No	☐ Successful ☐ Unsuccessful	Duration in months: _____
Other: _____	**Current** ☐ Yes ☐ No	☐ Successful ☐ Unsuccessful	Duration in months: _____
	Past ☐ Yes ☐ No	☐ Successful ☐ Unsuccessful	Duration in months: _____

MADRS SCORE	
Is the subject's MADRS score ≥ 22 for this visit?	☐ YES→ _____ **(score)** ☐ NO → ***Do not proceed. Subject does not qualify.***

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Clinically Significant Medical History

System	Description
HEENT ☐ Yes ☐ No	
Endocrine ☐ Yes ☐ No	
Cardiovascular ☐ Yes ☐ No	
Respiratory ☐ Yes ☐ No	
Gastrointestinal ☐ Yes ☐ No	
Musculoskeletal ☐ Yes ☐ No	
Psychological ☐ Yes ☐ No	
Neurological ☐ Yes ☐ No	
Skin ☐ Yes ☐ No	
Other: _____ ☐ Yes ☐ No	
Other: _____ ☐ Yes ☐ No	

☐ Additional comments ☐None

_____
_____
_____
_____
_____

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Brief Physical Exam

VITAL SIGNS

Blood Pressure (Systolic/ Diastolic) _____/_____ mmHg	**Heart Rate** (Beats Per Minute) _____ BPM

PREGNANCY TEST

☐ Positive ☐ Negative ☐ N/A (Male) ☐ N/A (Female non child bearing potential)

BRIEF PHYSICAL EXAM

System	IF ABNORMAL, PROVIDE DETAILS BELOW
HEENT ☐ Normal ☐ Abnormal ☐ Not Done	
Endocrine ☐ Normal ☐ Abnormal ☐ Not Done	
Cardiovascular ☐ Normal ☐ Abnormal ☐ Not Done	
Respiratory ☐ Normal ☐ Abnormal ☐ Not Done	
Gastrointestinal ☐ Normal ☐ Abnormal ☐ Not Done	
Musculoskeletal ☐ Normal ☐ Abnormal ☐ Not Done	
Psychological ☐ Normal ☐ Abnormal ☐ Not Done	
Neurological ☐ Normal ☐ Abnormal ☐ Not Done	
Skin ☐ Normal ☐ Abnormal ☐ Not Done	
Other: _____ ☐ Normal ☐ Abnormal ☐ Not Done	

☐Additional comments ☐None

_____

_____

_____

Physical Exam performed by:

_____ Signature

_____ Date (mm/ dd/ yyyy)

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials:	_____
Subject Number:	_____
Site Number:	_____

Modified ATHF Rating for Antidepressant Potency – DBS for TRD

FOR EACH TREATMENT, INDICATE WHETHER IT IS A LIFETIME AND/OR CURRENT TREATMENT. RATE EACH TREATMENT TRIAL SEPARATELY, EVEN IF TAKEN AT SAME TIME.

TCA/Tetracyclic

I. Amitriptyline (Elavil, Endep) ____ LIFETIME ____ CURRENT

By dosage:

1 < 4 wks OR < 100 mg/d

2 4 wks or more and 100-199 mg/d

3 4 wks or more and 200-299 mg/d

4 4 wks or more and ≥ 300 mg/d

II. Imipramine (Tofranil) ____ LIFETIME ____ CURRENT

By dosage:

1 < 4 wks OR < 100 mg/d

2 4 wks or more and 100-199 mg/d

3 4 wks or more and 200-299 mg/d

4 4 wks or more and ≥ 300 mg/d

By blood level (levels take precedence over dose)

4 4 wks or more and DMI level ≥ 125 ng/ml

4 4 wks or more and IMI + DMI ≥ 225 ng/ml

III. Desipramine (Norpramine, Pertofrane) ____ LIFETIME ____ CURRENT

By dosage:

1 < 4 wks OR < 100 mg/d

2 4 wks or more and 100-199 mg/d

3 4 wks or more and 200-299 mg/d

4 4 wks or more and ≥ 300 mg/d

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Modified ATHF Rating for Antidepressant Potency – DBS for TRD

By blood level (levels take precedence over dose)

4 4 wks or more and DMI level ≥ 125 ng/ml

IV. Trimipramine (Surmontil) ____ LIFETIME ____ CURRENT

By dosage:

1 < 4 wks OR < 100 mg/d

2 4 wks or more and 100-199 mg/d

3 4 wks or more and 200-299 mg/d

4 4 wks or more and ≥ 300 mg/d

V. Clomipramine (Anafranil) ____ LIFETIME ____ CURRENT

By dosage:

1 < 4 wks OR < 100 mg/d

2 4 wks or more and 100-199 mg/d

3 4 wks or more and 200-299 mg/d

4 4 wks or more and ≥ 300 mg/d

VI. Maprotiline (Ludiomil) ____ LIFETIME ____ CURRENT

By dosage:

1 < 4 wks OR < 100 mg/d

2 4 wks or more and 100-199 mg/d

3 4 wks or more and 200-299 mg/d

4 4 wks or more and ≥ 300 mg/d

VII. Doxepin (Sinequan, Adapin) ____ LIFETIME ____ CURRENT

By dosage:

1 < 4 wks OR < 100 mg/d

2 4 wks or more and 100-199 mg/d

3 4 wks or more and 200-299 mg/d

4 4 wks or more and ≥ 300 mg/d

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Modified ATHF Rating for Antidepressant Potency – DBS for TRD

VIII. Nomifensine ____ LIFETIME ____ CURRENT

By dosage:

1 < 4 wks OR < 100 mg/d

2 4 wks or more and 100-199 mg/d

3 4 wks or more and 200-299 mg/d

4 4 wks or more and ≥ 300 mg/d

IX. Nortriptyline (Pamelor, Aventyl) ____ LIFETIME ____ CURRENT

By dosage:

1 NT < 4 wks OR 4 wks or more and NT < 50 mg/d

2 4 wks or more and NT 50-75 mg/d

3 4 wks or more and NT 76-100 mg/d

4 4 wks or more and NT > 100 mg/d

By blood level: levels take precedence

1 Nortriptyline < 4 wks

2 4 wks or more and level < 50 ng/ml

3 4 wks or more and level 50-99 ng/ml

4 4 wks or more and level > 100 ng/ml

X. Protriptyline (Vivactil) ____ LIFETIME ____ CURRENT

1 drug < 4 wks OR 4 wks or more and dosage ≤ 30 mg/d

2 4 wks or more and dosage 31-40 mg/d

3 4 wks or more and dosage 41-60 mg/d

4 4 wks or more and dosage > 60 mg/d

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials:	_____
Subject Number:	_____
Site Number:	_____

Modified ATHF Rating for Antidepressant Potency – DBS for TRD

Selective Serotonin and Norepinephrine Reuptake Inhibitors (SSNRI)

I. Duloxetine (Cymbalta) ____ LIFETIME ____ CURRENT

1 drug < 4 wk or 4 wk or more and dosage <30 mg/d

2 4 wk or more and dosage 30 – 39 mg/d

3 4 wk or more and dosage 40 – 59 mg/d

4 4 wk or more and dosage ≥ 60 mg/d

II. Venlafaxine (Effexor and Effexor XR) ____ LIFETIME ____ CURRENT

1 less than 4 wks OR 4 wks or more and dosage < 75 mg/d

2 4 wks or more and dosage 75-224 mg/d

3 4 wks or more and dosage 225-374 mg/d

4 4 wks or more and dosage ≥ 375 mg/d

III. Desvenlafaxine (Pritiq) ____ LIFETIME ____ CURRENT

1 less than 4 weeks

2 4 wks or more and dosage 25-49 mg/d

3 4 wks or more and dosage 50-100 mg/d

4 4 wks or more and dosage ≥ 100 mg/d

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Modified ATHF Rating for Antidepressant Potency – DBS for TRD

SSRIs

I. Fluoxetine (Prozac) ____ LIFETIME ____ CURRENT

1 drug < 4 wks OR 4 wks or more and dosage 1-9 mg/d
2 4 wks or more and dosage 10-19 mg/d
3 4 wks or more and dosage 20-39 mg/d
4 4 wks or more and dosage ≥ 40 mg/d

II. Fluvoxamine (Luvox) ____ LIFETIME ____ CURRENT

1 drug < 4 wks OR drug < 100 mg/d
2 4 wks or more and 100-199 mg/d
3 4 wks or more and 200-299 mg/d
4 4 wks or more and ≥ 300 mg/d

Please document both below, but only one paroxetine trial (either Paxil or Paxil CR) can count as an adequate therapy, not both.

III a. Paroxetine (Paxil) ____ LIFETIME ____ CURRENT

1 drug < 4 wks OR 4 wks or more and dosage 1-9 mg/d
2 4 wks or more and dosage 10-19 mg/d
3 4 wks or more and dosage 20-29 mg/d
4 4 wks or more and dosage ≥ 30 mg/d

OR

III b. Paroxetine CR (Paxil CR) ____ LIFETIME ____ CURRENT

1 drug < 4 wk or 4 wk or more and dosage <12.5 mg/d
2 4 wk or more and dosage 12.5 mg/d
3 4 wk or more and dosage 25-50 mg/d
4 4 wk or more and dosage ≥ 62.5 mg/d

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials:	_____
Subject Number:	_____
Site Number:	_____

Modified ATHF Rating for Antidepressant Potency – DBS for TRD

IV. Sertraline (Zoloft) ____ LIFETIME ____ CURRENT

1 drug < 4 wks OR 4 wks or more and dosage < 50 mg/d

2 4 wks or more and dosage 50-149 mg/d

3 4 wks or more and dosage 150-199 mg/d

4 4 wks or more and dosage ≥ 200 mg/d

V. Citalopram (Celexa) ____ LIFETIME ____ CURRENT

1 drug < 4 wk or 4 wk or more and dosage 1-9 mg/d

2 4 wk or more and dosage 10-19 mg/d

3 4 wk or more and dosage 20-39 mg/d

4 4 wk or more and dosage ≥ 40 mg/d

VI. Escitalopram (Lexapro) ____ LIFETIME ____ CURRENT

1 drug < 4 wk or 4 wk or more and dosage 1-4 mg/d

2 4 wk or more and dosage 5-9 mg/d

3 4 wk or more and dosage 10-19 mg/d

4 4 wk or more and dosage ≥ 20 mg/d

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Modified ATHF Rating for Antidepressant Potency – DBS for TRD

Other Antidepressants

I. Bupropion (Wellbutrin, Wellbutrin SR, Wellbutrin XL) ____ LIFETIME ____ CURRENT

1 drug < 4 wks OR 4 wks or more and dosage < 150 mg/d
2 4 wks or more and dosage 150-299 mg/d
3 4 wks or more and dosage 300-449 mg/d
4 4 wks or more and dosage ≥ 450 mg/d

II. Mirtazapine (Remeron) ____ LIFETIME ____ CURRENT

1 less than 4 wks OR 4 wks or more and dosage < 15 mg/d
2 4 wks or more and dosage 15-29 mg/d
3 4 wks or more and dosage 30-44 mg/d
4 4 wks or more and dosage ≥ 45 mg/d

III. Nefazodone (Serzone) ____ LIFETIME ____ CURRENT

1 drug < 4 wks OR 4 wks or more and dosage < 150 mg/d
2 4 wks or more and dosage 150-299 mg/d
3 4 wks or more and dosage 300-599 mg/d
4 4 wks or more and dosage ≥ 600 mg/d

IV. Trazodone (Desyrel) ____ LIFETIME ____ CURRENT

1 drug < 4 wks OR 4 wks or more and dosage < 200 mg/d
2 4 wks or more and dosage 200-399 mg/d
3 4 wks or more and dosage 400-599 mg/d
4 4 wks or more and dosage ≥ 600 mg/d

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Modified ATHF Rating for Antidepressant Potency – DBS for TRD

VII. Amoxapine (Ascendin) ____ LIFETIME ____ CURRENT

1 drug < 4 wks OR 4 wks or more and dosage < 200 mg/d

2 4 wks or more and dosage 200-399 mg/d

3 4 wks or more and dosage 400-599 mg/d

4 4 wks or more and dosage ≥ 600 mg/d

VIII. Reboxetine ____ LIFETIME ____ CURRENT

1 drug < 4 wk or 4 wk or more and dosage <4 mg/d

2 4 wk or more and dosage 4 – 7 mg/d

3 4 wk or more and dosage 8 mg/d

4 4 wk or more and dosage ≥ 8 mg/d

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Modified ATHF Rating for Antidepressant Potency – DBS for TRD

MAOIs

I. Phenelzine (Nardil) ____ LIFETIME ____ CURRENT

1 drug < 4 wks OR 4 wks or more and dosage ≤ 30 mg/d

2 4 wks or more and dosage 31-60 mg/d

3 4 wks or more and dosage 61-90 mg/d

4 4 wks or more and dosage 91 mg/d or greater

II. Tranylcypromine (Parnate) ____ LIFETIME ____ CURRENT

1 drug < 4 wks OR 4 wks or more and dosage ≤ 20 mg/d

2 4 wks or more and dosage 21-40 mg/d

3 4 wks or more and dosage 41-60 mg/d

4 4 wks or more and dosage ≥ 61 mg/d

III. Isocarboxazid (Marplan) ____ LIFETIME ____ CURRENT

1 drug < 4 wks OR 4 wks or more and dosage ≤ 20 mg/d

2 4 wks or more and dosage 21-40 mg/d

3 4 wks or more and dosage 41-60 mg/d

4 4 wks or more and dosage ≥ 61 mg/d

IV. Moclobemide ____ LIFETIME ____ CURRENT

1 drug < 4 wks OR 4 wks or more and dosage < 150 mg/d

2 4 wks or more and dosage 150-299 mg/d (100-200mg =30mg Nardil)

3 4 wks or more and dosage 300-599 mg/d (300mg =60mg Nardil)

4 4 wks or more and dosage ≥ 600 mg/d (600mg = 90mg Nardil)

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials:	_____
Subject Number:	_____
Site Number:	_____

Modified ATHF Rating for Antidepressant Potency – DBS for TRD

Please document both below, but only either Eldepryl or EMSAM count as a therapy, not both.

Va. Selegiline (Eldepryl) ____ LIFETIME ____ CURRENT

1 drug < 4 wks OR 4 wks or more and dosage ≤ 20 mg/d

2 4 wks or more and dosage 21 - 40 mg/d

3 4 wks or more and dosage 41 - 59 mg/d

4 4 wks or more and dosage ≥ 60 mg/d

Vb. Transdermal Selegiline (EMSAM) ____ LIFETIME ____ CURRENT

1 drug < 4 wks OR 4 wks or more and dosage ≤ 6 mg/d

2 4 wks or more and dosage 6mg/d

3 4 wks or more and dosage 9 mg/d

4 4 wks or more and dosage ≥ 12 mg/d

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Modified ATHF Rating for Antidepressant Potency – DBS for TRD

Psychotherapy

I. Cognitive behavioral therapy ____ LIFETIME ____ CURRENT

1 Less than 4 visits
2 4-11 visits
3 12-15 visits
4 16 or more visits

II. Interpersonal therapy ____ LIFETIME ____ CURRENT

1 Less than 4 visits
2 4-11 visits
3 12-15 visits
4 16 or more visits

III. Behavioral activation therapy ____ LIFETIME ____ CURRENT

1 Less than 4 visits
2 4-11 visits
3 12-15 visits
4 16 or more visits

Note if subject has had other forms of psychotherapy (these will not count for definition of treatment resistance):

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Modified ATHF Rating for Antidepressant Potency – DBS for TRD

ECT

I. Unilateral or unilateral/bilateral combination ____ LIFETIME ____ CURRENT

1 1 - 3 treatments
2 4 - 6 treatments
3 7 - 9 treatments
4 ≥ 10 treatments

II. Bilateral ECT ____ LIFETIME ____ CURRENT

1 1 - 3 treatments
2 4 - 6 treatments
3 7 - 9 treatments
4 ≥ 10 treatments

II. ECT type unknown (but number of treatments are documented in acceptable medical records)

____ LIFETIME ____ CURRENT

1 1 - 3 treatments
2 4 - 6 treatments
3 7 - 9 treatments
4 ≥ 10 treatments

If ECT was attempted but not tolerated, please describe:

_____
_____
_____
_____
_____
_____
_____
_____

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Modified ATHF Rating for Antidepressant Potency – DBS for TRD

Non-pharmacologic Somatic Therapies

I. VNS ____ LIFETIME ____ CURRENT

1 < 6 Months
2 6-11 Months
3 12-24 Months
4 > 24 Months

II. TMS (left dorsolateral, >=5 Hz, >=100% motor threshold, >=1600 pulses per session)

____ LIFETIME ____ CURRENT

1 < 10 Sessions
2 10– 19 Sessions
3 20-29 Sessions
4 ≥ 30 Sessions

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Modified ATHF Rating for Antidepressant Potency – DBS for TRD

Augmentation Therapies

I. Lithium alone for MDD ____ LIFETIME ____ CURRENT

1 drug < 4 wks OR 4 wks or more

II. Lithium as an augmenting agent for MDD ____ LIFETIME ____ CURRENT

4 Any antidepressants rated level 3 or higher Li used for at least 2 wks at level ≥ 0.6 mEq/L

III. Lamotrigine (Lamictal) ____ LIFETIME ____ CURRENT

1 drug < 4 wks OR
4 wks or more and dosage < 50 mg/d

2 4 wks or more and dosage > 50 mg/d

IV. Valproic acid/valproate/Depakote/Depakene ____ LIFETIME ____ CURRENT

1 drug < 4 wks OR 4 wks or more and level < 50

2 4 wks or more and level > 50

V. Carbamazepine (Tegretol) ____ LIFETIME ____ CURRENT

1 CBZ < 4 wks OR 4 wks or more and level < 6

2 4 wks or more and level >6

VI. Thyroid Hormone ____ LIFETIME ____ CURRENT

1 drug < 4 wks

2 drug > 4 wks and dosage <25 mcg

3 drug > 4 wks and dosage 25-49 mcg

4 drug > 4 wks and dosage >=50 mcg

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Modified ATHF Rating for Antidepressant Potency – DBS for TRD

VII. Buspirone ____ LIFETIME ____ CURRENT

1 drug < 4 wks or dosage <= 15 mg/d
2 drug >4 wks and dosage 15-29 mg/d
3 drug >4 wks and dosage 30-59 mg/d
4 drug >4 wks and dosage >=60 mg/d

VI. Aripiprazole (Abilify) ____ LIFETIME ____ CURRENT

1 drug < 4 wks
2 drug > 4 wks and dosage <10 mg/d
3 drug > 4 wks and dosage 10-29 mg/d
4 drug > 4 wks and dosage >=30 mg/d

VII. Ziprasidone (Geodon) ____ LIFETIME ____ CURRENT

1 drug < 4 wks
2 drug > 4 wks; give highest dose achieved > 4 wks: _____

IX. Risperidone (Risperdal) ____ LIFETIME ____ CURRENT

1 drug < 4 wks
2 drug > 4 wks; give highest dose achieved > 4 wks: _____

X. Quetiapine (Seroquel) ____ LIFETIME ____ CURRENT

1 drug < 4 wks
2 drug > 4 wks; give highest dose achieved > 4 wks: _____

XI. Olanzapine (Zyprexa) ____ LIFETIME ____ CURRENT

1 drug < 4 wks
2 drug > 4 wks; give highest dose achieved > 4 wks: _____

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Modified ATHF Rating for Antidepressant Potency – DBS for TRD

XII. Olanzapine/fluoxetine (Symbax 6mg/25mg) ____ LIFETIME ____ CURRENT

1 drug < 4 wks

2 drug > 4 wks; give highest dose achieved > 4 wks: _____

3 Only score 3 if the fluoxetine/Prozac option in the SSRI section is not scored 3 or higher

XIII. Pramipexole (Mirapex) ____ LIFETIME ____ CURRENT

1 drug < 4 wks

2 drug > 4 wks; give highest dose achieved > 4 wks: _____

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Modified ATHF Rating for Antidepressant Potency – DBS for TRD

Other medications and treatments (cannot be used for definition of treatment resistance)

Include benzodiazepines, psychostimulants, light therapy, and all other pharmacologic and somatic treatments (e.g., testosterone, acupuncture) ***for depression or symptoms of depression***.

Treatment	Dose	Duration	Comments

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit: _____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Modified ATHF Rating for Antidepressant Potency – DBS for TRD

SUMMARY

Confidence rating for treatment history:

1 Minimal confidence

2 Moderate confidence

3 Good confidence (required for up to four antidepressant treatment

4 Excellent confidence (requires confirmatory records)

Comments on confidence rating:

Lifetime Summary

1. Total number of lifetime antidepressant **medications** and acceptable **medication augmentation** strategies: ____
2. Total number of lifetime antidepressant **medications** rated 3 or higher with at least good confidence: ____
3. Total number of lifetime antidepressant **treatments** rated 3 or higher (can include psychotherapy, ECT, VNS, TMS): ____
4. Total number of lifetime treatments for depression (including all others listed on this document): ____

Current Summary

1. Total number of current antidepressant **medications** and acceptable **medication augmentation** strategies: ____
2. Total number of current antidepressant **medications** rated 3 or higher: ____
3. Total number of current antidepressant **treatments** rated 3 or higher (can include psychotherapy, ECT, VNS, TMS): ____
4. Total number of current treatments for depression (including all others listed on this document): ____

M.I.N.I. PLUS

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 5.0.0

USA: D. Sheehan, J. Janavs, R. Baker, K.Harnett-Sheehan, E. Knapp, M. Sheehan
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M.I.N.I. Plus 5.0.0 (January 1, 2005)

Patient Name:		***Patient Number:***	
Date of Birth:		***Time Interview Began:***	
Interviewer's Name:		***Time Interview Ended:***	
Date of Interview:		***Total Time:***	

	MODULES	TIME FRAME	MEETS CRITERIA	DSM-IV	ICD-10
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks)	❑	296.20-296.26 Single	F32.x
		Recurrent	❑	296.30-296.36 Recurrent	F33.x
	MOOD DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current	❑	293.83	F06.xx
		Past	❑	293.83	F06.xx
	SUBSTANCE INDUCED MOOD DISORDER	Current	❑	29x.xx	none
		Past	❑	29x.xx	none
	MDE WITH MELANCHOLIC FEATURES	Current (2 weeks)	❑	296.20-296.26 Single	F32.x
				296.30-296.36 Recurrent	F33.x
B	DYSTHYMIA	Current (Past 2 years)	❑	300.4	F34.1
		Past	❑	300.4	F34.1
C	SUICIDALITY	Current (Past Month)	❑	none	none
		Risk: ❑ Low ❑ Medium ❑ High			
D	MANIC EPISODE	Current	❑	296.00-296.06	F30.x-F31.9
		Past	❑	296.00-296.06	F30.x-F31.9
	HYPOMANIC EPISODE	Current	❑	296.80-296.89	F31.8-F31.9/F34.0
		Past	❑	296.80-296.89	F31.8-F31.9/F34.0
	BIPOLAR I DISORDER	Current	❑	296.0x-296.6x	F30.x-F31.9
		Past	❑	296.0x-296.6x	F30.x-F31.9
	BIPOLAR II DISORDER	Current	❑	296.89	F31.8
		Past	❑	296.89	F31.8
	MANIC EPISODE DUE TO A GENERAL MEDICAL CONDITION	Current	❑	293.83	F06.30
		Past	❑	293.83	F06.30
	HYPOMANIC EPISODE DUE TO A GENERAL MEDICAL CONDITION	Current	❑	293.83	none
		Past	❑	293.83	none
	SUBSTANCE INDUCED MANIC EPISODE	Current	❑	291.8-292.84	none
		Past	❑	291.8-292.84	none
	SUBSTANCE INDUCED HYPOMANIC EPISODE	Current	❑	291.8-292.84	none
		Past	❑	291.8-292.84	none
E	PANIC DISORDER	Current (Past Month)	❑	300.01/300.21	F40.01-F41.0
		Lifetime	❑	300.01/300.21	F40.01-F41.0
	ANXIETY DISORDER WITH PANIC ATTACKS DUE TO A GENERAL MEDICAL CONDITION	Current	❑	293.89	F06.4
	SUBSTANCE INDUCED ANXIETY DISORDER WITH PANIC ATTACKS	Current	❑	291.8-292.89	none
F	AGORAPHOBIA	Current	❑	300.22	F40.00
G	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month)	❑	300.23	F40.1
H	SPECIFIC PHOBIA	Current	❑	300.29	F40.2
I	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	❑	300.3	F42.8
	OCD DUE TO A GENERAL MEDICAL CONDITION	Current	❑	293.89	F06.4
	SUBSTANCE INDUCED OCD	Current	❑	291.8-292.89	none
J	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	❑	309.81	F43.1
K	ALCOHOL DEPENDENCE	Past 12 Months	❑	303.9	F10.2x
	ALCOHOL DEPENDENCE	Lifetime	❑	303.9	F10.2x
	ALCOHOL ABUSE	Past 12 Months	❑	305.00	F10.1
	ALCOHOL ABUSE	Lifetime	❑	305.00	F10.1
L	SUBSTANCE DEPENDENCE (Non-alcohol)	Past 12 Months	❑	304.00-.90/305.20-.90	F11.0-F19.1
	SUBSTANCE DEPENDENCE (Non-alcohol)	Lifetime	❑	304.00-.90/305.20-.90	F11.0-F19.1
	SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months	❑	304.00-.90/305.20-.90	F11.0-F19.1
M	PSYCHOTIC DISORDERS	Lifetime	❑	295.10-295.90/297.1/	F20.xx-F29
		Current	❑	297.3/293.81/293.82/ 293.89/298.8/298.9	
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Current	❑	296.24	F32.3/F33.3
	SCHIZOPHRENIA	Current	❑	295.10-295.60	F20.xx
		Lifetime	❑	295.10-295.60	F20.xx
	SCHIZOAFFECTIVE DISORDER	Current	❑	295.70	F25.x
		Lifetime	❑	295.70	F25.x
	SCHIZOPHRENIFORM DISORDER	Current	❑	295.40	F20.8
		Lifetime	❑	295.40	F20.8

	BRIEF PSYCHOTIC DISORDER	Current	❑	298.8	F23.80-F23.81
		Lifetime	❑	298.8	F23.80-F23.81
	DELUSIONAL DISORDER	Current	❑	297.1	F22.0
		Lifetime	❑	297.1	F22.0
	PSYCHOTIC DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current	❑	293.xx	F06.0-F06.2
		Lifetime	❑	293.xx	F06.0-F06.2
	SUBSTANCE INDUCED PSYCHOTIC DISORDER	Current	❑	291.5-292.12	none
		Lifetime	❑	291.5-292.12	none
	PSYCHOTIC DISORDER NOS	Current	❑	298.9	F29
		Lifetime	❑	298.9 296.24	F29
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Lifetime	❑		F31.3/F31.2/F31.5
	MOOD DISORDER NOS	Lifetime	❑	296.90	F39
	MAJOR DEPRESSIVE DISORDER WITH PSYCHOTIC FEATURES	Current	❑	296.24	F33.X3
		Past	❑	296.24	F33.X3
	BIPOLAR I DISORDER WITH PSYCHOTIC FEATURES	Current	❑	296.04-296.64	F31.X2/F31.X5
		Past	❑	296.04-296.64	F31.X2/F31.X5
N	ANOREXIA NERVOSA	Current (Past 3 Months)	❑	307.1	F50.0
O	BULIMIA NERVOSA	Current (Past 3 Months)	❑	307.51	F50.2
	BULIMIA NERVOSA PURGING TYPE	Current	❑	307.51	F50.2
	BULIMIA NERVOSA NONPURGING TYPE	Current	❑	307.51	F50.2
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current	❑	307. 1	F50.0
	ANOREXIA NERVOSA, RESTRICTING TYPE	Current	❑	307. 1	F50.0
P	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	❑	300.02	F41.1
	GENERALIZED ANXIETY DISORDER DUE TO A GENERAL MEDICAL CONDITION	Current	❑	293.89	F06.4
	SUBSTANCE INDUCED GAD	Current	❑	291.8-292.89	none
Q	ANTISOCIAL PERSONALITY DISORDER	Lifetime	❑	301.7	F60.2
R	SOMATIZATION DISORDER	Lifetime	❑	330.81	F45.0
		Current	❑		
S	HYPOCHONDRIASIS	Current	❑	300.7	F45.2
T	BODY DYSMORPHIC DISORDER	Current	❑	300.7	F45.2
U	PAIN DISORDER	Current	❑	300.89/307.8	F45.4
V	CONDUCT DISORDER	Past 12 Months	❑	312.8	F91.8
W	ATTENTION DEFICIT/HYPERACTIVITY DISORDER (Children/Adolescents)	Past 6 Months	❑	314.00/314.01	F90.0/F90.9/ F98.8
	ATTENTION DEFICIT/HYPERACTIVITY DISORDER (Adults)	Lifetime	❑	314.00/314.01	F90.0/F98.8
		Current	❑		
X	ADJUSTMENT DISORDERS	Current	❑	309.xx	F43.xx
Y	PREMENSTRUAL DYSPHORIC DISORDER	Current	❑		
Z	MIXED ANXIETY-DEPRESSIVE DISORDER	Current	❑		

WARNING

EVEN IF A PATIENT HAS A CLEAR LIFE STRESS AGGRAVATING THEIR SYMPTOMS FIRST EXPLORE THE OTHER DIAGNOSES ABOVE. NEVER USE AN ADJUSTMENT DISORDER DIAGNOSIS IF THE DISTURBANCE MEETS CRITERIA FOR ANY OF THE ABOVE DISORDERS.

DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel.

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization for lay interviewers for ICD-10). The results of these studies show that the M.I.N.I. has acceptably high validation and reliability scores, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training. The M.I.N.I. Plus is a more detailed edition of the M.I.N.I. Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I. The M.I.N.I. Plus has questions that investigate these issues.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. Plus is divided into **modules** identified by letters, each corresponding to a diagnostic category.

•At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.

•At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them (➨) indicate that one of the criteria necessary for the diagnosis(es) is not met. In this case, the interviewer should go to the end of the module and circle « **NO** » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, questions M20-M23).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that <u>each dimension</u> of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).

<u>Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I.</u> The M.I.N.I. Plus has questions that investigate these issues.

For any questions, suggestions, need for a training session, or information about updates of the M.I.N.I., please contact :

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A. MAJOR DEPRESSIVE EPISODE

(➨ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

FOR PATIENTS WHO APPEAR PSYCHOTIC BEFORE STARTING THE INTERVIEW, OR WHO ARE SUSPECTED TO HAVE SCHIZOPHRENIA, PLEASE ADOPT THE FOLLOWING ORDER OF ADMINISTRATION OF MODULES:

1) PART 1 OF MODULE M (PSYCHOTIC DISORDERS M1-M18).
2) SECTIONS A-D (DEPRESSION TO (HYPO)MANIC EPISODE).
3) PART 2 OF MODULE M (PSYCHOTIC DISORDERS M19-M23).
4) OTHER MODULES IN THEIR USUAL SEQUENCE.

IF MODULE M HAS ALREADY BEEN EXPLORED AND PSYCHOTIC SYMPTOMS HAVE BEEN IDENTIFIED (M1 TO M10b), EXAMINE FOR EACH POSITIVE RESPONSE TO THE FOLLOWING QUESTIONS IF THE DEPRESSIVE SYMPTOMS ARE NOT BETTER EXPLAINED BY THE PRESENCE OF A PSYCHOTIC DISORDER AND CODE ACCORDINGLY.

A1	a	Have you **ever** been consistently depressed or down, most of the day, nearly every day, for at least two weeks?	NO	YES
		IF **A1a** = **YES**:		
	b	Have you been consistently depressed or down, most of the day, nearly every day, for the past 2 weeks?	NO	YES
A2	a	Have you **ever** been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time over at least 2 weeks?	NO	YES
		IF **A2a** = **YES**:		
	b	In the past 2 weeks, have you been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time.	NO	YES
			➨	
		IS **A1a** OR **A2a** CODED **YES?**	NO	YES

IF CURRENTLY DEPRESSED (**A1b** OR **A2b** = **YES**): EXPLORE ONLY CURRENT EPISODE.
IF **NO**: EXPLORE THE MOST SYMPTOMATIC PAST EPISODE.

A3 **Over the two week period when you felt depressed or uninterested,**

		Current Episode		Past Episode	
a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (I.E., BY ±5% OF BODY WEIGHT OR ±8 LBS. OR ±3.5 KGS. FOR A 160 LB./70 KGS. PERSON IN A MONTH)? IF **YES** TO EITHER, CODE **YES**.	NO	YES	NO	YES
b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES	NO	YES
c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?	NO	YES	NO	YES
d	Did you feel tired or without energy almost every day?	NO	YES	NO	YES
e	Did you feel worthless or guilty almost every day?	NO	YES	NO	YES

IF **A3e** = **YES**: ASK FOR AN EXAMPLE.
THE EXAMPLE IS CONSISTENT WITH A DELUSIONAL IDEA. ❑ NO ❑ YES

f	Did you have difficulty concentrating or making decisions almost every day?	NO	YES	NO	YES
g	Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead?	NO	YES	NO	YES
A4	ARE **3** OR MORE **A3** ANSWERS CODED **YES** (OR **4 A3** ANSWERS, IF **A1a** OR **A2a** ARE CODED **NO** FOR PAST EPISODE OR IF **A1b** OR **A2b** ARE CODED **NO** FOR CURRENT EPISODE)?	NO	YES	NO	YES

VERIFY IF THE POSITIVE SYMPTOMS OCCURRED DURING THE SAME 2 WEEK TIME FRAME.

IF **A4** IS CODED **NO** FOR CURRENT EPISODE THEN EXPLORE **A3a - A3g** FOR MOST SYMPTOMATIC PAST EPISODE.

A5 Did the symptoms of depression cause you significant distress or impair your ability to function at work, socially, or in some other important way? NO YES

A6 Are the symptoms due entirely to the loss of a loved one (bereavement) and are they similar in severity, level of impairment, and duration to what most others would suffer under similar circumstances? If so, this is uncomplicated bereavement.

HAS UNCOMPLICATED BEREAVEMENT BEEN RULED OUT? NO YES

A7 a Were you taking any drugs or medicines just before these symptoms began?
❒ No ❒ Yes

b Did you have any medical illness just before these symptoms began?
❒ No ❒ Yes

IN THE CLINICIAN'S JUDGMENT: ARE EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S DEPRESSION? IF NECESSARY ASK ADDITIONAL OPEN-ENDED QUESTIONS.

A7 (SUMMARY): HAS AN ORGANIC CAUSE BEEN RULED OUT? NO YES UNCERTAIN

A8 CODE **YES** IF **A7(SUMMARY) = YES** OR **UNCERTAIN**.

SPECIFY IF THE EPISODE IS CURRENT AND/ OR PAST OR BOTH (RECURRENT).

NO	YES
Major Depressive Episode	
Current	❑
Past	❑

A9 CODE **YES** IF **A7b = YES** AND **A7 (SUMMARY) = NO**.

SPECIFY IF THE EPISODE IS CURRENT AND/ OR PAST OR BOTH (RECURRENT).

NO	YES
Mood Disorder Due to a General Medical Condition	
Current	❑
Past	❑

A10 CODE **YES** IF **A7a = YES** AND **A7 (SUMMARY) = NO**.

SPECIFY IF THE EPISODE IS CURRENT AND/ OR PAST OR BOTH (RECURRENT).

NO	YES
Substance Induced Mood Disorder	
Current	❑
Past	❑

CHRONOLOGY

A11 How old were you when you first began having symptoms of depression? ☐ age

A12 During your lifetime, how many distinct times did you have these symptoms of depression (daily for at least 2 weeks)? ☐

MAJOR DEPRESSIVE EPISODE WITH MELANCHOLIC FEATURES (optional)

(➨ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

IF THE PATIENT CODES POSITIVE FOR A CURRENT MAJOR DEPRESSIVE EPISODE (**A8** = **YES**, **CURRENT**), EXPLORE THE FOLLOWING:

A13 a	During the most severe period of the current depressive episode, did you lose almost completely your ability to enjoy nearly everything ?	NO	YES
b	During the most severe period of the current depressive episode, did you lose your ability to respond to things that previously gave you pleasure, or cheered you up? **IF NO,** DOUBLE CHECK ANSWER BY ASKING: When something good happens, does it fail to make you feel better, even temporarily?	NO	YES
	➨ IS EITHER **A13a** OR **A13b** CODED **YES**?	NO	YES

A14 **Over the past two week period, when you felt depressed and uninterested:**

a	Did you feel depressed in a way that is different from the kind of feeling you experience when someone close to you dies?	NO	YES
b	Did you feel regularly worse in the morning, almost every day?	NO	YES
c	Did you wake up at least 2 hours before the usual time of awakening and have difficulty getting back to sleep, almost every day?	NO	YES
d	IS **A3c** CODED **YES** (PSYCHOMOTOR RETARDATION OR AGITATION)?	NO	YES
e	IS **A3a** CODED **YES** FOR ANOREXIA OR WEIGHT LOSS?	NO	YES
f	Did you feel excessive guilt or guilt out of proportion to the reality of the situation?	NO	YES

ARE **3** OR MORE **A14** ANSWERS CODED **YES**?

NO	**YES**
Major Depressive Episode **with** ***Melancholic Features, Current***	

SUBTYPES OF MAJOR DEPRESSIVE EPISODE	**Mark all that apply.**
Mild	❑ 296.21/296.31
Moderate	❑ 296.22/296.32
Severe without psychotic features	❑ 296.23
Severe with psychotic features	❑ 296.24
In partial remission	❑ 296.25
In full remission	❑ 296.26
Chronic	❑
With catatonic features	❑
With melancholic features	❑
With atypical features	❑
With postpartum onset	❑
With seasonal pattern	❑
With full interepisode recovery	❑
Without full interepisode recovery	❑

IF **A8** OR **A9** OR **A10** = **YES**, SKIP TO SUICIDALITY ➡

B. DYSTHYMIA

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

If patient's symptoms <u>currently</u> meet criteria for major depressive episode, do NOT explore <u>current</u> dysthymia, but do explore PAST dysthymia. Make sure that the past dysthymia explored is not one of the past major depressive episodes, and that it was separated from any prior major depressive episode by at least 2 months of full remission. [APPLY THIS RULE ONLY IF YOU ARE INTERESTED IN EXPLORING DOUBLE DEPRESSION.]

SPECIFY WHICH TIME FRAME IS EXPLORED BELOW: ❑ Current ❑ Past

		➡	
B1	Have you felt sad, low or depressed most of the time for the last two years? (OR IF EXPLORING PAST DYSTHYMIA: "In the past, did you ever feel sad, low or depressed for 2 years continuously?")	NO	YES
			➡
B2	Was this period interrupted by your feeling OK for two months or more?	NO	YES
B3	**During this period of feeling depressed most of the time:**		
a	Did your appetite change significantly?	NO	YES
b	Did you have trouble sleeping or sleep excessively?	NO	YES
c	Did you feel tired or without energy?	NO	YES
d	Did you lose your self-confidence?	NO	YES
e	Did you have trouble concentrating or making decisions?	NO	YES
f	Did you feel hopeless?	NO	YES
		➡	
	ARE **2** OR MORE **B3** ANSWERS CODED **YES**?	NO	YES
		➡	
B4	Did the symptoms of depression cause you significant distress or impair your ability to function at work, socially, or in some other important way?	NO	YES

B5 Were you taking any drugs or medicines just before these symptoms began?
Did you have any medical illness just before these symptoms began?
IN THE CLINICIAN'S JUDGMENT: ARE EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S DEPRESSION?

HAS AN ORGANIC CAUSE BEEN RULED OUT? NO YES

IS **B5** CODED **YES**?

NO	YES
DYSTHYMIA	
Current	❑
Past	❑

CHRONOLOGY

B6 How old were you when you first began having symptoms of 2 years of continuous depression? ☐ age

---

C. SUICIDALITY

In the past month did you:

				Points
C1	Think you would be better off dead or wish you were dead?	NO	YES	1
C2	Want to harm yourself?	NO	YES	2
C3	Think about suicide?	NO	YES	6
C4	Have a suicide plan?	NO	YES	10
C5	Attempt suicide?	NO	YES	10
	In your lifetime:			
C6	Did you ever make a suicide attempt?	NO	YES	4

IS AT LEAST **1** OF THE ABOVE CODED **YES**?

IF **YES,** ADD THE TOTAL NUMBER OF POINTS FOR THE ANSWERS (C1-C6) CHECKED 'YES' AND SPECIFY THE LEVEL OF SUICIDE RISK AS FOLLOWS:

NO	YES
SUICIDE RISK CURRENT	
1-5 points Low	❑
6-9 points Moderate	❑
≥ 10 points High	❑

D. (HYPO) MANIC EPISODE

(➨ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

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1) PART 1 OF MODULE M (PSYCHOTIC DISORDERS M1-M18).
2) SECTIONS A-D (DEPRESSION TO (HYPO)MANIC EPISODE).
3) PART 2 OF MODULE M (PSYCHOTIC DISORDERS M19-M23).
4) OTHER MODULES IN THEIR USUAL SEQUENCE.

IF MODULE M HAS ALREADY BEEN EXPLORED AND PSYCHOTIC SYMPTOMS HAVE BEEN IDENTIFIED (**M1** TO **M10b**), EXAMINE FOR EACH POSITIVE RESPONSE TO THE FOLLOWING QUESTIONS IF THE (HYPO)MANIC SYMPTOMS ARE NOT BETTER EXPLAINED BY THE PRESENCE OF A PSYCHOTIC DISORDER AND CODE ACCORDINGLY.

D1	a	Have you **ever** had a period of time when you were feeling 'up' or 'high' or 'hyper' or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.)	NO	YES
		IF NO, CODE NO TO **D1b**: IF **YES** ASK:		
	b	Are you **currently** feeling 'up' or 'high' or 'hyper' or full of energy?	NO	YES
		IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'HIGH', CLARIFY AS FOLLOWS: BY 'UP' OR 'HIGH' OR 'HYPER' I MEAN: HAVING ELATED MOOD; INCREASED ENERGY; NEEDING LESS SLEEP; HAVING RAPID THOUGHTS; BEING FULL OF IDEAS; HAVING AN INCREASE IN PRODUCTIVITY, MOTIVATION , CREATIVITY, OR IMPULSIVE BEHAVIOR.		
D2	a	Have you **ever** been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified?	NO	YES
		IF NO, CODE NO TO **D2b**: IF **YES** ASK:		
	b	Are you **currently** feeling persistently irritable?	NO	YES
			➨	
		IS **D1a** OR **D2a** CODED **YES**?	NO	YES

D3 IF **D1b** OR **D2b** = **YES**: EXPLORE ONLY **CURRENT** EPISODE, OTHERWISE
IF **D1b** AND **D2b** = **NO**: EXPLORE THE MOST SYMPTOMATIC **PAST** EPISODE

During the times when you felt high, full of energy, or irritable did you:

		Current Episode		Past Episode	
a	Feel that you could do things others couldn't do, or that you were an especially important person? IF **YES**, ASK FOR EXAMPLES. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. ❒ No ❒ Yes	NO	YES	NO	YES
b	Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES
c	Talk too much without stopping, or so fast that people had difficulty understanding?	NO	YES	NO	YES
d	Have racing thoughts?	NO	YES	NO	YES

e Become easily distracted so that any little interruption could distract you? NO YES | NO YES

f Become so active or physically restless that others were worried about you? NO YES | NO YES

g Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)? NO YES | NO YES

➡

D3(SUMMARY): ARE **3** OR MORE **D3** ANSWERS CODED **YES** (OR **4** OR MORE IF **D1a** IS **NO** (IN RATING PAST EPISODE) OR **D1b** IS **NO** (IN RATING CURRENT EPISODE)? RULE: ELATION/EXPANSIVENESS REQUIRES ONLY THREE D3 SYMPTOMS WHILE IRRITABLE MOOD ALONE REQUIRES **4** OF THE **D3** SYMPTOMS. NO YES | NO YES

VERIFY IF THE SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD.

D4 a Were you taking any drugs or medicines just before these symptoms began?
❒ No ❒ Yes

b Did you have any medical illness just before these symptoms began?
❒ No ❒ Yes

IN THE CLINICIAN'S JUDGMENT: ARE EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S (HYPO)MANIA? IF NECESSARY, ASK ADDITIONAL OPEN ENDED QUESTIONS.

D4 (SUMMARY): HAS AN ORGANIC CAUSE BEEN RULED OUT? NO YES | UNCERTAIN

D5 Did these symptoms last at least a week and cause problems beyond your control at home, work, school, or were you hospitalized for these problems? NO YES | NO YES

IF **D5** IS CODED **NO** FOR CURRENT EPISODE, THEN EXPLORE **D3, D4** AND **D5** FOR THE MOST SYMPTOMATIC PAST EPISODE.

D6

IF **D3** (SUMMARY) = **YES** AND **D4 (SUMMARY)** = **YES** OR **UNCERTAIN** AND **D5** = **NO**, AND NO DELUSIONAL IDEA WAS DESCRIBED IN **D3a**, CODE **YES** FOR HYPOMANIAC EPISODE.

SPECIFY IF THE EPISODE IDENTIFIED IS CURRENT OR PAST.

NO	YES
HYPOMANIC EPISODE	
Current	❑
Past	❑

D7 IF **D3 (SUMMARY)** = **YES** AND **D4 (SUMMARY)** = **YES** OR **UNCERTAIN** AND EITHER **D5** = **YES** OR A DELUSIONAL IDEA WAS DESCRIBED IN **D3a**, CODE **YES** FOR MANIC EPISODE.

SPECIFY IF THE EPISODE IDENTIFIED IS CURRENT OR PAST.

NO	YES
MANIC EPISODE	
Current	❑
Past	❑

D8 IF **D3 (SUMMARY)** AND **D4b** AND **D5** = **YES** AND **D4 (SUMMARY)** = **NO**, CODE **YES**?

SPECIFY IF THE EPISODE IDENTIFIED IS CURRENT OR PAST.

NO	YES
(Hypo) Manic Episode Due to a General Medical Condition	
Current	❑
Past	❑

D9 IF **D3 (SUMMARY)** AND **D4a** AND **D5** = **YES** AND **D4 (SUMMARY)** = **NO**, CODE **YES**?

SPECIFY IF THE EPISODE IDENTIFIED IS CURRENT OR PAST.

NO	YES
Substance Induced (Hypo) Manic Episode	
Current	❑
Past	❑

IF **D8** OR **D9** = **YES,** GO TO NEXT MODULE.

SUBTYPES

Rapid Cycling

Have you had four or more episodes of mood disturbance in 12 months?

NO	YES
Rapid Cycling	

Mixed Episode

PATIENT MEETS CRITERIA FOR BOTH MANIC EPISODE AND MAJOR DEPRESSIVE EPISODE NEARLY EVERY DAY DURING AT LEAST A ONE WEEK PERIOD.

NO	YES
Mixed Episode	

Seasonal Pattern

THE ONSET AND REMISSIONS OR SWITCHES FROM DEPRESSION TO MANIA OR HYPOMANIA CONSISTENTLY OCCUR AT A PARTICULAR TIME OF YEAR.

NO	YES
Seasonal Pattern	

With Full Inter-episode Recovery

Between the two most recent mood episodes did you fully recover?

NO	YES
With Full Interepisode Recovery	

CIRCLE ONE

MOST RECENT EPISODE WAS A **MANIC** / **HYPOMANIC** / **MIXED** / **DEPRESSED** EPISODE

SEVERITY

X1	Mild	❑
X2	Moderate	❑
X3	Severe without psychotic features	❑
X4	Severe with psychotic features	❑
X5	In partial remission	❑
X6	In full remission	❑

CHRONOLOGY

D10 How old were you when you first began having symptoms of manic/hypomanic episodes? ☐ age

D11 Since the first onset how many distinct times did you have significant symptoms of mania/ hypomania? ☐

E. PANIC DISORDER

(➨ MEANS: GO TO **E6** AND **E7** AND **E8** AND **E9** AND **E10**, CIRCLE **NO** TO ALL AND MOVE TO NEXT MODULE – MODULE F)

E1	a	Have you, on more than one occasion, had spells or attacks when you suddenly felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	➨ NO	YES
	b	Did the spells surge to a peak within 10 minutes of starting?	➨ NO	YES
E2		At any time in the past, did any of those spells or attacks come on unexpectedly or spontaneously, or occur in an unpredictable or unprovoked manner?	➨ NO	YES
E3		Have you ever had one such attack followed by a month or more of persistent concern about having another attack, or worries about the consequences of the attack?	NO	YES
E4		During the worst spell that you can remember:		
	a	Did you have skipping, racing or pounding of your heart?	NO	YES
	b	Did you have sweating or clammy hands?	NO	YES
	c	Were you trembling or shaking?	NO	YES
	d	Did you have shortness of breath or difficulty breathing?	NO	YES
	e	Did you have a choking sensation or a lump in your throat?	NO	YES
	f	Did you have chest pain, pressure or discomfort?	NO	YES
	g	Did you have nausea, stomach problems or sudden diarrhea?	NO	YES
	h	Did you feel dizzy, unsteady, lightheaded or faint?	NO	YES
	i	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO	YES
	j	Did you fear that you were losing control or going crazy?	NO	YES
	k	Did you fear that you were dying?	NO	YES
	l	Did you have tingling or numbness in parts of your body?	NO	YES
	m	Did you have hot flushes or chills?	NO	YES
		E4 (SUMMARY): ARE **4** OR MORE **E4** ANSWERS CODED **YES**?	NO	YES
E5	a	Were you taking any drugs or medicines just before these symptoms began? ❒ No ❒ Yes		
	b	Did you have any medical illness just before these symptoms began? ❒ No ❒ Yes		
		IN THE CLINICIAN'S JUDGMENT: ARE EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S PANIC DISORDER?		
		E5 (SUMMARY): HAS AN ORGANIC CAUSE BEEN RULED OUT? IF **E5 (SUMMARY)** IS CODED **NO**, SKIP TO **E9**.	NO	YES

E6 DOES **E3** AND **E4 (SUMMARY)** AND **E5 (SUMMARY)** = **YES**? NO YES

PANIC DISORDER
LIFETIME

IF **E6** = **YES**, SKIP TO E8.

E7 IF **E6** = **NO**, ARE ANY E4 ANSWERS CODED **YES**? NO YES

LIMITED SYMPTOM ATTACKS
LIFETIME

THEN SKIP TO **F1**.

E8 In the past month, did you have such attacks repeatedly (2 or more), followed by persistent concern about having another attack? NO YES

PANIC DISORDER
CURRENT

(IF THIS IS DENIED BY THE PATIENT—CHALLENGE BY REVIEWING THE SYMPTOMS ENDORSED IN **E4).**

E9 ARE **E3** AND **E4 (SUMMARY)** AND **E5b** ALL CODED **YES** AND **E5 (SUMMARY)** CODED **NO**?

NO **YES**

Anxiety Disorder with Panic Attacks Due to a General Medical Condition
CURRENT

E10 ARE **E3** AND **E4 (SUMMARY)** AND **E5a** ALL CODED **YES** AND **E5 (SUMMARY)** CODED **NO**?

NO **YES**

Substance Induced Anxiety Disorder with Panic Attacks
CURRENT

CHRONOLOGY

E11 How old were you when you first began having symptoms of panic attacks? ☐ age

E12 During the past year, for how many months did you have significant symptoms of panic attacks or worries about having an attack? ☐

F. AGORAPHOBIA

F1 Have you ever felt anxious or uneasy in places or situations where you might have a panic attack or the panic-like symptoms we just spoke about , or where help might not be available or escape might be difficult: like being in a crowd, standing in a line (queue), when you are alone away from home or alone at home, or when crossing a bridge, traveling in a bus, train or car? NO YES

IF **F1** = **NO**, CIRCLE **NO** IN **F2** AND IN **F3**.

F2 Have you ever feared these situations so much that you avoided them, or suffered through them, or needed a companion to face them? **NO** **YES**

AGORAPHOBIA
LIFETIME

F3 Do you **NOW** fear or avoid these places or situations? **NO** **YES**

AGORAPHOBIA
CURRENT

CHECK ONLY IF **YES**

IS AGORAPHOBIA CODED **YES**? **F2** ❑ lifetime **F3** ❑ current
IS PANIC DISORDER CODED **YES**? **E6** ❑ lifetime **E8** ❑ current

F4 a IS PANIC DISORDER, CURRENT (**E8)**, CODED **YES**,

AND

IS AGORAPHOBIA, CURRENT (**F3**), CODED **NO?**

NO **YES**

Panic Disorder, Current
without
AGORAPHOBIA

b IS PANIC DISORDER, CURRENT (**E8)**, CODED **YES**,

AND

IS AGORAPHOBIA, CURRENT (**F3**), CODED **YES?**

NO **YES**

Panic Disorder, Current
with
AGORAPHOBIA

c IS PANIC DISORDER, LIFETIME (**E6)**, CODED **NO**,

AND

IS AGORAPHOBIA, CURRENT (**F3**), CODED **YES?**

NO **YES**

AGORAPHOBIA, CURRENT
without history of
Panic Disorder

d IS AGORAPHOBIA, CURRENT (**F3**) CODED **YES**,

AND IS PANIC DISORDER CURRENT (**E8**) CODED **NO**,

AND IS PANIC DISORDER, LIFETIME (**E6**) CODED **YES**?

NO **YES**

AGORAPHOBIA, CURRENT
without current Panic Disorder but with a past history of Panic Disorder

e IS AGORAPHOBIA, CURRENT (**F3**) CODED **YES**, **NO** **YES**

AND LIMITED SYMPTOM ATTACKS (**E7**) CODED **NO**? ***AGORAPHOBIA, CURRENT*** **without history of Limited Symptom Attacks**

CHRONOLOGY

F5 How old were you when you first began to fear or avoid these situations (agoraphobia)? ☐ age

F6 During the past year, for how many months did you have significant fear or avoidance of these situations (agoraphobia)? ☐

G. SOCIAL PHOBIA (Social Anxiety Disorder)

(➨ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

G1 In the past month, were you fearful or embarrassed being watched, being the focus of attention, or fearful of being humiliated? This includes situations like speaking in public, eating in public or with others, writing while someone watches, or being in social situations. ➨ NO YES

G2 Is this fear excessive or unreasonable? ➨ NO YES

G3 Do you fear these situations so much that you avoid them or suffer through them? ➨ NO YES

G4 Does this fear disrupt your normal work or social functioning or cause you significant distress?

NO **YES**

SOCIAL PHOBIA
(Social Anxiety Disorder)
CURRENT

SUBTYPES

Do you fear and avoid 4 or more social situations? NO YES
If YES → generalized social phobia (social anxiety disorder)
If NO → social phobia (social anxiety disorder), not generalized

CHRONOLOGY

G5 How old were you when you first began to fear social situations? ☐ age

G6 During the past year, for how many months did have you have significant fear of social situations? ☐

H. SPECIFIC PHOBIA

(➨ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

H1	In the past month, have you been excessively afraid of things like: flying, driving, heights, storms, animals, insects, or seeing blood or needles?	➨ NO	YES
H2	Is this fear excessive or unreasonable?	➨ NO	YES
H3	Do you fear these situations so much that you avoid them or suffer through them?	➨ NO	YES
H4	Does this fear disrupt your normal work or social functioning or cause you significant distress?	**NO**	**YES**

SPECIFIC PHOBIA
CURRENT

CHRONOLOGY

H5	How old were you when you first began to fear or avoid this situation?	☐ age
H6	During the past year, how many times have you had significant fear of this situation?	☐

I. OBSESSIVE-COMPULSIVE DISORDER

(➨ ABOVE A NO MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

I1	In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? (For example, the idea that you were dirty, contaminated or had germs, **or** fear of contaminating others, **or** fear of harming someone even though you didn't want to, **or** fearing you would act on some impulse, **or** fear or superstitions that you would be responsible for things going wrong, **or** obsessions with sexual thoughts, images or impulses, **or** hoarding, collecting, **or** religious obsessions.) (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)	NO ➨ to **I4**	YES
I2	Did they keep coming back into your mind even when you tried to ignore or get rid of them?	NO ➨ to **I4**	YES
I3	Do you think that these obsessions are the product of your own mind and that they are not imposed from the outside?	NO	YES **obsessions**

I4 In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, arranging things, or other superstitious rituals? NO YES **compulsions**

IS **I3** OR **I4** CODED **YES**? ➡ NO YES

I5 Did you recognize that either these obsessional thoughts or compulsive behaviors were excessive or unreasonable? ➡ NO YES

I6 Did these obsessions or compulsions significantly interfere with your normal routine, occupational functioning, usual social activities, or relationships, or did they take more than one hour a day? NO YES

I7 a Were you taking any drugs or medicines just before these symptoms began?
❒ No ❒ Yes

b Did you have any medical illness just before these symptoms began?
❒ No ❒ Yes

IN THE CLINICIAN'S JUDGMENT: ARE EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S OBSESSIVE COMPULSIVE DISORDER***?***

I7 (SUMMARY): HAS AN ORGANIC CAUSE BEEN RULED OUT? NO YES

ARE **I6** AND **I7 (SUMMARY**) CODED **YES?**

NO **YES**

O.C.D.
CURRENT

I8 ARE **I6** AND **I7b** CODED **YES**

AND **I7 (SUMMARY)** CODED **NO**?

NO **YES**

O.C.D.
CURRENT
Due to a General Medical Condition

I9 ARE **I6** AND **I7a** CODED **YES**

AND **I7 (SUMMARY)** CODED **NO**?

NO **YES**

Current Substance Induced
O.C.D.

CHRONOLOGY

I10 How old were you when you first began having symptoms of OCD? ☐ age

I11 During the past year, for how many months did you have significant symptoms of OCD? ☐

J. POSTTRAUMATIC STRESS DISORDER (optional)

(➨ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

J1	Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else? EXAMPLES OF TRAUMATIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSAULT, A TERROIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, FIRE, DISCOVERING A BODY, SUDDEN DEATH OF SOMEONE CLOSE TO YOU, WAR, OR NATURAL DISASTER.	➨ NO	YES
J2	Did you respond with intense fear, helplessness or horror?	➨ NO	YES
J3	During the past month, have you re-experienced the event in a distressing way (such as, dreams, intense recollections, flashbacks or physical reactions)?	➨ NO	YES

J4	**In the past month:**		
a	Have you avoided thinking about or talking about the event ?	NO	YES
b	Have you avoided activities, places or people that remind you of the event?	NO	YES
c	Have you had trouble recalling some important part of what happened?	NO	YES
d	Have you become much less interested in hobbies or social activities?	NO	YES
e	Have you felt detached or estranged from others?	NO	YES
f	Have you noticed that your feelings are numbed?	NO	YES
g	Have you felt that your life will be shortened or that you will die sooner than other people?	NO	YES
	J4 (SUMMARY): ARE **3** OR MORE **J4** ANSWERS CODED **YES**?	➨ NO	YES
J5	**In the past month:**		
a	Have you had difficulty sleeping?	NO	YES
b	Were you especially irritable or did you have outbursts of anger?	NO	YES
c	Have you had difficulty concentrating?	NO	YES
d	Were you nervous or constantly on your guard?	NO	YES
e	Were you easily startled?	NO	YES
	J5 (SUMMARY): ARE **2** OR MORE **J5** ANSWERS CODED **YES**?	➨ NO	YES
J6	During the past month, have these problems significantly interfered with your work or social activities, or caused significant distress?	NO	YES

IS **J6** CODED **YES**?

NO	**YES**

Posttraumatic Stress Disorder
CURRENT

CHRONOLOGY

J7 How old were you when you first began having symptoms of PTSD? ☐ age

J8 Since the first onset how many illness periods of PTSD did you have? ☐

J9 During the past year, for how many months did you have significant symptoms of PTSD? ☐

K. ALCOHOL ABUSE AND DEPENDENCE

(➨ MEANS: GO TO THE DIAGNOSTIC BOXES, CIRCLE **NO** IN BOTH AND MOVE TO THE NEXT OPTIONAL **K.** MODULE)

		➨	
K1	**In the past 12 months**, have you had 3 or more alcoholic drinks within a 3 hour period on 3 or more occasions?	NO	YES

K2 **In the past 12 months**:

a	Did you need to drink more in order to get the same effect that you got when you first started drinking?	NO	YES
b	When you cut down on drinking, did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms or to avoid being hungover, for example, "the shakes", sweating or agitation? If **YES** to either question, code **YES**.	NO	YES
c	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	NO	YES
d	Have you tried to reduce or stop drinking alcohol but failed?	NO	YES
e	On the days that you drank, did you spend substantial time in obtaining alcohol, drinking, or in recovering from the effects of alcohol?	NO	YES
f	Did you spend less time working, enjoying hobbies, or being with others because of your drinking?	NO	YES
g	Have you continued to drink even though you knew that the drinking caused you health or mental problems?	NO	YES

ARE **3** OR MORE **K2** ANSWERS CODED **YES**?

* IF YES, SKIP K3 QUESTIONS, CIRCLE N/A IN THE ABUSE BOX AND MOVE TO THE NEXT DISORDER. DEPENDENCE PREEMPTS ABUSE.

NO **YES***

ALCOHOL DEPENDENCE
CURRENT

K3 **In the past 12 months:**

a	Have you been intoxicated, high, or hungover more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems? (CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)	NO	YES
b	Were you intoxicated more than once in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
c	Did you have legal problems more than once because of your drinking, for example, an arrest or disorderly conduct?	NO	YES
d	Did you continue to drink even though your drinking caused problems with your family or other people?	NO	YES

ARE **1** OR MORE **K3** ANSWERS CODED **YES?**

NO **N/A** **YES**

ALCOHOL ABUSE
CURRENT

(Optional) K. LIFETIME ALCOHOL ABUSE AND DEPENDENCE

(➨ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE **NO** IN BOTH, AND MOVE TO THE NEXT MODULE)

		➨ NO	YES
K4	**Did you ever** have 3 or more alcoholic drinks within a 3 hour period on 3 or more occasions?		

K5 **In your lifetime**:

a	Did you need to drink more in order to get the same effect that you did when you first started drinking?	NO	YES
b	When you cut down on drinking did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms or to avoid being hungover, for example, "the shakes", sweating or agitation? IF **YES** TO EITHER QUESTION, CODE **YES**.	NO	YES
c	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	NO	YES
d	Have you tried to reduce or stop drinking alcohol but failed?	NO	YES
e	On the days that you drank, did you spend substantial time in obtaining alcohol, drinking, or in recovering from the effects of alcohol?	NO	YES
f	Did you spend less time working, enjoying hobbies, or being with others because of your drinking?	NO	YES
g	Have you continued to drink even though you knew that the drinking caused you health or mental problems?	NO	YES

ARE **3** OR MORE **K5** ANSWERS CODED **YES?**

NO **YES***

* IF YES, SKIP K6 QUESTIONS, CIRCLE N/A IN THE ABUSE BOX AND MOVE TO THE NEXT DISORDER. DEPENDENCE PREEMPTS ABUSE.

ALCOHOL DEPENDENCE
LIFETIME

In your lifetime:

K6 a	Have you been intoxicated, high, or hungover more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems? (CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)	NO	YES
b	Were you intoxicated in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
c	Have you had any legal problems because of your drinking, for example, an arrest or disorderly conduct?	NO	YES
d	Have you continued to drink even though your drinking caused problems with your family or other people?	NO	YES

ARE **1** OR MORE **K6** ANSWERS CODED **YES?**

NO **N/A** **YES**

ALCOHOL ABUSE
LIFETIME

L. NON-ALCOHOL PSYCHOACTIVE SUBSTANCE USE DISORDERS

(➨ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

Now I am going to show you/read to you a list of street drugs or medicines.

			➨	
L1	a	**Have you ever taken** any of these drugs more than once to get high, to feel better, or to change your mood?	NO	YES

CIRCLE EACH DRUG TAKEN:

Stimulants: amphetamines, "speed", crystal meth, “crank”,”rush”, Dexedrine, Ritalin, diet pills.

Cocaine: snorting, IV, freebase, crack, "speedball".

Narcotics: heroin, morphine, Dilaudid, opium, Demerol, methadone, codeine, Percodan, Darvon, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, PCP ("Angel Dust", "peace pill"), psilocybin, STP, "mushrooms", ecstasy, MDA, MDMA or ketamine (“special K”).

Inhalants: "glue", ethyl chloride, "rush", nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Marijuana: hashish ("hash"), THC, "pot", "grass", "weed", "reefer".

Tranquilizers: Quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown, GHB, Roofinol, “Roofies”.

Miscellaneous: steroids, nonprescription sleep or diet pills. Any others?

Specify MOST USED Drug(s): _____

CHECK ONE BOX

ONLY ONE DRUG / DRUG CLASS HAS BEEN USED ☐

ONLY THE MOST USED DRUG CLASS IS INVESTIGATED. ☐

EACH DRUG CLASS USED IS EXAMINED SEPARATELY (PHOTOCOPY L2 AND L3 AS NEEDED) ☐

b SPECIFY WHICH DRUG/DRUG CLASS WILL BE EXPLORED IN THE INTERVIEW BELOW IF THERE IS CONCURRENT OR SEQUENTIAL POLYSUBSTANCE USE:_____

L2 **Considering the (name of drug / drug class selected), in your lifetime:**

	a	Have you found that you needed to use more (name of drug / drug class selected) to get the same effect that you did when you first started taking it?	NO	YES
	b	When you reduced or stopped using (name of drug / drug class selected), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better? IF **YES** TO EITHER QUESTION, CODE **YES**.	NO	YES
	c	Have you often found that when you used (name of drug / drug class selected), you ended up taking more than you thought you would?	NO	YES
	d	Have you tried to reduce or stop taking (name of drug / drug class selected), but failed?	NO	YES
	e	On the days that you used (name of drug / drug class selected), did you spend substantial time (> 2 hours) in obtaining, using or in recovering from drug(s), or thinking about drug(s)?	NO	YES

f Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use? NO YES

g Have you continued to use (name of drug / drug class selected) even though it caused you health or mental problems? NO YES

ARE **3** OR MORE **L2** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

NO **YES**

SUBSTANCE DEPENDENCE

LIFETIME

➡

L3 a Have you used (most used drug, any drug) in the past 12 months? NO YES

b ARE **3** OR MORE **L2** ANSWERS CODED **YES** WITHIN THE PAST 12 MONTHS? NO YES

ARE **L3a** AND **b** CODED **YES**?

SPECIFY DRUG(S): _____

* IF YES, SKIP L4 QUESTIONS, CIRCLE N/A IN THE ABUSE BOX FOR THIS SUBSTANCE AND MOVE TO THE NEXT DISORDER. DEPENDENCE PREEMPTS ABUSE.

NO **YES***

SUBSTANCE DEPENDENCE
CURRENT

Considering your use of (name the drug / drug class selected), in the past 12 months:

L4 a Have you been intoxicated, high, or hungover from (name of drug / drug class selected) more than once, when you had other responsibilities at school, at work, or at home? Did this cause any problem? (CODE **YES** ONLY IF THIS CAUSED PROBLEMS.) NO YES

b Have you been high or intoxicated from (name of drug / drug class selected) more than once, in any situation where you were physically at risk, (for example, driving a car, riding a motorbike, using machinery, boating, etc.)? NO YES

c Did you have legal problems more than once, because of your drug use, for example,an arrest or disorderly conduct? NO YES

d Did you continue to use (name of drug / drug class selected) even though it caused problems with your family or other people? NO YES

ARE **1** OR MORE **L4** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

NO **N/A** **YES**

SUBSTANCE ABUSE
CURRENT

CHRONOLOGY

L5 How old were you when you first began having problems with drug abuse? ☐ age

M. PSYCHOTIC DISORDERS - Part 1

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE YES ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS "BIZARRE".

DELUSIONS ARE "BIZARRE" IF: CLEARLY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDABLE, AND CANNOT DERIVE FROM ORDINARY LIFE EXPERIENCE.

HALLUCINATIONS ARE SCORED "BIZARRE" IF: A VOICE COMMENTS ON THE PERSON'S THOUGHTS OR BEHAVIOR, OR WHEN TWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.

ALL OF THE PATIENT'S RESPONSES TO THE QUESTIONS SHOULD BE CODED IN COLUMN A. USE THE CLINICIAN JUDGMENT COLUMN (COLUMN B) ONLY IF THE CLINICIAN KNOWS FROM OTHER OUTSIDE EVIDENCE (FOR EXAMPLE, FAMILY INPUT) THAT THE SYMPTOM IS PRESENT BUT IS BEING DENIED BY THE PATIENT.

Now I am going to ask you about unusual experiences that some people have.

			COLUMN A Patient Response			COLUMN B Clinician Judgment (if necessary)	
					BIZARRE		BIZARRE
M1	a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you?	NO	YES	YES	YES	YES
	b	IF **YES**: Do you currently believe these things? **NOTE**: ASK FOR EXAMPLES, TO RULE OUT ACTUAL STALKING.	NO	YES	YES ➡**M6**	YES	YES ➡**M6**
M2	a	Have you ever believed that someone was reading your mind or could hear your thoughts or that you could actually read someone's mind or hear what another person was thinking?	NO		YES		YES
	b	IF **YES**: Do you currently believe these things?	NO		YES ➡**M6**		YES ➡**M6**
M3	a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICIAN**:** ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	NO		YES		YES
	b	IF **YES**: Do you currently believe these things?	NO		YES ➡**M6**		YES ➡**M6**
M4	a	Have you ever believed that you were being sent special messages through the TV, radio, or newspaper, or that a person you did not personally know was particularly interested in you?	NO	YES	YES	YES	YES
	b	IF **YES**: Do you currently believe these things?	NO	YES	YES ➡**M6**	YES	YES ➡**M6**
M5	a	Have your relatives or friends ever considered any of your beliefs strange or unusual? **INTERVIEWER:** ASK FOR EXAMPLES. CODE **YES** ONLY IF THE EXAMPLES ARE **CLEARLY** DELUSIONAL IDEAS (FOR EXAMPLE, SOMATIC OR RELIGIOUS DELUSIONS OR DELUSIONS OF GRANDIOSITY, JEALOUSY, GUILT, RUIN OR DESTITUTION OR OTHERS NOT EXPLORED IN **M1** TO **M4**).	NO	YES	YES	YES	YES
	b	IF **YES**: Do they currently consider your beliefs strange?	NO	YES	YES	YES	YES

					BIZARRE			BIZARRE
M6	a	Have you ever heard things other people couldn't hear, such as voices? HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS YES TO THE FOLLOWING:	NO	YES			YES	YES
		IF **YES:** Did you hear a voice commenting on your thoughts or behavior,or did you hear two or more voices talking to each other?	NO		YES		NO	YES
	b	IF **YES**: Have you heard these things in the past month? SCORE AS "YES BIZARRE" IF PATIENT HEARD A VOICE COMMENTING ON THEIR THOUGHTS OR BEHAVIOR OR HEARD TWO OR MORE VOICES TALKING TO EACH OTHER.	NO	YES	YES ➡**M8**		YES	YES ➡**M8**
M7	a	Have you ever had visions when you were awake or have you ever seen things other people couldn't see? CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.	NO	YES			YES	
	b	IF **YES**: Have you seen these things in the past month?	NO	YES			YES	

CLINICIAN'S JUDGMENT

M8	b	Is the patient currently exhibiting incoherence, disorganized speech, or marked loosening of associations?	NO	YES
M9	b	Is the patient currently exhibiting disorganized or catatonic behavior?	NO	YES
M10	b	Are negative symptoms of schizophrenia, for example, significant affective flattening, poverty of speech (alogia) or an inability to initiate or persist in goal-directed activities (avolition) prominent during the interview?	NO	YES
M11	a	IS THERE AT LEAST ONE "**YES**" FROM **M1** TO **M10b**?	NO	YES

M11 b

ARE THE ONLY SYMPTOMS PRESENT THOSE IDENTIFIED BY THE CLINICIAN FROM **M1** TO **M7** (COLUMN B) AND FROM **M8b** OR **M9b** OR **M10b**?

IF **YES**, SPECIFY IF THE LAST EPISODE IS CURRENT (AT LEAST ONE "b" QUESTION IS CODED "**YES**" FROM **M1** TO **M10b**) AND/OR LIFETIME (ANY QUESTION CODED **YES** FROM **M1** TO **M10b**) AND PASS TO THE NEXT DIAGNOSTIC SECTION.

IF **NO**, CONTINUE.

NO **YES**

PSYCHOTIC DISORDER NOT OTHERWISE SPECIFIED*

Current ❑
Lifetime ❑

***Provisional diagnosis due to insufficient information available at this time.**

WARNING: IF AT LEAST ONE "b" QUESTION IS CODED **YES**, CODE **M11c** AND **M11d**.
IF ALL "b" QUESTIONS ARE CODED NO, CODE ONLY **M11d**.

M11c

FROM **M1** TO **M10b**: ARE ONE OR MORE "b" ITEMS CODED "**YES BIZARRE**"?

OR

ARE TWO OR MORE "b" ITEMS CODED "**YES**" BUT NOT "**YES BIZARRE**"?

NO
Then Criterion "A" of Schizophrenia is not currently met

YES
Then Criterion "A" of Schizophrenia is currently met

M11d FROM **M1** TO **M10b**: ARE ONE OR MORE "a" ITEMS CODED "**YES BIZARRE**"

OR

ARE TWO OR MORE "a" ITEMS CODED "**YES**" BUT NOT "**YES BIZARRE**"?
(CHECK THAT AT LEAST 2 ITEMS OCCURRED DURING THE SAME TIME PERIOD.)

NO
Then Criterion "A" of Schizophrenia is not met Lifetime

OR IS **M11c** CODED **"YES"**

YES
Then Criterion "A" of Schizophrenia is met Lifetime

M12 a Were you taking any drugs or medicines just before these symptoms began?
❒ No ❒ Yes

b Did you have any medical illness just before these symptoms began?
❒ No ❒ Yes

c IN THE CLINICIAN'S JUDGMENT, ARE EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S PSYCHOSIS?
(IF NECESSARY, ASK OTHER OPEN-ENDED QUESTIONS.)
❒ No ❒ Yes

d HAS AN ORGANIC CAUSE BEEN RULED OUT? NO YES UNCERTAIN

IF **M12d** = **NO**: SCORE **M13 (a, b)** AND GO TO THE NEXT DISORDER
IF **M12d** = **YES**: CODE **NO** IN **M13 (a, b)** AND GO TO **M14**
IF **M12d** = **UNCERTAIN**: CODE **UNCERTAIN** IN **M13 (a, b)** AND GO TO **M14**

M13a IS **M12d** CODED **NO** BECAUSE OF A GENERAL MEDICAL CONDITION?

IF **YES**, SPECIFY IF THE LAST EPISODE IS

CURRENT (AT LEAST ONE "b" QUESTION IS CODED **YES** FROM **M1** TO **M10b**) AND/OR LIFETIME ("a" OR "b") QUESTION IS CODED **YES** FROM **M1** TO **M10b**.

NO **YES**

PSYCHOTIC DISORDER
Due to a General Medical Condition
Current ❑
Lifetime ❑
Uncertain, code later ❑

M13 b IS **M12d** CODED **NO** BECAUSE OF A DRUG?

IF **YES**, SPECIFY IF THE LAST EPISODE IS

CURRENT (AT LEAST ONE QUESTION "b" IS CODED **YES** FROM **M1** TO **M10b**) AND/OR LIFETIME (ANY "a" OR "b" QUESTION CODED **YES** FROM **M1** TO **M10b**).

NO **YES**

Substance Induced
PSYCHOTIC DISORDER
Current ❑
Lifetime ❑
Uncertain, code later ❑

M14 How long was the longest period during which you had those beliefs or experiences? _____
IF <1 DAY, GO TO THE NEXT SECTION.

M15 a During or after a period when you had these beliefs or experiences, did you have difficulty working, or difficulty in your relationships with others, or in taking care of yourself? NO YES

b IF **YES**, how long did these difficulties last? _____
IF ≥6 MONTHS, GO TO **M16.**

c Have you been treated with medications or were you hospitalized because of these beliefs or experiences, or the difficulties caused by these problems? NO YES

d IF **YES**, what was the longest time you were treated with medication or were hospitalized for these problems? _____

M16 a THE PATIENT REPORTED DISABILITY (**M15a CODED YES**) OR WAS TREATED OR HOSPITALIZED FOR PSYCHOSIS (**M15c = YES**). NO YES

b CLINICIAN'S JUDGMENT: CONSIDERING YOUR EXPERIENCE, RATE THE PATIENT'S **LIFETIME** DISABILITY CAUSED BY THE PSYCHOSIS.

absent	❑	1
mild	❑	2
moderate	❑	3
severe	❑	4

M17 WHAT WAS THE TOTAL DURATION OF THE PSYCHOSIS, TAKING INTO ACCOUNT THE ACTIVE PHASE (**M14**) AND THE ASSOCIATED DIFFICULTIES (**M15b**) AND PSYCHIATRIC TREATMENT (**M15d**).

1 ❑ ≥1 day to <1 month
2 ❑ ≥1 month to <6 months
3 ❑ ≥>6 months

CHRONOLOGY

M18 a How old were you when you first began having these unusual beliefs or experiences? ☐ age

b Since the first onset how many distinct times did you have significant episodes of these unusual beliefs or experiences? ☐

PSYCHOTIC DISORDERS - PART 2

DIFFERENTIAL DIAGNOSIS BETWEEN PSYCHOTIC AND MOOD DISORDERS

CODE THE QUESTIONS **M19** TO **M23** ONLY IF THE PATIENT DESCRIBED AT LEAST 1 PSYCHOTIC SYMPTOM (**M11a = YES** AND **M11b = NO**), NOT EXPLAINED BY AN ORGANIC CAUSE (**M12d = YES** OR **UNCERTAIN**).

M19 a DOES THE PATIENT CODE POSITIVE FOR CURRENT AND/OR PAST MAJOR DEPRESSIVE EPISODE (QUESTION **A8** CODED **YES**)? NO YES

b IF **YES**: IS **A1** (DEPRESSED MOOD) CODED **YES**? NO YES

c DOES THE PATIENT CODE POSITIVE FOR CURRENT AND/OR PAST MANIC EPISODE (QUESTION **D7** IS CODED **YES**)? NO YES

d IS **M19a** OR **M19c** CODED **YES**? NO YES
↓
STOP. Skip to M24

NOTE: VERIFY THAT THE RESPONSES TO THE QUESTIONS **M20** TO **M23** REFER TO THE PSYCHOTIC, DEPRESSIVE (**A8**) AND MANIC EPISODES (**D7**), ALREADY IDENTIFIED IN **M11c** AND **M11d, A8 AND D7**.
IN CASE OF DISCREPANCIES, REEXPLORE THE SEQUENCE OF DISORDERS, TAKING INTO ACCOUNT IMPORTANT LIFE ANCHOR POINTS/MILESTONES AND CODE **M20** TO **M23** ACCORDINGLY.

M20 When you were having the beliefs and experiences you just described (GIVE EXAMPLES TO PATIENT), were you also feeling depressed/high/irritable at the same time?

NO YES
↓
STOP. Skip to M24

M21 Were the beliefs or experiences you just described (GIVE EXAMPLES TO PATIENT) restricted exclusively to times you were feeling depressed/high/irritable?

NO YES
↓
STOP. Skip to M24

M22 Have you ever had a period of two weeks or more of having these beliefs or experiences when you were not feeling depressed/high/irritable?

NO YES
↓
STOP. Skip to M24

M23 Which lasted longer: these beliefs or experiences or the periods of feeling depressed/high/irritable?

1 ❑ mood
2 ❑ beliefs, experiences
3 ❑ same

M24 AT THE END OF THE INTERVIEW, GO TO THE DIAGNOSTIC ALGORITHMS FOR PSYCHOTIC DISORDERS.

CONSULT ITEMS **M11a** AND **M11b**:

IF THE CRITERION "A" OF SCHIZOPHRENIA IS MET (**M11c** AND/OR **M11d** = **YES**) GO TO DIAGNOSTIC ALGORITHMS I

IF THE CRITERION "A" OF SCHIZOPHRENIA IS NOT MET (**M11c** AND/OR **M11d** = **NO**) GO TO DIAGNOSTIC ALGORITHMS II

FOR MOOD DISORDERS GO TO DIAGNOSTIC ALGORITHM III.

N. ANOREXIA NERVOSA

(➨ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE **NO**, AND MOVE TO THE NEXT MODULE)

N1 a How tall are you? ☐ft ☐☐in. / ☐☐☐cm.

b What was your lowest weight in the past 3 months? ☐☐☐lbs. / ☐☐☐kgs.

IS PATIENT'S WEIGHT EQUAL TO OR BELOW THE THRESHOLD CORRESPONDING TO HIS / HER HEIGHT? (SEE TABLE BELOW) ➨ NO YES

In the past 3 months:

N2 In spite of this low weight, have you tried not to gain weight? ➨ NO YES

N3 Have intensely you feared gaining weight or becoming fat, even though you were underweight? ➨ NO YES

N4 a Have you considered yourself too big / fat or that part of your body was too big / fat? NO YES

b Has your body weight or shape greatly influenced how you felt about yourself? NO YES

c Have you thought that your current low body weight was normal or excessive? NO YES

N5 ARE 1 OR MORE ITEMS FROM **N4** CODED **YES**? ➨ NO YES

N6 FOR WOMEN ONLY: During the last 3 months, did you miss all your menstrual periods when they were expected to occur (when you were not pregnant)? ➨ NO YES

FOR WOMEN: ARE **N5** AND **N6** CODED **YES**?
FOR MEN: IS **N5** CODED **YES**?

➨
NO **YES**

ANOREXIA NERVOSA
CURRENT

CHRONOLOGY

N7 How old were you when you first began having symptoms of anorexia? ☐ age

N8 Since the first onset how many distinct illness periods of anorexia did you have? ☐

N9 During the past year, for how many months did you have significant symptoms of anorexia? ☐

TABLE HEIGHT / WEIGHT TABLE CORRESPONDING TO A BMI THRESHOLD OF 17.5 KG/M^2

Height/Weight														
ft/in	4'9	4'10	4'11	5'0	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10
lbs.	81	84	87	89	92	96	99	102	105	108	112	115	118	122
cm	145	147	150	152	155	158	160	163	165	168	170	173	175	178
kgs	37	38	39	41	42	43	45	46	48	49	51	52	54	55

Height/Weight					
ft/in	5'11	6'0	6'1	6'2	6'3
lbs.	125	129	132	136	140
cm	180	183	185	188	191
kgs	57	59	60	62	64

The weight thresholds above are calculated using a body mass index (BMI) equal to or below 17.5 kg/m^2 for the patient's height. This is the threshold guideline below which a person is deemed underweight by the DSM-IV and the ICD-10 Diagnostic Criteria for Research for Anorexia Nervosa.

O. BULIMIA NERVOSA

(➨ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE **NO** IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

O1	In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?	➨ NO	YES
O2	In the last 3 months, did you have eating binges as often as twice a week?	➨ NO	YES
O3	During these binges, did you feel that your eating was out of control?	➨ NO	YES
O4	Did you do anything to compensate for, or to prevent a weight gain from these binges, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications?	➨ NO	YES
O5	Does your body weight or shape greatly influence how you feel about yourself?	➨ NO	YES
O6	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO ↓ Skip to O8	YES
O7	Do these binges occur only when you are under (_____lbs./kgs.)? **INTERVIEWER**: WRITE IN THE ABOVE PARENTHESIS THE THRESHHOLD WEIGHT FOR THIS PATIENT'S HEIGHT FROM THE HEIGHT/WEIGHT TABLE IN THE ANOREXIA NERVOSA MODULE.	NO	YES
O8	IS **O5** CODED **YES** AND IS EITHER **O6** OR **O7** CODED **NO**?	**NO**	**YES**

BULIMIA NERVOSA
CURRENT

CHRONOLOGY

O9	How old were you when you first began having symptoms of bulimia?	☐☐ age
O10	Since the first onset how many illness periods of bulimia did you have?	☐☐
O11	During the past year, for how many months did you have significant symptoms of bulimia?	☐☐

SUBTYPES OF BULIMIA NERVOSA

Do you regularly engage in self induced vomiting, misuse of laxatives, diuretics or enemas?

[IN THE NON-PURGING TYPE THE PATIENT HAS USED OTHER COMPENSATORY BEHAVIORS SUCH AS FASTING OR EXCESSIVE EXERCISE, BUT NOT PURGING.]

NO	YES
Non-Purging Type	Purging Type

BULIMIA NERVOSA

SUBTYPES OF ANOREXIA NERVOSA

Binge-Eating/Purging Type

IS **O7** CODED **YES**?

NO	YES

ANOREXIA NERVOSA
Binge Eating/Purging Type
CURRENT

Restricting Type

Do you lose weight without purging?

NO	YES

ANOREXIA NERVOSA
Restricting Type
CURRENT

P. GENERALIZED ANXIETY DISORDER

(➨ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE **NO** IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

P1	a	Have you worried excessively or been anxious about several things over the past 6 months?	NO ➨	YES
	b	Are these worries present most days?	NO ➨	YES
		IS THE PATIENT'S ANXIETY RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	NO	YES ➨
P2		Do you find it difficult to control the worries or do they interfere with your ability to focus on what you are doing?	NO ➨	YES
P3		FOR THE FOLLOWING, CODE **NO**, IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT.		
		When you were anxious over the past 6 months, most of the time did you:		
	a	Feel restless, keyed up or on edge?	NO	YES
	b	Feel tense?	NO	YES
	c	Feel tired, weak or exhausted easily?	NO	YES
	d	Have difficulty concentrating or find your mind going blank?	NO	YES
	e	Feel irritable?	NO	YES
	f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening, or sleeping excessively)?	NO	YES
		SUMMARY OF P3: ARE **3** OR MORE **P3** ANSWERS CODED **YES**?	NO ➨	YES
P4		Did these symptoms of anxiety cause you significant distress or impair your ability to function at work, socially, or in some other important way?	NO ➨	YES
P5	a	Were you taking any drugs or medicines just before these symptoms began? ❒ No ❒ Yes		
	b	Did you have any medical illness just before these symptoms began? ❒ No ❒ Yes		
		IN THE CLINICIAN'S JUDGMENT: ARE EITHER OF THESE LIKELY TO BE DIRECT CAUSES OF THE PATIENT'S GENERALIZED ANXIETY DISORDER?		
		P5 (SUMMARY): HAS AN ORGANIC CAUSE BEEN RULED OUT?	NO	YES
		IS **P5 (SUMMARY)** CODED **YES**?	**NO**	**YES**

Generalized Anxiety Disorder
CURRENT

P6 IS **P5 (SUMMARY)** CODED **NO** AND **P5b** CODED **YES**?

NO **YES**
Current
Generalized Anxiety Disorder.
Due to a General
Medical Condition

P7 IS **P5 (SUMMARY)** CODED **NO** AND **P5a** CODED **YES**?

NO **YES**
Current
Substance Induced
Generalized Anxiety Disorder

CHRONOLOGY

P8 How old were you when you first began having symptoms of generalized anxiety? ☐ age

P9 During the past year, for how many months did you have significant symptoms of generalized anxiety? ☐

Q. ANTISOCIAL PERSONALITY DISORDER (optional)

(➨ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

Q1 **Before you were 15 years old, did you:**

a	repeatedly skip school or run away from home overnight?	NO	YES
b	repeatedly lie, cheat, "con" others, or steal?	NO	YES
c	start fights or bully, threaten, or intimidate others?	NO	YES
d	deliberately destroy things or start fires?	NO	YES
e	deliberately hurt animals or people?	NO	YES
f	force someone to have sex with you?	NO ➨	YES
	ARE **2** OR MORE **Q1** ANSWERS CODED **YES?**	NO	YES

DO NOT CODE **YES** TO THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED**.**

Q2 **Since you were 15 years old, have you:**

a	repeatedly behaved in a way that others would consider irresponsible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself?	NO	YES
b	done things that are illegal even if you didn't get caught (for example, destroying property, shoplifting, stealing, selling drugs, or committing a felony)?	NO	YES
c	been in physical fights repeatedly (including physical fights with your spouse or children)?	NO	YES
d	often lied or "conned" other people to get money or pleasure, or lied just for fun?	NO	YES
e	exposed others to danger without caring?	NO	YES
f	felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property?	NO	YES

ARE **3** OR MORE **Q2** QUESTIONS CODED **YES**?

NO	**YES**
ANTISOCIAL PERSONALITY DISORDER **LIFETIME**	

R. SOMATIZATION DISORDER (optional)

(➨ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

R1	a	Have you had **many** physical complaints not clearly related to a specific disease beginning before age 30?	NO ➨	YES
	b	Did these physical complaints occur over several years?	NO ➨	YES
	c	Did these complaints lead you to seek treatment?	NO ➨	YES
	d	Did these complaints cause significant problems at school, at work, socially, or in other important areas?	NO ➨	YES
R2		Did you have pain in your: head	NO	YES
		abdomen	NO	YES
		back	NO	YES
		joints, extremities, chest, rectum	NO	YES
		during menstruation	NO	YES
		sexual intercourse	NO	YES
		urination	NO	YES
		ARE **2** OR MORE **R2** ANSWERS CODED **YES?** ➨	NO	YES
R3		Did you have any of the following abdominal symptoms:		
		nausea	NO	YES
		bloating	NO	YES
		vomiting	NO	YES
		diarrhea	NO	YES
		intolerance of several different foods	NO	YES
		ARE **2** OR MORE **R3** ANSWERS CODED **YES?** ➨	NO	YES
R4		Did you have any of the following sexual symptoms:		
		loss of sexual interest	NO	YES
		erection or ejaculation problems	NO	YES
		irregular menstrual periods	NO	YES
		excessive menstrual bleeding	NO	YES
		vomiting throughout pregnancy	NO	YES
		ARE **2** OR MORE **R4** ANSWERS CODED **YES?** ➨	NO	YES
R5		Did you have any of the following symptoms:		
		paralysis or weakness in parts of your body	NO	YES
		impaired coordination or imbalance	NO	YES
		difficulty swallowing or lump in throat	NO	YES
		difficulty speaking	NO	YES
		difficulty emptying your bladder	NO	YES
		loss of touch or pain sensation	NO	YES
		double vision or blindness	NO	YES
		deafness, seizures, loss of consciousness	NO	YES
		significant episodes of forgetfulness	NO	YES
		unexplained sensations in your body	NO	YES
		(CLINICIAN: PLEASE EVALUATE IF THESE ARE SOMATIC HALLUCINATIONS)		
		ARE **2** OR MORE **R5** ANSWERS CODED **YES?** ➨	NO	YES

R6 Were the symptoms investigated by your physician? NO YES

R7 Was any medical illness found, or were you using any drug or medication that could explain these symptoms?
❒ No ❒ Yes

R6 AND R7 (SUMMARY): CLINICIAN: HAS AN ORGANIC CAUSE BEEN RULED OUT? NO YES

R8 Were the complaints or disability out of proportion to the patient's physical illness? NO YES

➡

IS **R7 (SUMMARY)** OR **R8** CODED **YES**? NO YES

➡

R9 Were the symptoms a pretense or intentionally produced (as in factitious disorder)? NO YES

IS **R9** CODED **NO?**

NO **YES**

SOMATIZATION DISORDER
LIFETIME

R10 Are you currently suffering from these symptoms?

NO **YES**

SOMATIZATION DISORDER
CURRENT

S. HYPOCHONDRIASIS

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

➡

S1 In the past six months, have you worried a lot about having a serious physical illness? NO YES
DO NOT CODE **YES** IF ANY PHYSICAL DISORDER CAN ACCOUNT FOR THE PHYSICAL SENSATIONS OR SIGNS THE PATIENT DESCRIBES.

➡

S2 Have you had this worry for 6 months or more? NO YES

➡

S3 Have you ever been examined by a doctor for these symptoms? NO YES

➡

S4 Have your illness fears persisted in spite of the doctor's reassurance? NO YES

S5 Does this worry cause you significant distress, or does it interfere with your ability to function at work, socially, or in other important ways? NO YES

S6 IS **S5** CODED **YES?**

NO **YES**

HYPOCHONDRIASIS
CURRENT

T. BODY DYSMORPHIC DISORDER

(➨ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE **NO**, AND MOVE TO THE NEXT MODULE)

T1	Are you preoccupied with a defect in your appearance?	➨ NO	YES
T2	Has this preoccupation persisted in spite of others (including a physician) genuinely feeling that your worry was excessive?	➨ NO	YES
T3	Does this preoccupation cause you significant distress, or does it interfere significantly with your ability to function at work, socially, or in some other important way?	NO	YES
T4	IS **T3** CODED **YES?**	**NO**	**YES**

BODY DYSMORPHIC DISORDER
CURRENT

U. PAIN DISORDER

(➨ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE **NO** IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

U1	Currently, is pain your main problem?	➨ NO	YES
U2	Currently, is the pain severe enough to need medical attention?	➨ NO	YES
U3	Currently is the pain causing you significant distress, or interfering significantly with your ability to function at work, socially, or in some other important way?	➨ NO	YES
U4	Did psychological factors or stress have an important role in the onset of the pain, or did they make it worse, or keep it going?	➨ NO	YES
U5	Is the pain a pretense or intentionally produced or feigned? (As in factitious disorder?)	NO	➨ YES
U6	Did a medical condition have an important role in the onset of the pain, or did the medical condition make it worse, or keep it going?	NO	YES
U7	Has the pain been present for more than 6 months?	NO ↓ Acute	YES ↓ Chronic
U8	IS **U6** CODED **NO?**	**NO**	**YES**

PAIN DISORDER
associated with psychological factors
CURRENT

U9 IS **U6** CODED **YES?**

NO **YES**

IF **U8** OR **U9** ARE CODED YES
AND **U7** = **NO**, ADD: ACUTE TO DIAGNOSIS TITLE
AND **U7** = **YES**, ADD: CHRONIC TO DIAGNOSIS TITLE

PAIN DISORDER
associated with
psychological factors
and general medical condition
CURRENT

V. CONDUCT DISORDER Age 17 or Younger

(➨ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

Please involve the family or significant caregiver in eliciting this information.

V1 **In the past 12 months** have you:

a	bullied, threatened or intimidated others	NO	YES
b	started fights	NO	YES
c	used a weapon that could harm someone (for example, knife, gun, bat, broken bottle)	NO	YES
d	deliberately hurt people	NO	YES
e	deliberately hurt animals	NO	YES
f	stolen things using force (for example, armed robbery, mugging, purse snatching, extortion)	NO	YES
g	forced anyone to have sex with you	NO	YES
h	deliberately started fires to damage property	NO	YES
i	deliberately destroyed things belonging to others	NO	YES
j	broken into someone's house or car	NO	YES
k	lied repeatedly to get things or "conned" (tricked) other people	NO	YES
l	stolen things	NO	YES
m	stayed out late at night in spite of your parents forbidding you, starting before age 13 years	NO	YES
n	run away from home at least twice	NO	YES
o	often skipped school, starting before age 13 years	NO	YES
		➨	
	ARE **3** OR MORE **V1** ANSWERS CODED **YES** WITH AT LEAST ONE CODED **YES** IN THE PAST 6 MONTHS?	NO	YES

➨

V2 Did these behaviors cause significant problems at school, at work, or with friends and family? NO YES

IS **V2** CODED **YES?**

NO **YES**

CONDUCT DISORDER
CURRENT

Subtypes	**Mark all that apply.**
With ADHD	❑
With history of physical or sexual abuse	❑
With history of traumatic divorce	❑
With history of adoption	❑
With other stresses	❑

W. ATTENTION DEFICIT/HYPERACTIVITY DISORDER

(Children/Adolescents)

(➨ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

Please involve the family or significant caregiver in eliciting this information.

In the past 6 months have you often:

W1	a	Failed to pay attention to details or made careless mistakes in school, work or other activities?	NO	YES
	b	Had difficulty paying attention when playing or doing some work?	NO	YES
	c	Seemed not to listen when spoken to directly?	NO	YES
	d	Not followed instructions, or failed to finish schoolwork or chores (even though you understood the instructions and weren't trying to be difficult)?	NO	YES
	e	Had difficulty getting organized?	NO	YES
	f	Avoided or disliked things that require a lot of thinking (like schoolwork or homework)?	NO	YES
	g	Lost things you needed?	NO	YES
	h	Become easily distracted by little things?	NO	YES
	i	Become forgetful in your day to day activities?	NO	YES
		W1 (SUMMARY): ARE **6** OR MORE **W1** ANSWERS CODED **YES**?	NO	YES

In the past 6 months have you often:

W2	a	Squirmed in your seat or fidgeted with your hands or feet	NO	YES
	b	Left your seat in class when you were not supposed to?	NO	YES
	c	Run around and climbed a lot when you shouldn't or others didn't want you to?	NO	YES
	d	Had difficulty playing quietly?	NO	YES
	e	Felt like you were "driven by a motor" or were always "on the go"?	NO	YES
	f	Talked too much?	NO	YES
	g	Blurted out an answer before the question was completed?	NO	YES
	h	Had difficulty waiting your turn?	NO	YES
	i	Interrupted or intruded on others?	NO ➨	YES
		W2 (SUMMARY): ARE **6** OR MORE **W2** ANSWERS CODED **YES**?	NO ➨	YES
W3		Did you have some of these hyperactive-impulsive or inattentive symptoms before you were 7 years old?	NO ➨	YES
W4		Have some of these symptoms caused significant problems in two or more of the following situations: at school, at work, at home, or with family or friends?	NO	YES

IS **W4** CODED **YES?**

NO	YES
Attention Deficit/Hyperactivity Disorder	
CURRENT	

ATTENTION DEFICIT/HYPERACTIVITY DISORDER
(Adult)

(➨ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

As a child:

W5	a	Were you active, fidgety, restless, always on the go?	NO	YES
	b	Were you inattentive and easily distractible?	NO	YES
	c	Were you unable to concentrate at school or while doing your homework?	NO	YES
	d	Did you fail to finish things, such as school work, projects, etc.?	NO	YES
	e	Were you short tempered, irritable, or did you have a "short fuse", or tend to explode.	NO	YES
	f	Did things have to be repeated to you many times before you did them?	NO	YES
	g	Did you tend to be impulsive without thinking of the consequences?	NO	YES
	h	Did you have difficulty waiting for your turn, frequently needing to be first?	NO	YES
	i	Did you get into fights and/or bother other children?	NO	YES
	j	Did your school complain about your behavior?	NO ➨	YES
		W5 (SUMMARY): ARE **6** OR MORE **W5** ANSWERS CODED **YES**?	NO ➨	YES
W6		Did you have some of these hyperactive-impulsive or inattentive symptoms before you were 7 years old?	NO	YES

As an adult:

W7	a	Are you still distractible?	NO	YES
	b	Are you intrusive, or do you butt in, or say things that you later regret either to friends, at work, or home?	NO	YES
	c	Are you impulsive, even if you have better control than when you were a child?	NO	YES
	d	Are you still fidgety, restless, always on the go, even if you have better control than when you were a child?	NO	YES
	e	Are you still irritable and get angrier than you need to?	NO	YES
	f	Are you still impulsive? For example, do you tend to spend more money than you really should?	NO	YES
	g	Do you have difficulty getting work organized?	NO	YES
	h	Do you have difficulty getting organized even outside of work?	NO	YES
	i	Are you under-employed or do you work below your capacity?	NO	YES

	j	Are you not achieving according to people's expectations of your ability?	NO	YES
	k	Have you changed jobs or have been asked to leave jobs more frequently than other people?	NO	YES
	l	Does your spouse complain about your inattentiveness or lack of interest in him/her and/or the family?	NO	YES
	m	Have you gone through two or more divorces, or changed partners more than others?	NO	YES
	n	Do you sometimes feel like you are in a fog, like a snowy television or out of focus?	NO	YES
		W7 (SUMMARY): ARE **9** OR MORE **W7** ANSWERS CODED **YES**?	NO	YES
W8		Have some of these symptoms caused significant problems in two or more of the following situations: at school, at work, at home, or with family or friends?	NO	YES

IS **W8** CODED **YES?**

NO	**YES**
	Adult Attention Deficit/Hyperactivity Disorder

X. ADJUSTMENT DISORDERS

(➨ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

EVEN IF A LIFE STRESS IS PRESENT OR A STRESS PRECIPITATED THE PATIENT'S DISORDER, DO NOT USE AN ADJUSTMENT DISORDER DIAGNOSIS IF ANY OTHER PSYCHIATRIC DISORDER IS PRESENT. SKIP THE ADJUSTMENT DISORDER SECTION IF THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOTHER SPECIFIC AXIS I DISORDER OR ARE MERELY AN EXACERBATION OF A PREEXISTING AXIS I OR II DISORDER.

ONLY ASK THESE QUESTIONS IF PATIENT CODES NO TO ALL OTHER DISORDERS.

X1		Are you having emotional or behavioral symptoms as a result of a life of stress? [Examples include anxiety/depression/misbehavior/physical complaints (examples of misbehavior include fighting, driving recklessly, skipping school, vandalism, violating the rights of others, or doing illegal things)].	NO	YES
X2		Did these emotional/behavioral symptoms start within 3 months of the onset of the stressor?	NO	YES
X3	a	Are these emotional/behavioral symptoms causing marked distress beyond what would be expected?	NO	YES
	b	Are these emotional/behavioral symptoms causing significant impairment in your ability to function socially, at work, or at school?	NO	YES
X4		Are these emotional/behavioral symptoms due entirely to the loss of a loved one (bereavement) and are they similar in severity, level of impairment and duration to what most others would suffer under similar circumstances? (If so this is uncomplicated bereavement.)		
		HAS UNCOMPLICATED BEREAVEMENT BEEN RULED OUT?	NO	YES
X5		Have these emotional/behavioral symptoms continued for more than 6 months after the stress stopped?	NO	YES

WHICH OF THESE EMOTIONAL / BEHAVIORAL SUBTYPES ARE PRESENT? MARK ALL THAT APPLY

A Depression, tearfulness or hopelessness. ❑

B Anxiety, nervousness, jitteriness, worry. ❑

C Misbehavior (for example, fighting, driving recklessly, skipping school, vandalism, violating other's rights, doing illegal things). ❑

D Work problems, school problems, physical complaints or social withdrawal. ❑

IF MARKED:

- A only, then code as Adjustment disorder **with depressed mood**. 309.0
- B only, then code as Adjustment disorder **with anxious mood**. 309.24
- C only, then code as Adjustment disorder **of conduct**. 309.3
- A and B only, then code as Adjustment disorder **with mixed anxiety and depressed mood**. 309.28
- C and (A or B), then code as Adjustment disorder **of emotions and conduct**. 309.4
- D only, then code as Adjustment Disorder **unspecified**. 309.9

IF **X5** IS CODED **NO,** THEN CODE DISORDER **YES** WITH SUBTYPE**.**

NO **YES**
Adjustment Disorder with_____
(see above for subtypes)

Y. PREMENSTRUAL DYSPHORIC DISORDER

(➨ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

Y1	During the past year, were most of your menstrual periods preceded by a period lasting about one week when your mood changed significantly?	NO ➨	YES
Y2	During these periods, do you have difficulty in your usual activities or relationships with others, are you less efficient at work, or do you avoid other people?	NO ➨	YES
Y3	During these premenstrual episodes (but not at in the week after your period ends) do you have the following problems most of the time:		
a	Do you feel sad, low, depressed, hopeless, or self-critical?	NO	YES
b	Do you feel particularly anxious, tense, keyed up or on edge?	NO	YES
c	Do you often feel suddenly sad or tearful, or are you particularly sensitive to others' comments?	NO	YES
d	Do you feel irritable, angry or argumentative?	NO	YES
	ARE **1** OR MORE **Y3** ANSWERS CODED **YES**?	NO ➨	YES
e	Are you less interested in your usual activities, such as work, hobbies or meeting with friends?	NO	YES
f	Do you have difficulty concentrating?	NO	YES
g	Do you feel exhausted, tire easily, or lack energy?	NO	YES
h	Does your appetite change, or do you overeat or have specific food cravings?	NO	YES

i	Do you have difficulty sleeping or do you sleep excessively?	NO	YES
j	Do you feel you are overwhelmed or out of control?	NO	YES
k	Do you have physical symptoms such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of bloating, or weight gain?	NO	YES

ARE **5** OR MORE **Y3** ANSWERS CODED **YES**?

IF **YES,** DIAGNOSIS MUST BE CONFIRMED BY PROSPECTIVE DAILY RATINGS DURING AT LEAST 2 CONSECUTIVE CYCLES.

NO **YES**
Premenstrual Dysphoric Disorder Probable
CURRENT

Z. MIXED ANXIETY-DEPRESSIVE DISORDER

DO NOT USE THIS MODULE ALONE WITHOUT FIRST COMPLETING ALL THE ANXIETY AND MOOD DISORDERS.

(➨ MEANS : GO TO THE DIAGNOSTIC BOX AND CIRCLE NO.

[SKIP THIS DISORDER IF PATIENT 'S SYMPTOMS HAVE ALREADY MET CRITERIA FOR ANY OTHER DISORDER AND CODE **NO** IN THE DIAGNOSTIC BOX.]

Z1	Have you been depressed or down consistently for at least a **month**?	➨ NO	YES	
Z2	When you felt depressed did you have any of the following symptoms for at least **one month**:			
	a. Did you have difficulty concentrating or find your mind going blank?	NO	YES	
	b. Did you have trouble sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening, or sleeping excessively)?	NO	YES	
	c. Did you feel tired or low in energy?	NO	YES	
	d. Did you feel irritable?	NO	YES	
	e. Did you worry too persistently for at least a month?	NO	YES	
	f. Did you cry easily?	NO	YES	
	g. Were you always on the lookout for possible dangers?	NO	YES	
	h. Did you fear the worst?	NO	YES	
	i. Did you feel hopeless about the future?	NO	YES	
	j. Was your self-confidence low, or did you feel worthless?	NO	YES	
	Summary of Z2: ARE **4** OR MORE **Z2** ANSWERS CODED **YES**?	➨ NO	YES	
Z3	Do these symptoms cause you significant distress or impair your ability to function at work, socially, or in some other important way?	➨ NO	YES	

Z4 a Were you taking any drugs or medicines just before these symptoms began?

b Did you have any medical illness just before these symptoms began?

IN THE CLINICIAN'S JUDGMENT are either of these likely to be direct causes of the patient's symptoms?

	HAS AN ORGANIC CAUSE BEEN RULED OUT?		NO ➡	YES UNCERTAIN
Z5 a.	The patient's symptoms meet criteria for:	Major Depression **LIFETIME**	NO ➡	YES
		Dysthymia **LIFETIME**	NO ➡	YES
		Panic Disorder **LIFETIME**	NO ➡	YES
		Generalized Anxiety Disorder **LIFETIME**	NO ➡	YES
b.	The patient's symptoms **CURRENTLY** meet criteria for:	any other anxiety disorder	NO ➡	YES
		any other mood disorder	NO ➡	YES
c.	The patient's symptoms are better accounted for by another psychiatric disorder.		NO	YES

Z6 IS **Z5c** CODED **YES?**

NO	**YES**
	MIXED ANXIETY - DEPRESSIVE DISORDER **CURRENT**

THIS CONCLUDES THE INTERVIEW

DSM-IV/ICD-10 DIAGNOSTIC/BILLING CODES FOR M.I.N.I. DIAGNOSES

Major Depressive Disorder

Single Episode/F32.x

296.20/F32.9	Unspecified
296.21/F32.0	Mild
296.22/F32.1	Moderate
296.23/F32.2	Severe Without Psychotic Features
296.24/F32.3	Severe With Psychotic Features
296.25/F32.4	In Partial Remission
296.26/F32.4	In Full Remission

Recurrent/F33.x

296.30/F33.9	Unspecified
296.31/F33.0	Mild
296.32/F33.1	Moderate
296.33/F33.2	Severe Without Psychotic Features
296.34/F33.3	Severe With Psychotic Features
296.35/F33.4	In Partial Remission
296.36/F33.4	In Full Remission

Dysthymia

300.4/F34.1

Mania

Bipolar I, Single Manic Episode/F30.x

296.00	Unspecified
296.01/F30.1	Mild
296.02/F30.1	Moderate
296.03/F30.1	Severe Without Psychotic Features
296.04/F30.2	Severe With Psychotic Features
296.05/F30.8	In Partial Remission
296.06/F30.8	In Full Remission

Bipolar I, Most Recent Episode: Manic/F31.x

296.40/F31.0	Hypomanic
296.40	Unspecified
296.41/F31.1	Mild
296.42/F31.1	Moderate
296.43/F31.1	Severe Without Psychotic Features
296.44/F31.2	Severe With Psychotic Features
296.45/F31.7	In Partial Remission
296.46/F31.7	In Full Remission

Bipolar I, Most Recent Episode: Depression/F31.x

296.50	Unspecified
296.51/F31.3	Mild
296.52/F31.3	Moderate
296.53/F31.4	Severe Without Psychotic Features
296.54/F31.5	Severe With Psychotic Features
296.55/F31.7	In Partial Remission
296.56/F31.7	In Full Remission

Bipolar I, Most Recent Episode: Mixed/F31.6

296.60	Unspecified
296.61/F31.3	Mild
296.62/F31.3	Moderate
296.63/F31.4	Severe Without Psychotic Features
296.64/F31.5	Severe With Psychotic Features
296.65/F31.7	In Partial Remission
296.66/F31.7	In Full Remission
296.70/F31.9	Bipolar I Disorder, Most Recent Episode: Unspecified
296.80/F31.9	Bipolar I Disorder, NOS
296.89/F31.8	Bipolar II Disorder

Panic Disorder/F40.01

300.01/F41.0	Without Agoraphobia
300.21/F40.01	With Agoraphobia

Agoraphobia

300.22/F40.00	Without History of Panic Disorder

Social Phobia (Social Anxiety Disorder)

300.23/F40.1

Specific Phobia

300.29/F40.2

Obsessive-Compulsive Disorder

300.30/F42.8

Generalized Anxiety Disorder

300.02/F41.1

Substance Dependence/Abuse

303.90/F10.2x	Alcohol Dependence
305.00/F10.1	Alcohol Abuse
305.20/F12.1	Cannabis Abuse
305.30/F16.1	Hallucinogen Abuse
305.40/F13.1	Sedative, Hypnotic, or Anxiolytic Abuse
305.50/F11.1	Opioid Abuse
305.60/F14.1	Cocaine Abuse
305.70/F15.1	Amphetamine Abuse
305.90/F15.00	Caffeine Intoxication
305.90/F18.1	Inhalant Abuse
305.90/ F19.00-F19.1	Other (or Unknown) Substance Abuse
305.90/F19.1	Phencyclidine Abuse

Psychotic Disorders

295.10/F20.1x	Schizophrenia, Disorganized Type
295.20/F20.2x	Schizophrenia, Catatonic Type
295.30/F20.0x	Schizophrenia, Paranoid Type
295.40/F20.8	Schizophreniform Disorder
295.60/F20.5x	Schizophrenia, Residual Type
295.70/F25.x	Schizoaffective Disorder
295.90/F20.3x	Schizophrenia, Undifferentiated Type
297.10/F22.0	Delusional Disorder
297.30/F24	Shared Psychotic Disorder
293.81/F06.2	Psychotic Disorder Due to..... (Indicate the General Medical Condition) With Delusions
293.82/F06.0	Psychotic Disorder Due to ..... (Indicate the General Medical Condition) With Hallucinations
293.89/F06.4	Anxiety Disorder Due to..... (Indicate the General Medical Condition)
293.89/F06.x	Catatonic Disorder Due to..... (Indicate the General Medical Condition)
298.80/F23.xx	Brief Psychotic Disorder
298.90/F29	Psychotic Disorder NOS

Anorexia Nervosa

307.10/F50.0

Bulimia Nervosa

307.51/F50.2

Posttraumatic Stress Disorder

309.81/F43.1

Suicidality

no code assigned

Antisocial Disorder

301.70/F60.2

Somatoform Disorders

300.81/F45.0	Somatization Disorder
300.70/F45.2	Hypochondriasis
300.70/F45.2	Body Dysmorphic Disorder

Pain Disorders

307.80/F45.4 Pain Disorder Associated with Psychological Factors

307.89/F45.4 Pain Disorder Associated with Both Psychological Factors and a General Medical Condition

Conduct Disorder

312.80/F91.8

Attention Deficit Disorder

314.01/F90.0 Attention Deficit/Hyperactivity Disorder, Combined Type

314.00/F98.8 Attention Deficit/Hyperactivity Disorder, Predominately Inattentive Type

314.01/F90.0 Attention Deficit/Hyperactivity Disorder, Predominately Hyperactive-Impulsive Type

Adjustment Disorders

309.00/F43.20 Adjustment Disorder with Depressed Mood

309.24/F43.28 Adjustment Disorder with Anxiety

309.28/F43.22 Adjustment Disorder with Mixed Anxiety & Depressed Mood

309.30/F43.24 Adjustment Disorder with Disturbance of Conduct

309.40/F43.25 Adjustment Disorder with Mixed Disturbance of Emotions & Conduct

309.90/F43.9 Adjustment Disorder, Unspecified

Premenstrual Dysphoric Disorder

no code assigned

CRITERION FOR RULING OUT OTHER AXIS I DISORDERS

[In the event of comorbidity, the following algorithm (or hierarchy of disorders based on DSM-IV) can be used to reduce the number of comorbid disorders down to those likely to be clinically meaningful.]

Question			Yes	No
Are the symptoms of X	restricted exclusively to or better explained by	Y, Z?	❑	❑

If diagnosis X is made, call up question, insert diagnosis X in column 1, and the corresponding Y, Z diagnosis in Column 2.

In any mix where:

	Diagnosis X			**Diagnosis Y, Z, etc.**
A	Major Depressive Disorder (MDE)	is present, leave it unless disorder is restricted exclusively		Manic, Hypomanic, or Mixed Episodes, Schizoaffective Disorder, Schizophreniform Disorder, Delusional Disorder or Psychotic Disorder NOS
B	Dysthymia	to, or better explained by, diagnosis Y, Z:		MDE or Mania
C	Suicidality			Can coexist with any other Axis I disorder
D	(Hypo)Manic Episode	"	"	MDE concurrently during the same week = mixed episode
E	Panic Disorder (PD)	"	"	Social Phobia, Specific Phobia, OCD, PTSD
F	Agoraphobia (AG)	"	"	Social Phobia, Specific Phobia, OCD or PTSD
G	Social Phobia (Soc Ph) (Social Anxiety Disorder)	"	"	PD or Agoraphobia
H	Specific Phobia (Sp Ph)	"	"	PD or AG or OCD or PTSD
I	Obsessive-Compulsive Disorder	"	"	Any Axis I Disorder
J	Posttraumatic Stress Disorder	"	"	Agoraphobia
K	Alcohol Dependence/Abuse	"	"	Can coexist with any other Axis I disorder
L	Drug Dependence/Abuse (Non-alcohol)	"	"	Can coexist with any other Axis I disorder
M	Psychotic Disorders (Psy)	"	"	Can coexist with any other Axis I disorder
N	Anorexia Nervosa (AN)	"	"	Can coexist with any other Axis I disorder
O	Bulimia Nervosa (BN)	"	"	Can coexist with any other Axis I disorder
P	Generalized Anxiety Disorder	"	"	MDE, Dys, Mania, PD, Psy, Soc Ph, Sp Ph, OCD, PTSD, Anxiety Disorder
Q	Antisocial Personality Disorder	"	"	Mania or Psychotic
R	Somatization Disorder	"	"	Can coexist with any other Axis I disorder
S	Hypochondriasis	"	"	GAD, OCD, PD, MDE, Separation Anxiety Disorder, another Somatoform disorder, Delusional disorder, Body Dysmorphic Disorder
T	Body Dysmorphic Disorder	"	"	MDE, PD, AN, Soc Ph, Sp Ph, OCD, PTSD, Psychotic
U	Pain Disorder	"	"	MDE, Mania, PD, GAD, OCD, PTSD, Soc Ph, Sp Ph, Psy, Dyspareunia
V	Conduct Disorder	"	"	Can coexist with any other Axis I disorder, ADHD
W	Attention Deficit Hyperactivity Disorder (ADHD)	"	"	Psychotic, Mania, Anxiety Disorder, MDE, Conduct Disorder
X	Adjustment Disorders	"	"	Any Axis I Disorder
Y	Premenstrual Dysphoric Dis.	"	"	PD, MDE, Dysthymic Disorder or a Personality Disorder
Z	Mixed Anxiety-Depressive Dis.	"	"	Any other psychiatric disorder.

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Translations	**M.I.N.I. 4.4 or earlier versions**	**M.I.N.I. 4.6/5.0, M.I.N.I. Plus 4.6/5.0 and M.I.N.I. Screen 5.0:**
Afrikaans	R. Emsley	W. Maartens
Arabic		O. Osman, E. Al-Radi
Bengali		H. Banerjee, A. Banerjee
Brazilian Portuguese	P. Amorim	P. Amorim
Bulgarian	L.G.. Hranov	
Chinese		L. Carroll, Y-J. Lee, Y-S. Chen, C-C. Chen, C-Y. Liu, C-K. Wu, H-S. Tang, K-D. Juang, Yan-Ping Zheng.
Croatian		In preparation
Czech		P. Zvlosky
Danish	P. Bech	P. Bech, T. Schütze
Dutch/Flemish	E. Griez, K. Shruers, T. Overbeek, K. Demyttenaere	I. Van Vliet, H. Leroy, H. van Megen
English	D. Sheehan, J. Janavs, R. Baker, K. Harnett-Sheehan, E. Knapp, M. Sheehan	D. Sheehan, R. Baker, J. Janavs, K. Harnett-Sheehan, M. Sheehan
Estonian		J. Shlik, A.Aluoja, E. Khil
Farsi/Persian		K. Khooshabi, A. Zomorodi
Finnish	M. Heikkinen, M. Lijeström, O. Tuominen	M. Heikkinen, M. Lijeström, O. Tuominen
French	Y. Lecrubier, E. Weiller, LI. Bonora, P. Amorim, J.P. Lepine	Y. Lecrubier, E. Weiller, P. Amorim, T. Hergueta
German	I. v. Denffer, M. Ackenheil, R. Dietz-Bauer	G. Stotz, R. Dietz-Bauer, M. Ackenheil
Greek	S. Beratis	T. Calligas, S. Beratis
Gujarati		M. Patel, B. Patel
Hebrew	J. Zohar, Y. Sasson	R. Barda, I. Levinson, A. Aviv
Hindi		C. Mittal, K. Batra, S. Gambhir
Hungarian	I. Bitter, J. Balazs	I. Bitter, J. Balazs
Icelandic		J.G. Stefansson
Italian	I. Bonora, L. Conti, M. Piccinelli, M. Tansella, G. Cassano, Y. Lecrubier, P. Donda, E. Weiller	L. Conti, A. Rossi, P. Donda
Japanese		T. Otsubo, H. Watanabe, H. Miyaoka, K. Kamijima, J. Shinoda, K. Tanaka, Y. Okajima
Lithuanian		A. Bacevicius
Latvian	V. Janavs, J. Janavs, I. Nagobads	V. Janavs, J. Janavs
Norwegian	G. Pedersen, S. Blomhoff	K.A. Leiknes , U. Malt, E. Malt, S. Leganger
Polish	M. Masiak, E. Jasiak	M. Masiak, E. Jasiak
Portuguese	P. Amorim	P. Amorim, T. Guterres
Punjabi		A. Gahunia, S. Gambhir
Romanian		O. Driga
Russian		A. Bystritsky, E. Selivra, M. Bystritsky
Serbian	I. Timotijevic	I. Timotijevic
Setswana		K. Ketlogetswe
Slovenian	M.Kocmur	M. Kocmur
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Urdu		A. Taj, S. Gambhir

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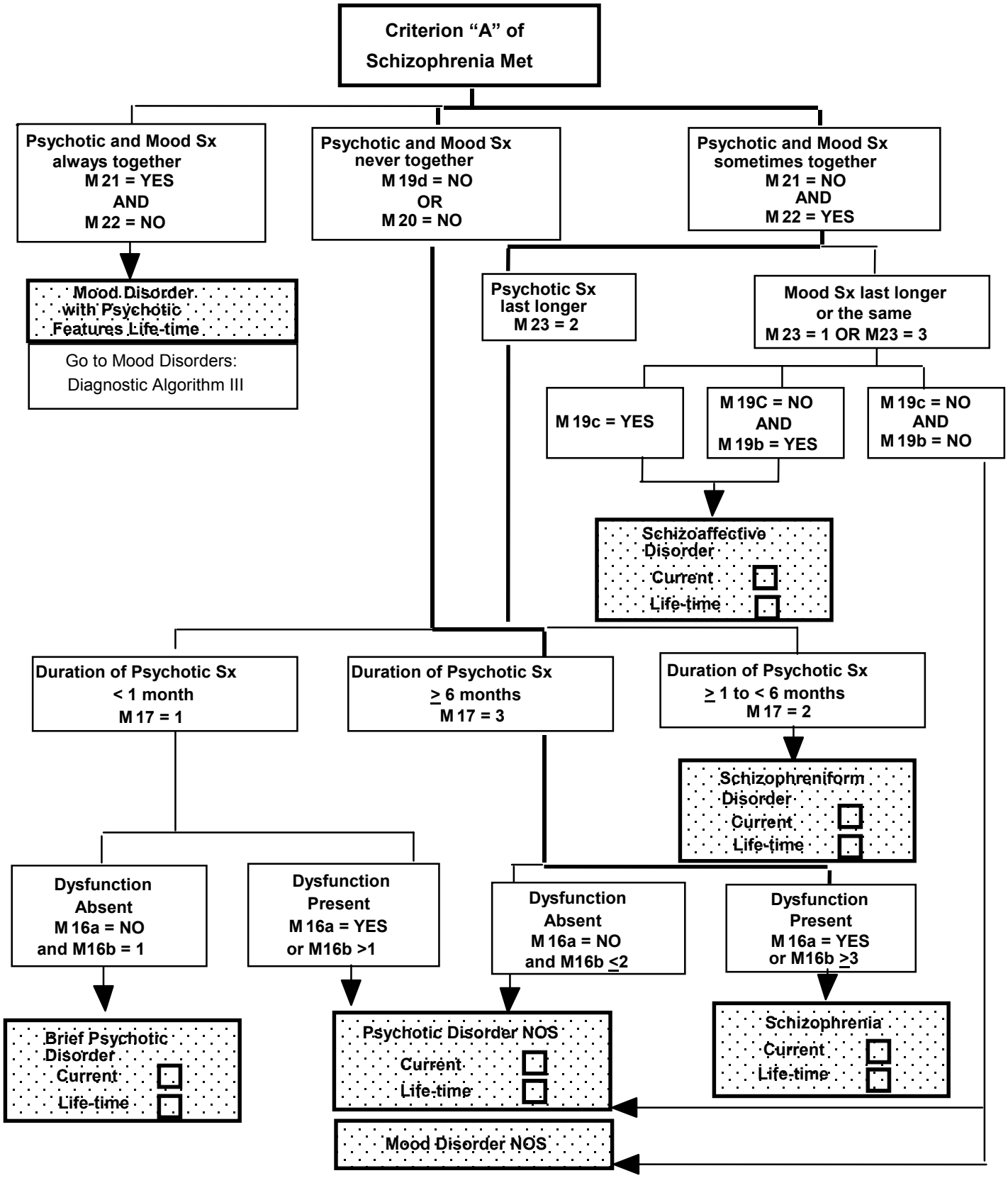
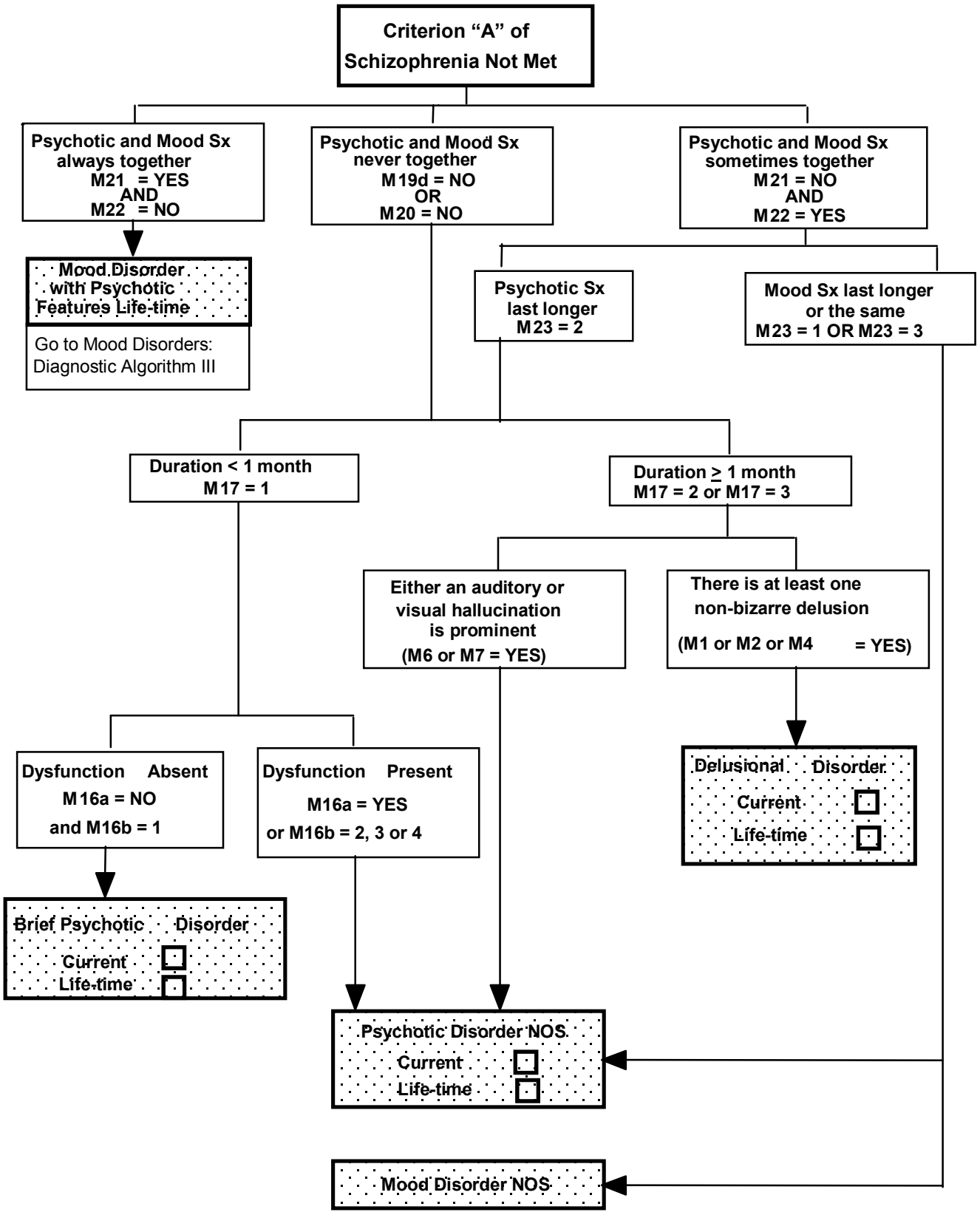
PSYCHOTIC DISORDERS: DIAGNOSTIC ALGORITHMS I

Circle the appropriated diagnostic box both for current and life-time diagnosis. One positive diagnosis excludes the others. If criterion A of schizophrenia is not currently met, but is present in life-time, current and life-time diagnosis may be different.



PSYCHOTIC DISORDERS: DIAGNOSTIC ALGORITHMS II

Circle the appropriated diagnostic box both for current and life-time diagnosis. One diagnosis excludes the others. If criterion A of schizophrenia is not currently met, but present in life-time, current and life-time diagnosis may be



MOOD DISORDERS: DIAGNOSTIC ALGORITHM III

Consult Modules: A [Major Depressive Episode]
D [(Hypo)manic Episode]
M [Psychotic Disorders]

MODULE M:

1 a IS **M20** CODED **NO**? NO YES → GO TO **2c**

b IS **M21** CODED **NO** AND **M22** CODED **YES**? NO YES → CODE **NO** IN **2c**, **2d** AND **2e**

c IS **M21** CODED **YES** OR **M22** CODED **NO**? NO YES

MODULES A and D:

2 a IS A DELUSIONAL IDEA IDENTIFIED IN **A3e**? No ❑ Yes ❑

b IS A DELUSIONAL IDEA IDENTIFIED IN **D3a**? No ❑ Yes ❑

c Is **A8 = YES** (Major Depressive Episode present)
and
D6 and D7 = NO (Hypomanic and Manic Episodes absent)?

Specify:
WITHOUT Psychotic Features: IF **1a = YES** and **2a** = **NO**
WITH Psychotic Features: IF **1a = NO** and **2a** = **YES**

Specify if last depressive episode is current or past (Question A8)

NO	**YES**
MAJOR DEPRESSIVE DISORDER	
without PF	❑
with PF	❑
current	❑
past	❑

d Is **D7 = YES** (Manic Episode present)?

Specify:
WITHOUT Psychotic Features: IF **1a = YES** and **2a** = **NO** and **2b** = **NO**
WITH Psychotic Features: IF **1a = NO** and **2a** = **YES** and **2b** = **YES**

Specify if the last mood episode is current or past (Question A8 or D6 or D7)

NO	**YES**
BIPOLAR I DISORDER	
without PF	❑
with PF	❑
current	❑
past	❑

e Is **A8 = YES** (Major Depressive Episode present)
and
D6 = YES (Hypomanic Episode present)
and
D7 = NO (Manic Episode absent)?

Specify if the last mood episode is current or past (Question A8 or D6)

NO	**YES**
BIPOLAR II DISORDER	
current	❑
past	❑

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit:_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Systematic Assessment for Treatment Emergent Events (SAFTEE-SI)

Instructions: Below is a list of Symptoms people sometimes have. Please read each item. Indicate how bothersome each symptom has been for you in the **last week** by circling the appropriate number to the right of the item.

	NONE	MILD	MODERATE	SEVERE
1. Trouble Sleeping	0	1	2	3
2. Nightmares or other sleep disturbance	0	1	2	3
3. Feeling drowsy or sleepy	0	1	2	3
4. Feeling nervous or hyper	0	1	2	3
5. Weakness or fatigue	0	1	2	3
6. Irritable	0	1	2	3
7. Poor memory	0	1	2	3
8. Trouble concentrating	0	1	2	3
9. Feeling strange	0	1	2	3
10. Hearing or seeing things	0	1	2	3
11. Abnormal sensations	0	1	2	3
12. Numbness or tingling	0	1	2	3
13. Dizziness or faintness	0	1	2	3
14. Headache	0	1	2	3
15. Blurred vision	0	1	2	3
16. Ringing in the ears or trouble hearing	0	1	2	3
17. Stuffy nose	0	1	2	3
18. Dry mouth	0	1	2	3
19. Drooling or increased salivation	0	1	2	3
20. Muscle cramps or stiffness	0	1	2	3
21. Muscle twitching or movements	0	1	2	3
22. Trouble sitting still	0	1	2	3
23. Tremor or shakiness	0	1	2	3
24. Poor coordination or unsteadiness	0	1	2	3
25. Slurred speech	0	1	2	3
26. Heartbeat rapid or pounding	0	1	2	3
27. Trouble catching breath or hyperventilation	0	1	2	3
28. Chest pain	0	1	2	3
29. Nausea or vomiting	0	1	2	3
30. Stomach or abdominal discomfort	0	1	2	3
31. Constipation	0	1	2	3
32. Diarrhea	0	1	2	3
33. Difficulty starting urination	0	1	2	3
34. Frequent need to urinate	0	1	2	3
35. Menstrual irregularities	0	1	2	3

Initials_____

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit:_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Systematic Assessment for Treatment Emergent Events (SAFTEE-SI)

	NONE	MILD	MODERATE	SEVERE
36. Loss of sexual interest	0	1	2	3
37. Problems with sexual arousal (erection or lubrication)	0	1	2	3
38. Delayed or absent orgasm	0	1	2	3
39. Sweating excessively	0	1	2	3
40. Fluid retention or swelling	0	1	2	3
41. Appetite decreased	0	1	2	3
42. Appetite increased	0	1	2	3
43. Weight gain	0	1	2	3
44. Weight loss	0	1	2	3
45. Skin rash or allergy	0	1	2	3
46. Diminished mental acuity/sharpness	0	1	2	3
47. Difficulties finding words	0	1	2	3
48. Apathy/Emotional Indifference	0	1	2	3
49. Dizziness when you stand up	0	1	2	3
50. Bruising	0	1	2	3
51. Hair thinning/loss	0	1	2	3
52. Hot flashes	0	1	2	3
53. Clenching of teeth at night	0	1	2	3
54. Strange taste in mouth	0	1	2	3
55. Unable to sit still	0	1	2	3
	No Side Effects	**Mildly**	**Moderately**	**Markedly**
How much have all these side-effects bothered you/interfered with your daily activities:	0	1	2	3

Initials_____

STRUCTURED INTERVIEW GUIDE FOR THE MONTGOMERY AND ASBERG DEPRESSION RATING SCALE (SIGMA)

Janet B.W. Williams, D.S.W. and Kenneth A. Kobak, Ph.D.

INTERVIEWER: The questions in bold for each item should be asked exactly as written. Often these questions will elicit enough information about the severity and frequency of a symptom for you to rate the item with confidence. Follow-up questions are provided, however, for use when further exploration or additional clarification of symptoms is necessary. The specified questions should be asked until you have enough information to rate the item confidently. In some cases, you may also have to add your own follow-up questions to obtain necessary information. Note that questions in parentheses are optional, i.e., if information is unknown.

NOTES:

Time period. The ratings should be based on the patient's condition in the past week.

Change from baseline. In general, a symptom is rated as present only when it reflects a change from before the depression began. The interviewer should try to identify a 2-month period of non-depressed functioning and use this as a reference point. In some cases, such as when the patient has Dysthymia, the referent should be to the last time they felt OK (i.e., not depressed or high) for at least a few weeks.

This interview guide is based on the Montgomery and Asberg Depression Rating Scale (MADRS) (Montgomery SA, Asberg M: A new depression scale designed to be sensitive to change. Brit J Psychiat 134:382-389, 1979). The scale itself has been retained in its original form, except for reversing the order of the first two items. This guide adds interview questions to aid in the assessment and application of the MADRS. Previous versions of this guide appeared in 1988, 1992, 1996, and 2005.

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STRUCTURED INTERVIEW GUIDE FOR THE MONTGOMERY AND ASBERG DEPRESSION RATING SCALE (SIGMA)

PT'S INITIALS: _____ PT'S ID: _____ **TIME BEGAN SIGMA: _____**

INTERVIEWER: _____ **DATE: __ __ __ __ __ __**

OVERVIEW: I'd like to ask you some questions about the past week. How have you been feeling since last (DAY OF WEEK)? IF OUTPATIENT: Have you been working? (What kind of work do you do?) IF NOT: Why not?

In the last week, have you been feeling sad or unhappy? (Depressed at all?) IF YES: Can you describe what this has been like for you? (IF UNKNOWN: How bad has that been?)

IF DEPRESSED: Does the feeling lift at all if something good happens? How much does your mood lift? Does the feeling ever go away completely? (What things have made you feel better?)

How often did you feel (depressed/OWN EQUIVALENT) this past week? (IF UNKNOWN: How many days this week did you feel that way? How much of each day?)

In the past week, how have you been feeling about the future? (Have you been discouraged or pessimistic?) What have your thoughts been? How (discouraged or pessimistic) have you been? How often have you felt that way? Do you think things will ever get better for you?

IF ACKNOWLEDGES DEPRESSED MOOD, TO GET CONTEXT ASK: How long have you been feeling this way?

1. REPORTED SADNESS. Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration, and the extent to which the mood is reported to be influenced by events.

0 - Occasional sadness in keeping with the circumstances.
1 –
2 - Sad or low but brightens up without difficulty.
3 –
4 - Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
5 –
6 – Continuous or unvarying sadness, misery, or despondency.

RATING BASED ON OBSERVATION DURING INTERVIEW AND THE FOLLOWING QUESTIONS.

In the past week, do you think you have looked sad or depressed to other people? Did anyone say you looked sad or down?

How about when you've looked in the mirror? Did you look gloomy or depressed?

IF YES: How sad or depressed do you think you have looked? How much of the time over the past week do you think you have looked depressed or down?

IF APPEARANCE WAS DEPRESSED IN PAST WEEK: Have you been able to laugh or smile at all during the past week? IF YES: How hard has it been for you to laugh or smile, even if you weren't feeling happy inside?

2. APPARENT SADNESS. Representing despondency, gloom and despair. (More than just ordinary transient low spirits) reflected in speech, facial expressions, and posture. Rate by depth and inability to brighten up.

0 – No sadness
1 –
2 - Looks dispirited but does brighten up without difficulty.
3 -
4 - Appears sad and unhappy most of the time.
5 –
6 – Looks miserable all the time. Extremely despondent.

Have you felt tense or edgy in the last week? Have you felt anxious or nervous?
IF YES: Can you describe what that has been like for you? How bad has that gotten? (Have you felt panicky?)

What about feeling fearful that something bad is about to happen?

How hard has it been to control these feelings? (What has it taken to help you feel calmer? Has anything worked to calm you down?)

How much of the time have you felt this way over the past week?

3. INNER TENSION. Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread, or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.

0 - Placid. Only fleeting inner tension.
1 -
2 - Occasional feelings of edginess and ill-defined discomfort.
3 –
4 – Continuous feelings of inner tension or intermittent panic which the patient can master with some difficulty.
5 –
6 – Unrelenting dread or anguish. Overwhelming panic.

How has your sleeping been in the last week? (How many hours have you been sleeping, compared to usual?)

Have you had trouble falling asleep? (How long has it been taking you to fall asleep this past week?)

Have you been able to stay asleep through the night? (Have you been waking up at all in the middle of the night? How long does it take you to fall back asleep?)

Has your sleeping been restless or disturbed?

4. REDUCED SLEEP. Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

0 - Sleeps as usual.
1 -
2 - Slight difficulty dropping off to sleep or slightly reduced, light, or fitful sleep.
3 –
4 – Sleep reduced or broken by at least two hours.
5 –
6 – Less than two or three hours sleep.

How has your appetite been this past week? (What about compared to your usual appetite?)

Have you been less interested in food? (How much less?)

Does food taste as good as usual? IF LESS: How much less?

Have you had to force yourself to eat?

Have other people had to urge you to eat?

5. REDUCED APPETITE. Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

0 - Normal or increased appetite.
1 –
2 - Slightly reduced appetite.
3 –
4 – No appetite. Food is tasteless.
5 –
6 – Needs persuasion to eat at all.

Have you had trouble concentrating or collecting your thoughts in the past week? (How about at home or at work?) IF YES: Can you give me some examples? (Have you been able to concentrate on reading a newspaper or magazine? Do you need to read things over and over again?)

How often has that happened in the past week? Has this caused any problems for you? IF YES: Can you give me some examples?

Has your trouble concentrating been so bad at any time in the past week that it has been difficult to follow a conversation? (IF YES: How bad has that been? How often has that happened this past week?)

NOTE: ALSO CONSIDER BEHAVIOR DURING INTERVIEW.

6. CONCENTRATION DIFFICULTIES. Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

0 - No difficulties in concentration.
1 -
2 - Occasional difficulties in collecting one's thoughts.
3 –
4 – Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
5 –
6 – Unable to read or converse without great difficulty.

Have you had any trouble getting started at things in the past week? IF YES: What things?

Have you had to push yourself to do things? IF YES: What things? How hard have you had to push yourself? Are you OK once you get started or is it still more of an effort to get something done? What about getting started at simple routine everyday things (like getting dressed)?

Have you done everyday things more slowly than usual? (Have you been sluggish?) IF YES: Like what, for example? How bad has that been?

7. LASSITUDE. Representing a difficulty getting started, or slowness initiating and performing everyday activities.

0 - Hardly any difficulty in getting started. No sluggishness.
1 -
2 - Difficulties in starting activities.
3 –
4 – Difficulties in simple routine activities which are carried out with effort.
5 –
6 – Complete lassitude. Unable to do anything without help.

Have you been less interested in things around you, or in activities you used to enjoy? IF YES: What things? How bad has that been? How much less interested in (those things) are you now compared to before?

Have you been less able to enjoy the things you usually enjoy?

Has there been any change in your ability to feel emotions? (Do you feel things less intensely than you used to, things like anger, grief, pleasure?) IF YES: Can you tell me more about that? (IF UNKNOWN: Are you able to feel any emotions at all?)

How do you feel toward your family and friends? Is that different from usual? IF REDUCED: Do you feel less than you used to towards them?

8. INABILITY TO FEEL. Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

0 - Normal interest in the surroundings and in other people.
1 -
2 - Reduced ability to enjoy usual interests.
3 –
4 – Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
5 –
6 – The experience of being emotionally paralyzed, inability to feel anger, grief, or pleasure, and a complete or even painful failure to feel for close relatives and friends.

Have you been putting yourself down, or feeling that you're a failure in some way, over the past week? (Have you been blaming yourself for things that you've done, or not done?) IF YES: What have your thoughts been? How often have you felt that way?

Have you been feeling guilty about anything in the past week? What about feeling as if you have done something bad or sinful? IF YES: What have your thoughts been? How often have you felt that way?

ALSO CONSIDER RESPONSES TO QUESTIONS ABOUT PESSIMISM FROM ITEM #1.

9. PESSIMISTIC THOUGHTS. Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse, and ruin.

0 - No pessimistic thoughts.
1 -
2 - Fluctuating ideas of failure, self-reproach, or self-depreciation.
3 –
4 – Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
5 –
6 – Delusions of ruin, remorse, or unredeemable sin. Self-accusations which are absurd and unshakable.

This past week, have you felt like life isn't worth living? IF YES: Tell me about that. IF NO: What about feeling like you're tired of living?

This week, have you thought that you would be better off dead? IF YES: Tell me about that.

Have you had thoughts of hurting or even killing yourself this past week? IF YES: What have you thought about? How often have you had these thoughts? How long have they lasted? Have you actually made plans? IF YES: What are these plans? Have you made any preparations to carry out these plans? (Have you told anyone about it?)

10. SUICIDAL THOUGHTS. Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparation for suicide. Suicidal attempts should not in themselves influence this rating.

0 - Enjoys life or takes it as it comes.
1 –
2 - Weary of life. Only fleeting suicidal thoughts.
3 -
4 - Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
5 –
6 – Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

TOTAL MADRS SCALE SCORE: _____ _____

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Hamilton Rating Scale for Depression (HRSD-17)

For each item, write the correct number on the line next to the item. Select only one response per item.

1. Depressed Mood: (sad, blue, gloomy, weepy, pessimistic, helpless, hopeless, worthless)	☐ (0) Not depressed ☐ (1) Feeling state only elicited on questioning ☐ (2) Occasional weeping. Spontaneously reports feeling states. ☐ (3) Frequent weeping. Obvious behavioral evidences in face, posture, voice. Speaks mostly about feeling state. ☐ (4) Exhibits virtually only these feeling states verbally and non-verbally. May have gone beyond weeping.
2. Guilt Feelings and Delusions:	☐ (0) Absent. ☐ (1) Self-reproach, feels they have let people down. ☐ (2) Expresses guilt regarding past errors or misdeeds. ☐ (3) Present illness is deserved punishment. Ruminates over past errors and sins. ☐ (4) Severe self-reproach. Guilty delusions, e.g. making other people ill. Deserves to die. May have accusatory/denouncing hallucinations.
3. Suicide:	☐ (0) Absent. ☐ (1) Feels life is empty, not worth living. ☐ (2) Recurrent thoughts or wishes about death of self. ☐ (3) Active suicidal thoughts, threats, gestures. ☐ (4) Serious suicide attempt.
4. Initial Insomnia:	☐ (0) Absent. ☐ (1) Mild, infrequent; more than ½ hr occasionally. ☐ (2) Obvious and severe; more than ½ hr usually.
5. Middle Insomnia:	☐ (0) Absent (rate 1 if hypnotic is being used). ☐ (1) Complains of feeling restless and disturbed during night. ☐ (2) Wakes during night; reads/smokes in bed, up out of bed except to void.
6. Delayed Insomnia:	☐ (0) Absent ☐ (1) Wakes earlier than usual but goes back to sleep. ☐ (2) Wakes 1-3 hours before usual; unable to sleep again.

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Hamilton Rating Scale for Depression (HRSD-17)

For each item, write the correct number on the line next to the item. Select only one response per item.

7. Work And Interests: (Apathy: loss of interest in work, hobbies, social life. Anhedonia: unable to feel pleasure)	☐ (0) No disturbance. ☐ (1) Feels incapable, listless, less efficient (rate fatigue under # 13). ☐ (2) Has to push to work/play. No active interests, little satisfaction. ☐ (3) Clearly decreased efficiency. No spontaneous activity. Marked loss of interest. ☐ (4) Stopped working because of present illness. Doesn't shave, bathe, etc. Avoids ward chores, needs urging.
8. Psychomotor Retardation: (Slowing of thought, speech, movement)	☐ (0) Absent. ☐ (1) Slightly flattened affect fixed facial expression. ☐ (2) Monotonous voice, delayed answering, sits motionless. ☐ (3) Interview difficult and prolonged. Moves slowly. ☐ (4) Depressive stupor. Interview impossible.
9. Agitation: (may co-exist with retardation)	☐ (0) Absent. ☐ (1) Fidgety. Clenching fists or chair arm. Kicking feet. ☐ (2)Wringing hands, pulling hair, picking at hands or clothes. Restless, pacing ☐ (3) Can't sit still. Much movement and restlessness/pacing. ☐ (4) Interview conducted "on the run", constant pacing, pulling off clothes, tearing at hair, constant picking at face/hands.
10. Psychic Anxiety: (present illness- not prior disposition. Tense, irritable, apprehensive, fearful, phobic, panic attacks)	☐ (0) Absent. ☐ (1) Minimal distress, admitted only on direct questioning. ☐ (2) Spontaneously expresses discomfort; worries over trivia. ☐ (3) Obviously apprehensive in facial expressions and speech. ☐ (4) Severely anxious, panicky, forgetful.
11. Somatic Anxiety: (Physio symptoms of anxiety; fainting, blurry vision, headache, tremor, sweating, flushing, hyperventilation, palpatations, indigestion, etc.)	☐ (0) Absent. ☐ (1) Trivial. ☐ (2) Mild. ☐ (3) Moderate. ☐ (4) Severe.
12. Appetite:	☐ (0) Normal. ☐ (1) Eats spontaneously, but without pleasure ☐ (2) Marked decrease of appetite and food intake. Eats only with urging, requests laxatives.

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Hamilton Rating Scale for Depression (HRSD-17)

For each item, write the correct number on the line next to the item. Select only one response per item.	
13. Somatic Energy:	☐ (0) Normal. ☐ (1) Occasional, mild fatigue, easy tiring, aching. ☐ (2) Obviously low in energy, constantly tired, heavy dragging feeling in limbs.
14. Libido:	☐ (0) Normal for age and marital status. ☐ (1) Mildly decreased drive and satisfaction. ☐ (2) Definite loss of desire, functional impotence.
15. Hypochondreasis:	☐ (0) Absent. ☐ (1) Mildly preoccupied w/bodily functions & physical symptoms. ☐ (2) Moderately concerned with physical health. ☐ (3) Morbid convictions of organic disease – brain tumor, cancer. ☐ (4) Bizarre delusions- worms eating head, rotting inside, bowels blocked.
16. Loss Of Insight:	☐ (0) Acknowledges being depressed and ill. ☐ (1) Acknowledges illness but attributes to bad food, climate, work, virus, need for rest. ☐ (2) Denies being ill at all.
17. Weight Loss:	☐ (0) No weight loss; less than 1 lb by scale. ☐ (1) Probable weight loss; or greater than 1 lb by scale. ☐ (2) Definite weight loss; or greater than 2 lbs by scale.
SIGNATURE	
HRSD Administered by: _____ Signature	
Total Hamilton Rating Scale for Depression (HRSD) Score:	_____

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Inventory of Depressive Symptomatology (IDS-C)

Please check one response to each item that best describes the patient for the last seven days	
1. Sleep Onset Insomnia:	☐ (0) Never takes longer than 30 minutes to fall asleep. ☐ (1) Takes at least 30 minutes to fall asleep, less than half the time. ☐ (2) Takes at least 30 minutes to fall asleep, more than half the time. ☐ (3) Takes more than 60 minutes to fall asleep, more than half the time.
2. Mid-Nocturnal Insomnia:	☐ (0) Does not wake up at night. ☐ (1) Restless, light sleep with few awakenings. ☐ (2) Wakes up at least once a night, but goes back to sleep easily. ☐ (3) Awakens more than once a night and stays awake for 20 minutes or more, more than half the time.
3. Early Morning Insomnia:	☐ (0) Less than half the time, awakens no more than 30 minutes before necessary. ☐ (1) More than half the time, awakens more than 30 minutes before need be. ☐ (2) Awakens at least one hour before need be, more than half the time. ☐ (3) Awakens at least two hours before need be, more than half the time.
4. Hypersomnia:	☐ (0) Sleeps no longer than 7-8 hours/night, without naps. ☐ (1) Sleeps no longer than 10 hours in a 24 hour period (include naps). ☐ (2) Sleeps no longer than 12 hours in a 24 hour period (include naps). ☐ (3) Sleeps longer than 12 hours in a 24 hour period (include naps).
5. Mood (Sad):	☐ (0) Does not feel sad. ☐ (1) Feels sad less than half the time. ☐ (2) Feels sad more than half the time. ☐ (3) Feels intensely sad virtually all of the time.
6. Mood (Irritable):	☐ (0) Does not feel irritable. ☐ (1) Feels irritable less than half the time. ☐ (2) Feels irritable more than half the time. ☐ (3) Feels extremely irritable virtually all of the time.
7. Mood (Anxious):	☐ (0) Does not feel anxious or tense. ☐ (1) Feels anxious/tense less than half the time. ☐ (2) Feels anxious/tense more than half the time. ☐ (3) Feels extremely anxious/tense virtually all of the time.
8. Reactivity of Mood:	☐ (0) Mood brightens to normal level and lasts several hours when good events occur. ☐ (1) Mood brightens but does not feel like normal self when good events occur. ☐ (2) Mood brightens only somewhat with few selected, extremely desired events. ☐ (3) Mood does not brighten at all, even when very good or desired events occur.

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Inventory of Depressive Symptomatology (IDS-C)

Please check one response to each item that best describes the patient for the last seven days	
9. Mood Variation: 9A. Is mood typically worse: in morning, afternoon, or night? **(circle one).** 9B. Is mood variation attributed to environment by the patient? yes or no **(circle one)**	☐ (0) Notes no regular relationship between mood and time of day. ☐ (1) Mood often relates to time of day due to environmental circumstances. ☐ (2) For most of the week, mood appears more related to time of day than to events. ☐ (3) Mood is clearly, predictably, better or worse at fixed time each day.
10. Quality of Mood:	☐ (0) Mood is virtually identical to feelings associated with bereavement or is undisturbed. ☐ (1) Mood is largely like sadness in bereavement, although it may lack explanation, be associated with more anxiety, or be much more intense. ☐ (2) Less than half the time, mood is qualitatively distinct from grief and therefore difficult to explain to others. ☐ (3) Mood is qualitatively distinct from grief nearly all of the time.
Complete <u>either</u> 11 <u>or</u> 12	
11. Appetite (Decreased):	☐ (0) No change from usual appetite. ☐ (1) Eats somewhat less often and/or lesser amounts than usual. ☐ (2) Eats much less than usual and only with personal effort. ☐ (3) Eats rarely within a 24-hour period, and only with extreme personal effort with persuasion by others.
12. Appetite (Increased):	☐ (0) No change from usual appetite. ☐ (1) More frequently feels a need to eat than usual. ☐ (2) Regularly eats more often and/or greater amounts than usual. ☐ (3) Feels driven to overeat at and between meals
Complete <u>either</u> 13 <u>or</u> 14	
13. Weight (Decrease) Within the Last Two Weeks:	☐ (0) Has experienced no weight change. ☐ (1) Feels as if some slight weight loss has occurred. ☐ (2) Has lost 2 pounds or more. ☐ (3) Has lost 5 pounds or more.
14. Weight (Increase) Within the Last Two Weeks:	☐ (0) Has experienced no weight change. ☐ (1) Feels as if some slight weight gain has occurred. ☐ (2) Has gained 2 pounds or more. ☐ (3) Has gained 5 pounds or more.

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Inventory of Depressive Symptomatology (IDS-C)

Check the one response to each item that best describes you for the past seven days.	
15. Concentration/Decision:	☐ (0) No change in usual capacity to concentrate and decide. ☐ (1) Occasionally feels indecisive or notes that attention often wanders. ☐ (2) Most of the time struggles to focus attention or make decisions. ☐ (3) Cannot concentrate well enough to read or cannot make even minor decisions.
16. Outlook (Self):	☐ (0) Sees self as equally worthwhile and deserving as others. ☐ (1) Is more self-blaming than usual. ☐ (2) Largely believes that he/she causes problems for others. ☐ (3) Ruminates over major and minor defects in self.
17. Outlook (Future):	☐ (0) Views future with usual optimism. ☐ (1) Occasionally has pessimistic outlook that can be dispelled by others or events. ☐ (2) Largely pessimistic for the near future. ☐ (3) Sees no hope for self/situation anytime in the future.
18. Suicidal Ideation:	☐ (0) Does not think of suicide or death. ☐ (1) Feels life is empty or is not worth living. ☐ (2) Thinks of suicide/death several times a week for several minutes. ☐ (3) Thinks of suicide/death several times a day in depth, or has made specific plans, or attempted suicide.
19. Involvement:	☐ (0) No change from usual level of interest in other people and activities. ☐ (1) Notices a reduction if former interests/activities. ☐ (2) Finds only one or two former interests remain. ☐ (3) Has virtually no interest in formerly pursued activities.
20. Energy/Fatiguability:	☐ (0) No change in usual level of energy. ☐ (1) Tires more easily than usual. ☐ (2) Makes significant personal effort to initiate or maintain usual daily activities. ☐ (3) Unable to carry out most of usual daily activities due to lack of energy.
21. Pleasure/Enjoyment (exclude sexual activity):	☐ (0) Participates in and derives usual sense of enjoyment from pleasurable activities. ☐ (1) Does not feel usual enjoyment from pleasurable activities. ☐ (2) Rarely derives pleasure from any activities. ☐ (3) Is unable to register any sense of pleasure/enjoyment from anything
22. Sexual <u>Interest</u>:	☐ (0) Has usual interest in or derives usual pleasure from sex. ☐ (1) Has near usual interest in or derives some pleasure from sex. ☐ (2) Has little desire for or rarely derives pleasure from sex. ☐ (3) Has absolutely no interest in or derives no pleasure from sex.

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Inventory of Depressive Symptomatology (IDS-C)

Check the one response to each item that best describes you for the past seven days.	
23. Psychomotor:	☐ (0) Normal speed of thinking, gesturing, and speaking. ☐ (1) Patient notes slowed thinking, and voice modulation is reduced. ☐ (2) Takes several seconds to respond to most questions; reports slowed thinking. ☐ (3) Is largely unresponsive to most questions without strong encouragement.
24. Psychomotor Agitation:	☐ (0) No increased speed or disorganization in thinking or gesturing. ☐ (1) Fidgets, wrings hands and shifts positions often. ☐ (2) Describes impulse to move about and displays motor restlessness. ☐ (3) Unable to stay seated. Paces about with or without permission.
25. Somatic Complaints:	☐ (0) States there is no feeling of limb heaviness or pains. ☐ (1) Complains of headaches, abdominal, back or joint pains that are intermittent and not disabling. ☐ (2) Complains that the above pains are present most of the time. ☐ (3) Functional impairment results from the above pain.
26. Sympathetic Arousal:	☐ (0) Reports no palpitations, tremors, blurred vision, tinnitus or increased sweating, dyspnea, hot and cold flashes, chest pain. ☐ (1) The above are mild and only intermittently present. ☐ (2) The above are moderate and present more than half the time. ☐ (3) The above result in functional impairment.
27. Panic/Phobic Symptoms:	☐ (0) Has neither panic episodes nor phobic symptoms. ☐ (1) Has mild panic episodes or phobias that do not usually alter behavior or incapacitate. ☐ (2) Has significant panic episodes or phobias that modify behavior or incapacitate. ☐ (3) Has incapacitating panic episodes at least once a week or severe phobias that lead to complete and regular avoidance behavior.
28. Gastrointestinal:	☐ (0) Has no change in usual bowel habits. ☐ (1) Has intermittent constipation and/or diarrhea that is mild. ☐ (2) Has diarrhea and/or constipation most of the time that does not impair functioning. ☐ (3) Has intermittent presence of constipation and/or diarrhea that requires treatment or causes functional impairment.
29. Interpersonal Sensitivity:	☐ (0) Has not felt easily rejected, slighted, criticized or hurt by others at all. ☐ (1) Occasionally feels rejected, slighted, criticized or hurt by others. ☐ (2) Often feels rejected, slighted, criticized or hurt by others, but with only slight effects on social/occupational functioning. ☐ (3) Often feels rejected, slighted, criticized or hurt by others that results in impaired social/occupational functioning.

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Inventory of Depressive Symptomatology (IDS-C)

Check the one response to each item that best describes you for the past seven days.	
30. Leaden Paralysis/Physical Energy:	☐ (0) Does not experience the physical sensation of feeling weighted down and without physical energy. ☐ (1) Occasionally experiences periods of feeling physically weighted down and without physical energy, but without a negative effect on work, school, or activity. ☐ (2) Feels physically weighted down (without physical energy) more than half the time. ☐ (3) Feels physically weighted down (without physical energy) most of the time, several hours per day, several days per week.

SIGNATURE
IDS-C Administered by: _____ Signature

Inventory of Depressive Symptomatology (IDS-C) TOTAL SCORE:	_____

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Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR)

Check the one response to each item that best describes you for the past seven days.	
1. Falling Asleep:	☐ (0) I never take longer than 30 minutes to fall asleep. ☐ (1) I take at least 30 minutes to fall asleep, less than half the time. ☐ (2) I take at least 30 minutes to fall asleep, more than half the time. ☐ (3) I take more than 60 minutes to fall asleep, more than half the time.
2. Sleep During the Night:	☐ (0) I do not wake up at night. ☐ (1) I have a restless, light sleep with a few brief awakenings each night. ☐ (2) I wake up at least once a night, but I go back to sleep easily ☐ (3) I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.
3. Waking Up Too Early:	☐ (0) Most of the time, I awaken no more than 30 minutes before I need to get up. ☐ (1) More than half the time, I awaken more than 30 minutes before I need to get up. ☐ (2) I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually. ☐ (3) I awaken at least one hour before I need to, and can't go back to sleep.
4. Sleeping Too Much:	☐ (0) I sleep no longer than 7-8 hours/night, without napping during day. ☐ (1) I sleep no longer than 10 hours in a 24-hour period including naps. ☐ (2) I sleep no longer than 12 hours in a 24-hour period. ☐ (3) I sleep longer than 12 hours in a 24-hour period including naps.
Enter highest score on any 1 of the 4 sleep items (1-4 above)	
5. Feeling Sad:	☐ (0) I do not feel sad. ☐ (1) I feel sad less than half the time. ☐ (2) I feel sad more than half the time. ☐ (3) I feel sad nearly all of the time.
6. Decreased Appetite:	☐ (0) There is no change in my usual appetite. ☐ (1) I eat somewhat less often or lesser amounts of food than usual. ☐ (2) I eat much less than usual and only with personal effort. ☐ (3) I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.
7. Increased Appetite:	☐ (0) There is no change from my usual appetite. ☐ (1) I feel a need to eat more frequently than usual. ☐ (2) I regularly eat more often and/or greater amounts of food than usual. ☐ (3) I feel driven to overeat both at mealtime and between meals.

Initials_____

ANS C-07-01
Date of Visit: ___/___/_____
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Subject Initials: _____
Subject Number: _____
Site Number: _____

Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR)

Check the one response to each item that best describes you for the past seven days.	
8. Decreased Weight (Within the Last Two Weeks):	☐ (0) I have not had a change in my weight. ☐ (1) I feel as if I have had a slight weight loss. ☐ (2) I have lost 2 pounds or more. ☐ (3) I have lost 5 pounds or more.
9. Increased Weight (Within the Last Two Weeks):	☐ (0) I have not had a change in my weight. ☐ (1) I feel as if I have had a slight weight gain. ☐ (2) I have gained 2 pounds or more. ☐ (3) I have gained 5 pounds or more.
Enter the highest score on any 1 of 4 appetite/weight change items (6-9 above)	
10. Concentration/Decision Making:	☐ (0) There is no change in my usual capacity to concentrate or make decisions. ☐ (1) I occasionally feel indecisive or find that my attention wanders. ☐ (2) Most of the time, I struggle to focus my attention or to make decisions. ☐ (3) I cannot concentrate well enough to read or cannot make even minor decisions.
11. View of Myself:	☐ (0) I see myself as equally worthwhile and deserving as other people. ☐ (1) I am more self-blaming than usual. ☐ (2) I largely believe that I cause problems for others. ☐ (3) I think almost constantly about major and minor defects in myself.
12. Thoughts of Death or Suicide:	☐ (0) I do not think of suicide or death. ☐ (1) I feel that life is empty or wonder if it's worth living. ☐ (2) I think of suicide or death several times a week for several minutes. ☐ (3) I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.
13. General Interests:	☐ (0) There is no change from usual in how interested I am in other people or activities. ☐ (1) I notice that I am less interested in people or activities. ☐ (2) I find I have interest in only one or two of my formerly pursued activities. ☐ (3) I have virtually no interest in formerly pursued activities.
14. Energy Level:	☐ (0) There is no change in my usual level of energy. ☐ (1) I get tired more easily than usual. ☐ (2) I have to make big effort to start or finish my usual daily activities (for example, shopping, homework, cooking, or going to work). ☐ (3) I really cannot carry out most of my usual daily activities because I just don't have the energy.

Initials_____

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Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR)

15. Feeling Slowed Down:	☐ (0) I think, speak, and move at my usual rate of speed. ☐ (1) I find that my thinking is slowed down or my voice sounds dull or flat. ☐ (2) It takes me several seconds to respond to most questions and I'm sure my thinking is slowed. ☐ (3) I am often unable to respond to questions without extreme effort.
16. Feeling Restless:	☐ (0) I do not feel restless. ☐ (1) I'm often fidgety, wringing my hands, or need to shift how I am sitting. ☐ (2) I have impulses to move about and am quite restless. ☐ (3) At times, I am unable to stay seated and need to pace around.
Enter Highest score on either of the 2 psychomotor items (15-16 above)	
TOTAL	
Total QIDS-SR Sore: **((highest score of 1-4)+5+(highest score of 6-9)+10+11+12+13+14+(highest score of 15-16))**	_____ **(range 0-27)**

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit:_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Young Mania Rating Scale (YMRS)

For each item, check one number per item. Select only one response per item	
1. Elevated Mood	☐ (0) Absent ☐ (1) Mildly or possibly increased on questioning ☐ (2) Definite subjective elevation; optimistic, self-confident; cheerful; and appropriate to content ☐ (3) Elevated; inappropriate to content; and humorous ☐ (4) Euphoric; inappropriate laughter; and singing
2. Increased motor activity/energy	☐ (0) Absent. ☐ (1) Subjectively increased ☐ (2) Animated; and gestures increased ☐ (3) Excessive energy; hyperactive at times; and restless (can be calmed) ☐ (4) Motor excitement; and continuous hyperactivity (cannot be calmed)
3. Sexual interest	☐ (0) Normal; not increased ☐ (1) Mildly or possibly increased ☐ (2) Definite subjective increase on questioning ☐ (3) Spontaneous sexual content; elaborates on sexual matters; and hypersexual by self-report ☐ (4) Overt sexual acts (towards patients, staff or interviewer)
4. Sleep	☐ (0) Reports no decrease in sleep ☐ (1) Sleeping less than normal amount by up to one hour ☐ (2) Sleeping less than normal by at least one hour ☐ (3) Reports decreased needs for sleep ☐ (4) Denies need for sleep
5. Irritability	☐ (0) Absent ☐ (2) Subjectively increased ☐ (4) Irritable at times during interview; and recent episodes of anger or annoyance on the ward ☐ (6) Frequently irritable during interview; and short curt throughout ☐ (8) Hostile, uncooperative; and interview impossible
6. Speech (rate and amount)	☐ (0) No increase ☐ (2) Subjectively increased ☐ (4) Increased rate or amount at times; and verbose at times ☐ (6) Push; consistently increased rate and amount; and difficult to interrupt ☐ (8) Pressured; and uninterruptible, continuous speech

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit:_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Young Mania Rating Scale (YMRS)

For each item, check one number per item. Select only one response per item	
7. Language-thought disorder	☐ (0) Absent ☐ (1) Circumstantial; mild distractibility; and quick thoughts ☐ (2) Distractible; loses goal of thought; changes topics frequently; and racing thoughts ☐ (3) Push; consistently increased rate and amount; and difficult to interrupt ☐ (4) Incoherent; and communication impossible
8. Content	☐ (0) Normal ☐ (2) Questionable plans, new interests ☐ (4) Special projects(s); and hyperreligious ☐ (6) Grandiose or paranoid ideas; and terms of reference ☐ (8) Delusions; and hallucinations
9. Disruptive-aggressive behavior	☐ (0) Absent. Cooperative ☐ (2) Sarcastic; and loud at times; guarded ☐ (4) Demanding; and threats on ward ☐ (6) Threatens interviewer; shouting; and interview difficult ☐ (8) Assaultive; destructive; and interview impossible
10. Appearance	☐ (0) Appropriate dress and grooming ☐ (1) Minimally unkempt ☐ (2) Poorly groomed; moderately disheveled; and overdressed ☐ (3) Disheveled; partly clothes; and garish make-up ☐ (4) Completely unkempt; decorated; and bizarre garb
11. Insight	☐ (0) Present; admits illness; and agrees with need for treatment ☐ (1) Possibly ill ☐ (2) Admits change in behavior, but denies illness. ☐ (3) Admits *possible* change in behavior, but denies illness ☐ (4) Denies any behavior change

SIGNATURE

YMRS Administered by:

_____

Signature

Young Mania Rating Scale (YMRS) TOTAL SCORE:	_____

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit:_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Work and Social Adjustment Scale (WSAS)

Instructions: Rate each of the following questions on a 0 to 8 scale: 0 indicates no impairment at all and 8 indicates very severe impairment.	
1. Because of my depression, my ability to work is impaired.	Rating: _____ 0 means not at all impaired and 8 indicates very severe impairment.
2. Because of my depression, my home management (cleaning, tidying, shopping, cooking, looking after home or children, paying bills) is impaired.	Rating: _____ 0 means not at all impaired and 8 indicates very severe impairment.
3. Because of my depression, my social leisure activities (with other people, such as parties, bars, clubs, outings, visits, dating, home entertainment) are impaired.	Rating: _____ 0 means not at all impaired and 8 indicates very severe impairment.
4. Because of my depression, my private leisure activities (done alone, such as reading gardening, collecting, sewing, walking alone) are impaired.	Rating: _____ 0 means not at all impaired and 8 indicates very severe impairment.
5. Because of my depression, may ability to form and maintain close relationships with others, including those I live with, is impaired.	Rating: _____ 0 means not at all impaired and 8 indicates very severe impairment.

TOTAL	
Work and Social Adjustment Scale (WSAS) TOTAL SCORE:	_____

Initials_____

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit:_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Global Assessment of Functioning (GAF)

Consider psychological, social and occupational functioning on a hypothetical continuum of mental health-illness. Do not include impairment in functioning due to physical (or environmental) limitations.	
Code	[Note: Use intermediate codes when appropriate, e.g., 45, 68, 72]
100 to 91	Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his or her many positive qualities. No symptoms.
90 to 81	Absent or minimal symptoms (e.g., mild anxiety before an exam), good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns (e.g., an occasional argument with family members).
80 to 71	If symptoms are present, they are transient and expectable reactions to psychosocial stressors (e.g., difficulty concentrating after family argument); no more than slight impairment in social, occupational or school functioning (e.g., temporarily falling behind in schoolwork).
70 to 61	Some mild symptoms (e.g., depressed mood and mild insomnia) OR some difficulty in social, occupational or school functioning (e.g., occasional truancy or theft within the household), but generally functioning pretty well, has some meaningful interpersonal relationships.
60 to 51	Moderate symptoms (e.g., flat affect and circumstantial speech, occasional panic attacks) OR any moderate difficulty in social, occupational or school functioning (e.g., few friends, conflicts with peers or co-workers).
50 to 41	Serious symptoms (e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting) OR any serious impairment in social, occupational or school functioning (e.g., no friends, unable to keep a job).
40 to 31	Some impairment in reality testing or communication (e.g., speech is at times illogical, obscure or irrelevant) OR major impairment in several areas, such as work or school, family relations, judgment, thinking or mood (e.g., expressed man avoids friends, neglects family and is unable to work; child frequently beats up younger children, is defiant at home and is failing at school).
30 to 21	Behavior is considerably influenced by delusions or hallucinations OR serious impairment in communication or judgment (e.g., sometimes incoherent, acts grossly inappropriately, suicidal preoccupation) OR inability to function in almost all areas (e.g., stays in bed all day; no job, home or friends).
20 to 11	Some danger of hurting self or others (e.g., suicide attempts without clear exception of death; frequently violent, manic excitement) OR occasionally fails to maintain minimal personal hygiene (e.g., smears feces) OR gross impairment in communication (e.g., largely incoherent or mute).
10 to 1	Persistent danger of severely hurting self or others (e.g., recurrent violence) OR persistent inability to maintain minimal personal hygiene OR serious suicidal act with clear exception of death.
0	Inadequate information.

Total GAF Score: _____ **Performed by: _____**

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit:_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Quality of Life Enjoyment and Satisfaction (QOL)

Check one response to each item that best describes you for the past seven days.	
1. Overall physical health—During the past week, think about your overall physical health-feeling well, having aches and pains, your energy, coordination and memory, and so forth. How would you rate your level of satisfaction with your physical health?	☐ (1) Very Poor ☐ (2) Poor ☐ (3) Fair ☐ (4) Good ☐ (5) Very Good
2. Mood—Now think about your mood over the past week. In terms of feeling content, relaxed, anxious, nervous, sad, or all other emotions, how would you rate your level of satisfaction with your mood?	☐ (1) Very Poor ☐ (2) Poor ☐ (3) Fair ☐ (4) Good ☐ (5) Very Good
3. Work performance—Think about how you have performed your work this past week. By work I mean job, volunteering, taking courses or going to school, or whatever work you do. This past week how would you rate your level of satisfaction with your work performance?	☐ (1) Very Poor ☐ (2) Poor ☐ (3) Fair ☐ (4) Good ☐ (5) Very Good
4. Household activities—If you're responsible for any household duties such as cleaning, shopping, food preparation, or other household tasks, either for yourself or for others, how satisfied have you been with your performance of household activities over the last week?	☐ (1) Very Poor ☐ (2) Poor ☐ (3) Fair ☐ (4) Good ☐ (5) Very Good
5. Social relationships—How satisfied have you been with your social relationships with friends, neighbors, co-workers, or other people this week?	☐ (1) Very Poor ☐ (2) Poor ☐ (3) Fair ☐ (4) Good ☐ (5) Very Good
6. Familial relationships—How about family relationships? How would you rate your level of satisfaction with family relationships during the past week?	☐ (1) Very Poor ☐ (2) Poor ☐ (3) Fair ☐ (4) Good ☐ (5) Very Good
7. Leisure activities—How much satisfaction have you had from leisure time activities such as watching TV, reading, gardening, hobbies, outings or sports events during the past week?	☐ (1) Very Poor ☐ (2) Poor ☐ (3) Fair ☐ (4) Good ☐ (5) Very Good

Initials_____

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit:_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Quality of Life Enjoyment and Satisfaction (QOL)

Check the one response to each item that best describes you for the past seven days.	
8. Ability to function—Over the past week, how satisfied have you been with your ability to function in daily life?	☐ (1) Very Poor ☐ (2) Poor ☐ (3) Fair ☐ (4) Good ☐ (5) Very Good
9. Sexual drive—During the past week, how satisfied have you been with your sexual drive and interest?	☐ (1) Very Poor ☐ (2) Poor ☐ (3) Fair ☐ (4) Good ☐ (5) Very Good
10. Economic status—What about your economic status…how would you rate your level of satisfaction with your economic status the past week?	☐ (1) Very Poor ☐ (2) Poor ☐ (3) Fair ☐ (4) Good ☐ (5) Very Good
11. Housing situation—How satisfied have you felt with your living or housing situation this past week?	☐ (1) Very Poor ☐ (2) Poor ☐ (3) Fair ☐ (4) Good ☐ (5) Very Good
12. Physical mobility—How satisfied are you with your ability to get around physically, without feeling dizzy or unsteady, or falling, during this past week?	☐ (1) Very Poor ☐ (2) Poor ☐ (3) Fair ☐ (4) Good ☐ (5) Very Good
13. Vision—How satisfied have you been during the past week with your vision? Has it impaired your ability to do work or hobbies?	☐ (1) Very Poor ☐ (2) Poor ☐ (3) Fair ☐ (4) Good ☐ (5) Very Good
14. Overall well-being—Taking everything into consideration during the past week, how satisfied have you been with your overall sense of well being?	☐ (1) Very Poor ☐ (2) Poor ☐ (3) Fair ☐ (4) Good ☐ (5) Very Good

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit:_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Quality of Life Enjoyment and Satisfaction (QOL)

Quality of Life Enjoyment and Satisfaction Questionnaire TOTAL SCORE:	_____
Check the one response to each item that best describes you for the past seven days. **(Please do not include 15 and 16 in the total score)**	
15. Treatment—During the past week, how satisfied have you been with your treatment?	☐ (1) Very Poor ☐ (2) Poor ☐ (3) Fair ☐ (4) Good ☐ (5) Very Good
16. Overall contentment—How would you rate your overall life satisfaction and contentment during the past week?	☐ (1) Very Poor ☐ (2) Poor ☐ (3) Fair ☐ (4) Good ☐ (5) Very Good

Initials_____

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit:_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Clinical Global Impression of Severity and Improvement (CGI)

Instructions: Circle the appropriate number after each of the following two items. Complete item 1- SEVERITY OF ILLNESS at the initial and subsequent assessments. Item 2 will be omitted at the initial assessment by marking 0- "Not Assessed".

1. Severity of Illness

0 = Not Assessed
1 = Normal, not ill at all
2 = Borderline mentally ill
3 = Mildly ill
4 = Moderately ill
5 = Markedly ill
6 = Severely ill
7 = Among the most extremely ill

The assessment below will be omitted at the initial assessment by marking "Not Assessed".

2. Global Improvement

Compared to these conditions on study Day 1, how much has the subject changed?

0 = Not Assessed
1 = Very much improved
2 = Much improved
3 = Minimally improved
4 = No change
5 = Minimally worse
6 = Much worse
7 = Very much worse

CGI Administered by: _____

ANS C-07-01
Date of Visit: ___/___/_____
Name of Visit:_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Patient Global Impression Index (PGI)

Instructions: Circle the appropriate number after each of the following two items. Complete item 1- SEVERITY OF ILLNESS at the initial and subsequent assessments. Item 2 will be omitted at the initial assessment by marking 0- "Not Assessed".

1. Severity of Illness

0 = Not Assessed
1 = Normal, not ill at all
2 = Borderline mentally ill
3 = Mildly ill
4 = Moderately ill
5 = Markedly ill
6 = Severely ill
7 = Among the most extremely ill

The assessment below will be omitted at the initial assessment by marking "Not Assessed"

2. Global Improvement

Compared to these conditions on study Day 1, how much have you changed?

0 = Not Assessed
1 = Very much improved
2 = Much improved
3 = Minimally improved
4 = No change
5 = Minimally worse
6 = Much worse
7 = Very much worse

Initials_____

Hamilton Anxiety Rating Scale (HAM-A)

1. Anxious Mood (covers the emotional condition of uncertainty about the future, ranging from worry, insecurity, irritability and apprehension to overpowering dread)

_____ 0= Not present; the patient is neither more or less insecure or irritable than usual

_____ 1= Doubtful whether the patient is more insecure or irritable than usual

_____ 2= Patient expresses more clearly to be in a state of anxiety, apprehension or irritability, which he/she may find difficult to control. However, worrying is still about minor matters and thus without influence on the patient's daily life

_____ 3= At times the anxiety or insecurity is more difficult to control because the worrying is about major injuries or harms which might occur in the future. Has occasionally interfered with the patient's daily life.

_____ 4= Severe. The feeling of dread is present so often that it markedly interferes with the patient's daily life

2. Tension (includes inability to relax, nervousness, bodily tensions, trembling and restless fatigue)

_____ 0= Not present; the patient is neither more nor less tense than usual

_____ 1= Patient seems somewhat more nervous and tense than usual

_____ 2= Patients expresses clearly unable to relax and full of inner unrest, which he/she finds difficult to control, but it is still without influence on the patient's daily life

_____ 3= The inner unrest and nervousness is so intense or frequent that it occasionally interferes with the patient's daily work

_____ 4= Severe. Tensions and unrest interfere with the patient's life and work at all times

3. Fears (includes fear of being in a crowd, of animals, of being in public places, of being alone, of traffic, of strangers, of dark, etc.

_____ 0= Not present

_____ 1= Doubtful whether present

_____ 2= Patient experiences phobic anxiety but is able to fight it

_____ 3= It is difficult to fight or overcome the phobic anxiety, which thus to some extent interferes with daily life and work

_____ 4= Severe. The phobic anxiety clearly interferes with the patient's daily life and work

4. Insomnia (covers the patient's subjective experience of sleep duration and sleep depth during the three preceding nights. Note: administration of hypnotics or sedatives is disregarded)

_____ 0= Not present; usual sleep duration and sleep depth

_____ 1= Sleep duration is doubtfully or slightly reduced (e.g. due to difficulties falling asleep), but no change in sleep depth

_____ 2= Sleep depth is also reduced, sleep being more superficial. Sleep as a whole is somewhat disturbed

_____ 3= Sleep duration and sleep depth is markedly changed. Sleep periods total only a few hours per 24 hours

_____ 4= Severe. Sleep depth is so shallow that the patient speaks of short periods of slumber or dozing, but no real sleep

5. Difficulties in concentration and memory (covers difficulties in concentration, making decisions about everyday matters, and memory)

_____ 0= Not present; the patient has neither more nor less difficulty in concentration and/or memory than usual

_____ 1= Doubtful whether the patient has difficulty in concentration and/or memory

_____ 2= Even with a major effort it is difficult for the patient to concentrate on his/her daily routine work

_____ 3= Patient has pronounced difficulties with concentration, memory, or decision making (e.g. in reading a newspaper article or watching a television program to the end)

_____ 4= Severe. During the interview the patient shows difficulty in concentration, memory, or decision making

Hamilton Anxiety Rating Scale (HAM-A)

6. Depressed Mood (covers both the verbal and non-verbal communication of sadness, depression, despondency, helplessness, and hopelessness)

_____ 0= Not present
_____ 1= Doubtful whether the patient is more despondent or sad than usual, or is only vaguely so
_____ 2= Patient is clearly concerned with unpleasant experiences, although he/she still lacks helplessness or hopelessness
_____ 3= Patient shows clear non-verbal signs of depression and/or hopelessness
_____ 4= Severe. Patient remarks on despondency and helplessness or the non-verbal signs dominate the interview and the patient cannot be distracted

7. General Somatic Complaints/Symptoms: Muscular (weakness, stiffness, soreness or real pain, more or less diffusely localized in the muscles, such as jaw ache or neck ache)

_____ 0= Not present; the patient is neither more nor less sore or stiff in the muscles than usual
_____ 1= Patient seems somewhat more stiff or sore in the muscles than usual
_____ 2= Symptoms have the character of pain
_____ 3= Muscle pain interferes to some extent with the patient's daily work and life
_____ 4= Severe. Muscle pain is present most of the time and clearly interferes with the patient's daily work and life

8. General Somatic Complaints/Symptoms: Sensory (includes increased fatigability and weakness or real functional disturbances of the senses, including tinnitus, blurring of vision, hot and cold flashes and prickling sensations

_____ 0= Not present
_____ 1= Doubtful whether the patient's indications of symptoms are more pronounced than usual
_____ 2= Sensations of pressure reach the character of buzzing in the ears, visual disturbances and prickling or itching sensations in the skin
_____ 3= The generalized sensory symptoms interfere to some extent with the patient's daily life and work
_____ 4= Severe. Generalized sensory symptoms are present most of the time and clearly interfere with the patient's daily life and work

9. Cardiovascular Symptoms (includes tachycardia, palpitations, oppression, chest pain, throbbing in the blood vessels, and feelings of faintness)

_____ 0= Not present
_____ 1= Doubtful whether present
_____ 2= Cardiovascular symptoms are present, but the patient can still control them
_____ 3= Patient has occasional difficulty controlling the cardiovascular symptoms, which thus to some extent interfere with his/her daily life and work
_____ 4= Severe. Cardiovascular symptoms are present most of the time and clearly interfere with the patient's daily life and work

Hamilton Anxiety Rating Scale (HAM-A)

10. Respiratory Symptoms (feelings of constriction or contraction in throat or chest, dyspnoea or choking sensations and sighing respiration)

_____ 0= Not present
_____ 1= Doubtful whether present
_____ 2= Respiratory symptoms are present, but the patient can still control them
_____ 3= Patient has occasional difficulty controlling the respiratory symptoms, which thus to some extent interfere with his/her daily life and work
_____ 4= Severe. Respiratory symptoms are present most of the time and clearly interfere with the patient's daily life and work

11. Gastrointestinal Symptoms (covers difficulties in swallowing, "sinking" sensations in stomach, dyspepsia (heartburn or burning sensation in the stomach, abdominal pains related to meals, fullness, nausea and vomiting), abdominal rumbling and diarrhea)

_____ 0= Not present
_____ 1= Doubtful whether present
_____ 2= One or more gastrointestinal symptoms are present, but the patient can still control them
_____ 3= Patient has occasional difficulty controlling the gastrointestinal symptoms, which to some extent interfere with his/her daily life and work
_____ 4= Severe. The gastrointestinal symptoms are present most of the time and interfere clearly with daily life and work

12. Genitourinary Symptoms (includes non-organic or psychic symptoms such as frequent or more pressing passing of urine, menstrual irregularities, anorgasmia, dyspareunia, premature ejaculation, loss of erection)

_____ 0= Not present
_____ 1= Doubtful whether present (or doubtful if different from usual)
_____ 2= One or more genitor-urinary symptoms are present, but do not interfere with the patient's daily life and work
_____ 3= Occasionally, one or more genito-urinary symptoms are present to such a degree that they interfere to some extent with the patient's daily life and work
_____ 4= Severe. The genitor-urinary symptoms are present most of the time and interfere clearly with life and work

13. Other Autonomic Symptoms (includes dryness of the mouth, blushing or pallor, sweating and dizziness)

_____ 0= Not present
_____ 1= Doubtful whether present
_____ 2= One or more autonomic symptoms are present, but they do not interfere with the patient's daily life and work
_____ 3= Occasionally, one or more autonomic symptoms are present to such a degree that they interfere to some extent with the patient's daily life and work
_____ 4= Severe. Autonomic symptoms are present most of the time and clearly interfere with daily life and work

14. Behavior During Interview (patient may appear tense, nervous, agitated, restless, tremulous, pale, hyperventilating or sweating during the interview. Based on such observations a global estimate is made)

_____ 0= The patient does not appear anxious
_____ 1= It is doubtful whether the patient is anxious
_____ 2= Patient is moderately anxious
_____ 3= Patient is markedly anxious
_____ 4= Severe. Patient is overwhelmed by anxiety, for example with shaking and trembling all over

Total Score: _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Lifetime: Time He/She Felt Most Suicidal

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?

If yes, describe:

Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".*
Have you been thinking about how you might do this?

If yes, describe:

Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".*
Have you had these thoughts and had some intention of acting on them?

If yes, describe:

Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could /can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others.
(2) Mostly to get attention, revenge or a reaction from others.
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(0) Does not apply

____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

ANS C-07-01
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Health and Labor Questionnaire (HLQ)

This questionnaire asks about the effects of health problems on paid and unpaid work (domestic). The term 'health problems' refers to acute or chronic physical illnesses symptoms or handicaps. Other health problems like chronic fatigue or pain are also covered by this. Furthermore, psychological disorders, are also included. At the end of the questionnaire you will be asked for your age and some other personal details. These details will assist us in gaining a more clear understanding of your answers. There are no 'correct' or 'incorrect' answers to the questions asked. We are interested only in your personal opinion.

*In addition to the questions relating to paid work there are some concerning unpaid work such as domestic chores. Throughout this questionnaire please limit your answers to your personal situation during the **PAST TWO WEEKS.***

1. Do you have paid employment?

☐ Yes, I work……..hours per WEEK, divided over……DAYS; my profession is…….., function…….

Go to the section Paid Work

☐ No

Please continue with question 14

*If your answer to the above question was **yes**, please continue by answering questions 2 to 13 (even if you are suffering from a short term illness at the present moment). If your answer to the above question was **no** please ignore questions 2 to 13 and continue with question 14.*

PAID WORK

We would like you to indicate on which working days in the **past two weeks** you were unable to perform paid work due to health problems. You are requested to complete this section using the following codes. In filling in the table on the following page you may use more then one letter.
'W' = performed paid work
'U' = unable to perform paid work due to health problems
'O' = no paid work performed due to other reasons (weekend, holidays etc.)
If you have part-time employment then fill in 'O' for the days on which you were not required to work. When you worked for half a day please indicate this e.g. by writing 'W/O' if you did not work in that afternoon.
In case of illness during the weekend fill in 'O' if you were not required to work and 'U' if you were required to work.

Initials_____

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Health and Labor Questionnaire (HLQ)

Example:
Imagine you have four days paid employment per week, but last week you were unable to work n Thursday and Friday due to health problems. You always have Wednesdays off. Then the table would appear as follows:

MO	TU	WE	TH	FR	SA	SU	MO	TU	WE	TH	FR	SA	SU
W	W	O	W	W	O	O	W	W	O	U	U	O	O

The week before last ***Last Week***

2. Please complete the table below in the same manner. Remember that the time period concerned is the past two full weeks, counting back from last weekend.
'W' = performed paid work
'U' = unable to perform paid work due to health problems
'O' = no paid work performed due to other reasons (weekend, holidays etc.)

MO	TU	WE	TH	FR	SA	SU	MO	TU	WE	TH	FR	SA	SU

The week before last ***Last Week***

Only answer the following question if you have been completely unable to perform paid work dueto health problems during the past two weeks.

3. When did this period of illness start? Enter the date on which you reported sick.
Day……Month……Year……..

Health problems sometimes force employees to be absent from their work. It is also possible that employees go to work but are unable to perform their duties with the same efficiency as usual due to health problems. Questions 4 to 13 relate to this subject.

4. Were you hindered by health problems at your paid work over the past two weeks?

☐ No, not at all → **go to question 13**

☐ Yes, to a degree

☐ Yes, very much

Initials_____

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Health and Labor Questionnaire (HLQ)

Below you find a number of statements that could be applicable to people with health problems in relation to their current work situation. Please indicate for each statement that is mentioned how often it applied to you in the past two weeks.

I **did** go to work but as a result of health problems ….

	Never	Sometimes	Often	Always
5. …I had a problem concentrating	☐	☐	☐	☐
6. …I had to go to work at a slower pace	☐	☐	☐	☐
7. …I had to seclude myself	☐	☐	☐	☐
9. …I had to put off some of my work	☐	☐	☐	☐
8. …I found decision-making more difficult	☐	☐	☐	☐
10. …Others had to take over some of my work	☐	☐	☐	☐

11. …I had other problems, namely (please state)……

12. How many **extra** hours would you have to work to catch up on tasks you were unable to complete in normal working hours due to health problems over the past two weeks?
NOTE: Do **not** count the days on which you reported sick……...…….Hours

13. We would now like to know what your **net** earnings are from your paid work.
NOTE: This concerns your income, not including that of your partner (if any). You only need to fill out **one** of the following options.

☐My own net income from paid work is approximately:
…… per WEEK
…….per 4 WEEKS
…….per MONTH
…….per YEAR

☐I do not know what my income is or I would rather not say
Now go to question 15

Initials_____

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Health and Labor Questionnaire (HLQ)

Question 14 should only be answered by people who do not/no longer have paid work at the present time.

14. You have no paid work. Which of the following situations is most applicable to you?

☐I have the daily task of running a household

☐I receive a pension or have taken early retirement

☐I am still at school or a student

☐I am unable to perform paid work due to health problems
(If you did have paid work before would you fill out your profession and the function you held:

profession……...……...function held …….……)

☐I have no paid work

Initials_____

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Health and Labor Questionnaire (HLQ)

TO BE COMPLETED BY ALL RESPONDENTS

The following questions concern unpaid work. Here a distinction has been made between work in the household; shopping; odd jobs and chores and activities for or with the children. We would everyone to please answer these questions. Firstly you will be asked how many hours a week you spent on each activity. If you did not perform a particular activity than simply write "0" hours. Secondly, we would like to know whether you were hindered in any of the activities mentioned by health problems.
Please remember that your answers should relate to the PAST TWO WEEKS.

15. How many hours a week did you spend on:

• Work in the household (e.g. preparing meals, cleaning the house, washing clothes)	……....hours per week
• Shopping (e.g. shopping for the daily groceries, other types of shopping, going to the bank or post office)	……...…hours per week
• Odd jobs and chores (e.g. house repairs, gardening, fixing the car)	..……..…hours per week
• Doing things for or with your own children (e.g. caring for them, taking them to school, helping with homework)	……...…..hours per week

16. It may be that people with health problems who normally do household tasks (cleaning the house, shopping, taking care of the children) must leave these tasks to be done by others due to their health problems.

Have others taken over any of your household tasks due to your health problems? (You may tick more then one box if applicable)

☐ Yes, family members (e.g. partner, children) have taken over my household tasks for . ..…..…….hours **per week**

☐ Yes, others (e.g. neighbors or volunteers) have taken over my household tasks for ……..hours **per week**

☐ Yes, I have had a home-help for …...…….hours **per week**

☐ Yes, I have had another type of paid help for ……..……hours **per week**

☐ No, I have performed my household tasks myself.

Initials_____

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Health and Labor Questionnaire (HLQ)

In the next table we would like you to indicate which of the following unpaid activities you have performed in the PAST TWO WEEKS and whether or not you were hindered by health problems. Please tick the appropriate answer.

These were two examples.

Example 1
During the PAST TWO WEEKS Mrs. Johnson did no go shopping in the city due to her health problems. She did manage to go to her local corner shop in spite of her problems. She indicates this as follows:

	DID DO		DID NOT DO	
	Was hindered by health problems	Was not hindered by health problems	Due to health problems	Other reasons.
Shopping	**X**			

Example 2
Mr. Cook never vacuums. His son always performs this task because Mr. Cook hates doing it. Mr. Cook answered the question on vacuuming as follows:

	DID DO		DID NOT DO	
	Was hindered by health problems	Was not hindered by health problems	Due to health problems	Other reasons.
Vacuuming				**X**

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Health and Labor Questionnaire (HLQ)

17. Would you now complete the table below in the same way as shown in the two examples. Put a cross next to an activity if you have performed it in the PAST TWO WEEKS your answer is "DID DO" then indicate whether or not you were hindered by health problems. If your answer is "DID NOT DO" then please indicate whether or not this was due to health problems.

	DID DO		DID NOT DO	
	Was hindered by health problems	Was not hindered by health problems	Due to health problems	Other reasons.
Household work at home (for example, preparing meals, cleaning, washing clothes)				
Shopping (for example, daily groceries, other shopping, going to the bank or post office)				
Odd jobs and chores (for example, house repairs, gardening, fixing the car)				
Doing things for or with your own children (for example, caring for them, playing, taking them to school, helping with homework)				

Initials_____

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Health and Labor Questionnaire (HLQ)

The following questions concern a general nature

1. Are you:

☐ Male

☐ Female

2. What is your date of birth?

day……month……....19…..……

3. Which of the following levels of education have you completed? (you may tick more than one answer if applicable)

☐ None ☐ Intermediate vocation education

☐ Primary school ☐ Grammar school

☐ Lower vocational education ☐ Polytechnic Higher vocational education

☐ General secondary education ☐University

4. How many people live in your household?

☐I live alone

☐I live with one or more people

5. Are there any children in your household?

☐Yes, the age of the youngest child in the household is……..……...months/years

☐No

Initials_____

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Health and Labor Questionnaire (HLQ)

6. Below is a list of chronic conditions and illnesses. Would you please indicate whether you are suffering from or have suffered from any of these conditions in the LAST TWELVE MONTHS?

Suffering from now or have suffered in the LAST TWELVE MONTHS:

	YES	NO
Asthma or chronic bronchitis		
Serious heart condition or heart Infarct		
High blood pressure		
A stroke or its consequences		
Stomach or duodenal ulcer		
Serious intestinal disturbance lasting more than three months		
Gall stones or infection of the gall bladder		
Liver condition or cirrhosis of the liver		
Kidney stones		
Serious kidney condition		
Complaint of the prostate gland		
Diabetes		
Thyroid gland condition		
Back problems of a persistent nature, hernia, ischia or "worn out" back		
Arthritis of the knees, hips or hands		
Rheumatism of the hands and/or feet		
Other rheumatic conditions		
Epilepsy		
Other nervous disorders such as Parkinson's disease, multiple sclerosis		
Serious headaches		
Migraine		
Malignant condition or cancer		
Overexertion, depression, serious nervousness		
Chronic skin condition or eczema		
Prolapsus		
Varicose veins		
Injury due to an accident in or around the house, a road traffic accident, sports injury at school or at work		

Initials_____

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Health and Labor Questionnaire (HLQ)

This is the end of the questionnaire. Thank you very much for your co-operation. The space below has been provided for any remarks you may wish to make about this questionnaire.

_____
_____
_____
_____
_____
_____

Initials_____

ANS C-07-01
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BASELINE 1 VISIT REQUIREMENTS:

- ❑ MADRS (VIDEO TAPED)
- ❑ HRSD-17
- ❑ IDS-C
- ❑ QIDS-SR
- ❑ MINI PLUS
- ❑ MMSE
  Score: _____
- ❑ SCID II
  Did any cluster B meet diagnosis? _____
- ❑ YMRS
- ❑ WSAS
- ❑ GAF
- ❑ QOL
- ❑ CGI
- ❑ PGI
- ❑ HAM-A
- ❑ C-SSRS
- ❑ HLQ
- ❑ ATHF
- ❑ SAFTEE-SI
- ❑ Brief Physical/Neurological exam
- ❑ Urine pregnancy test
- ❑ Psychiatric concomitant med log

🗓 **Scheduled Date of Next Visit (within 2-4 weeks): ___/___/_____**

Coordinator Signature: _____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

BASELINE 2 VISIT FORM

Have any unscheduled visits taken place since the last study visit?
☐ YES→ How many times? _____ (complete form)
☐ NO

Have any "depression" related medications changed since the last study visit?
☐ YES→ *Do not proceed, subject does not qualify*
☐ NO

ADVERSE EVENTS
Have there been any adverse events since the last visit?
☐ YES→ *Record details on AE form*
☐ NO

Have there been any serious adverse events since the last visit?
☐ YES→ *Record details on AE form and report to sponsor and IRB*
☐ NO

MADRS SCORE
Is the subject's MADRS score ≥ 22 for this visit?
☐ YES→ Score: _____
☐ NO→ *Do not proceed, subject does not qualify*

VISIT REQUIREMENTS:

- ❑ MADRS
- ❑ QIDS-SR
- ❑ HAM-A
- ❑ C-SSRS
- ❑ SAFTEE-SI

🗓 Scheduled Date of Next Visit (within 2-6 weeks): ___/___/_____

Coordinator Signature: _____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

BASELINE 3 VISIT FORM

Have any unscheduled visits taken place since the last study visit?
☐ YES→ How many times? _____(complete form)
☐ NO

Have any "depression" related medications changed since the last study visit?
☐ YES→ *Do not proceed, subject does not qualify*
☐ NO

ADVERSE EVENTS
Have there been any adverse events since the last visit?
☐ YES→ *Record details on AE form*
☐ NO

Have there been any serious adverse events since the last visit?
☐ YES→ *Record details on AE form and report to sponsor and IRB*
☐ NO

MADRS SCORE
Were the 3 baseline MADRS scales rated by 2 separate psychiatrists?
☐ YES
☐ NO→ *Do not proceed, subject does not qualify*

Is the subject's MADRS score ≥ 22 for this visit?
☐ YES→ Score: _____
☐ NO→ *Do not proceed, subject does not qualify*

Has the MADRS score improved by 20%?
☐ YES→ *Do not proceed, subject does not qualify*
☐ NO

Average baseline MADRS score of all visits? _____

VISIT REQUIREMENTS:

- ❑ MADRS
- ❑ QIDS
- ❑ HAM-A
- ❑ Neuropsych Battery
- □ C-SSRS
- □ SAFTEE-SI
- □ MRI

🗓 Scheduled Date of Next Visit (within 2-4 weeks): ___/___/_____

Coordinator Signature: _____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Baseline Neuropsychological Examination

☐ **Hopkins Verbal Learning Test Revised (HVLT-R)** **Form # ____ (1-6)** **Initial: _____**

	Raw Score	**T-score**
Total recall	_____ (0-36)	_____ (20-80)
Delayed recall	_____ (0-12)	_____ (20-80)
Retention %	_____ (0-150+)	_____ (20-80)
Recognition Discrimination Index	_____ (<4-12)	_____ (20-80)

NOTES: _____

_____

☐ **Ruff 2& 7 Selective Attention Test** **Initial: _____**

	Raw Score	**T-score**
Automatic Detection Speed	_____ (0-300)	_____ (20-80)
Automatic Detection Accuracy	_____ (0-100)	_____ (20-80)
Controlled Search Speed	_____ (0-300)	_____ (20-80)
Controlled Search Accuracy	_____ (0-100)	_____ (20-80)
Total Speed	_____ (40-160)	_____ (20-80)
Total Accuracy	_____ (40-119)	_____ (20-80)

NOTES: _____

_____

☐ **Stroop Color Word Test (Golden version)** **Initial: _____**

	Raw Score	**T-score**
Word score (number correct responses)	_____ (max 150)	_____ (3-98)
Color score (number correct responses)	_____ (max 150)	_____ (3-98)
Color/Word score (# correct responses)	_____ (max 150)	_____ (3-98)
Interference	_____ (max 150)	_____ (20-80)

NOTES: _____

_____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Baseline Neuropsychological Examination

☐ **Brief Visual Memory Test- Revised (BVMT-R)** **Form #_____ (1,2,3,4,5,6)** **Initial: _____**

	Raw Score	**T-score**
Trial 1	_____ (0-12)	_____ (38-80)
Trial 2	_____ (0-12)	_____ (38-80)
Trial 3	_____ (0-12)	_____ (38-80)
Total	_____ (0-36)	_____ (38-80)
Delayed Recall	_____ (0-12)	_____ (38-80)
Recognition Hits	_____ (0-6)	_____ NA
Recognition Discrimination	_____ (-6 to +6)	_____ NA

NOTES: _____

_____

☐ **Delis-Kaplan Executive Function Scale (D-KEFS)** **Form #_____ (1 or 2)** **Initial:_____**

	Raw Score	**Scaled Score**
Letter fluency	_____ (0-> 67)	_____ (0-19)
Category fluency	_____ (0-> 61)	_____ (0-19)
Switching fluency (2 scores)		
o Total correct	_____(0-> 21)	_____(0-19)
o Switching accuracy	_____(0->20)	_____(0-19)

NOTES:_____

_____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Baseline Neuropsychological Examination

☐ **Wechsler Memory Scale – Third Edition Abbreviated (WMS-III-A)** **Initial: _____**

	Raw Score	**Age corrected scale score**
Letter number sequencing	_____	_____

NOTES: _____

_____

☐ **Behavior Rating Inventory of Executive Functions (BRIEF-A)** **Initial: _____**

	Raw Score	**T-score**
Inhibit	_____ (0-24)	_____ (30-105)
Shift	_____ (0-18)	_____ (30-105)
Emotional Control	_____ (0-30)	_____ (30-105)
Self-Monitor	_____ (0-18)	_____ (30-105)
Behavioral Regulation Index	_____ (0-90)	_____ (30-105)
Initiate	_____ (0-24)	_____ (30-105)
	Raw Score	**T-score**
Working Memory	_____ (0-24)	_____ (30-105)
Plan/Organize	_____ (0-30)	_____ (30-105)
Task Monitor	_____ (0-18)	_____ (30-105)
Organization of Materials	_____ (0-24)	_____ (30-105)
Metacognition Index	_____ (0-120)	_____ (30-105)
Global Executive Composition	_____ (0-210)	_____ (30-105)

NOTES: _____

_____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

WEEK 0
SURGERY FORM

LEADS/EXTENSIONS		
Lead Implant Date	____/____/_____ (mm/dd/yyyy)	
	Right Side **If XP: □ Lead 1(1-4) □ Lead 2 (5-8)**	**Left Side** **If XP: □ Lead 1(1-4) □ Lead 2 (5-8)**
Lead Model Number	□ 6143DE-01 (30 cm) □ 6145DE-01 (40 cm)	□ 6143DE-01 (30 cm) □ 6145DE-01 (40 cm)
Extension Model Number	□ 6345DE-01 (50 cm) □ 6346DE-01 (60 cm)	□ 6345DE-01 (50 cm) □ 6346DE-01 (60 cm)
IPG		
IPG Implant Date	____/____/_____ (mm/dd/yyyy)	
	Right Side □ N/A	**Left Side** □ N/A
IPG used	□ Libra XP 6644DE-01 □ Libra 6608DE-01	□ Libra XP 6644DE-01 □ Libra 6608DE-01
IPG Serial Number (on package and IPG)	Lft. IPG __ __ __ __ __ __ __ __	Rt. IPG __ __ __ __ __ __ __ __
What size-tunneling tool was used for surgery?	□ Tunneling tool (0.156 diameter) □ Other: _____	
Were any other ANS components used in addition to what was included in the kit?	□ No □ Yes	
If Yes (check all that apply)	□ Stylet □ Lead □ IPG □ Extension □ Tunneling tool (.156 diameter) □ Burr Hole Base and Cap, Unilateral □ Other: _____ Please Explain why: _____ _____	□ Torque Wrench □ Trial Cable □ Connector strain relief □ Lead Stop 1140DE
Did any Adverse Events occur during the surgery?	□ No □ Yes – Record details on AE section	

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Week 2 Follow-up Visit Form

SUBJECT WELLBEING

Has the subject had contact with the case worker since the last visit?
☐ YES→ How many times? By Phone:_____ In person_____
☐ NO *(You do not need to fill out an unscheduled visit form)*

Have any unscheduled visits taken place since the last study visit?
☐ YES→ How many times? _____(complete form)
☐ NO

ADVERSE EVENTS

Have there been any adverse events since the last visit?
☐ YES→ *Record details on AE form*
☐ NO

Have there been any serious adverse events since the last visit?
☐ YES→ *Record details on AE form and report to sponsor and IRB*
☐ NO

SUBJECT STATUS

Have any "depression" related medications changed since the last study visit?
☐ YES→ *Update con-med log and report to Sponsor*
☐ NO

Has the subject changed their psychotherapy regimen since the last visit?
☐ Decreased ☐ Stopped ☐ Increased ☐ Same ☐ N/A

Did the subject use any "additional" Sleep aids since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Did the subject use any "additional" anti-anxiolytics since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Have any additional depression related medications been *"added"* since the last study visit?
☐ YES→ *Update con-med log and report to Sponsor Immediately*
☐ NO

Please update the con-med log.

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Week 2 Follow-up Visit Form

VISIT REQUIREMENTS

- ❑ MADRS
- ❑ HAM-A
- ❑ C-SSRS
- ❑ Randomization by blinded programmer

🗓 Scheduled Date of Next Visit (14 days): ___/___/_____

Coordinator Signature: _____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Week 4 Follow-up Visit Form

SUBJECT STATUS CONTINUED

Have any additional depression related medications been *"added"* since the last study visit?

☐ YES→ *Update con-med log and report to Sponsor Immediately*
☐ NO

Does the subject believe they have been receiving active therapy?
☐ YES ☐ NO

*Why or why not? _____
_____

Does the PI believe they have been receiving active therapy?
☐ YES ☐ NO

*Why or why not? _____
_____

VISIT REQUIREMENTS

- ❑ MADRS
- ❑ IDS
- ❑ QIDS-SR
- ❑ WSAS
- ❑ GAF
- ❑ CGI
- ❑ PGI
- ❑ HAM-A
- ❑ C-SSRS
- ❑ SAFTEE
- ❑ Programming by blinded programmer

🗓 Scheduled Date of Next Visit (14 days): ___/___/_____

Coordinator Signature: _____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Week 6 Follow-up Visit Form

SUBJECT WELLBEING

Has the subject had contact with the case worker since the last visit?
☐ YES→ How many times? By Phone:_____ In person_____
☐ NO *(You do not need to fill out an unscheduled visit form)*

Have any unscheduled visits taken place since the last study visit?
☐ YES→ How many times? _____(complete form)
☐ NO

ADVERSE EVENTS

Have there been any adverse events since the last visit?
☐ YES→ *Record details on AE form*
☐ NO

Have there been any serious adverse events since the last visit?
☐ YES→ *Record details on AE form and report to sponsor and IRB*
☐ NO

SUBJECT STATUS

Have any "depression" related medications changed since the last study visit?
☐ YES→ *Update con-med log and report to Sponsor*
☐ NO

Has the subject changed their psychotherapy regimen since the last visit?
☐ Decreased ☐ Stopped ☐ Increased ☐ Same ☐ N/A

Did the subject use any "additional" Sleep aids since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Did the subject use any "additional" anti-anxiolytics since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Have any additional depression related medications been *"added"* since the last study visit?
☐ YES→ *Update con-med log and report to Sponsor Immediately*
☐ NO

Please update the con-med log.

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Week 8 Follow-up Visit Form

SUBJECT WELLBEING

Has the subject had contact with the case worker since the last visit?
☐ YES→ How many times? By Phone:_____ In person_____
☐ NO *(You do not need to fill out an unscheduled visit form)*

Have any unscheduled visits taken place since the last study visit?
☐ YES→ How many times? _____(complete form)
☐ NO

ADVERSE EVENTS

Have there been any adverse events since the last visit?
☐ YES→ *Record details on AE form*
☐ NO

Have there been any serious adverse events since the last visit?
☐ YES→ *Record details on AE form and report to sponsor and IRB*
☐ NO

SUBJECT STATUS

Have any "depression" related medications changed since the last study visit?
☐ YES→ *Update con-med log and report to Sponsor*
☐ NO

Has the subject changed their psychotherapy regimen since the last visit?
☐ Decreased ☐ Stopped ☐ Increased ☐ Same ☐ N/A

Did the subject use any "additional" Sleep aids since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Did the subject use any "additional" anti-anxiolytics since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Week 8 Follow-up Visit Form

SUBJECT STATUS CONTINUED

Have any additional depression related medications been *"added"* since the last study visit?

☐ YES→ *Update con-med log and report to Sponsor Immediately*
☐ NO

Does the subject believe they have been receiving active therapy?
☐ YES ☐ NO

*Why or why not? _____
_____

Does the PI believe they have been receiving active therapy?
☐ YES ☐ NO

*Why or why not? _____
_____

Please update the con-med log.

VISIT REQUIREMENTS

- ❑ MADRS
- ❑ IDS
- ❑ QIDS-SR
- ❑ WSAS
- ❑ GAF
- ❑ CGI
- ❑ PGI
- ❑ HAM-A
- ❑ C-SSRS
- ❑ Programming by blinded programmer

🗓 Scheduled Date of Next Visit (1 month not 4 weeks): ___/___/_____

Example: if today's visit is on March 17th, the next visit would be April 17th

Coordinator Signature: _____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 3 Follow-up Visit Form
Must Video Tape MADRS

SUBJECT WELLBEING

Has the subject had contact with the case worker since the last visit?
☐ YES→ How many times? By Phone:_____ In person_____
☐ NO *(You do not need to fill out an unscheduled visit form)*

Have any unscheduled visits taken place since the last study visit?
☐ YES→ How many times? _____(complete form)
☐ NO

ADVERSE EVENTS

Have there been any adverse events since the last visit?
☐ YES→ *Record details on AE form*
☐ NO

Have there been any serious adverse events since the last visit?
☐ YES→ *Record details on AE form and report to sponsor and IRB*
☐ NO

SUBJECT STATUS

Have any "depression" related medications changed since the last study visit?
☐ YES→ *Update con-med log and report to Sponsor*
☐ NO

Has the subject's living situation changed since baseline?
☐ No Change ☐ Lives with spouse and/or children
☐ Lives Alone ☐ Lives in boarding home
☐ Hospitalized ☐ Lives with other family
☐ Other:_____

Has the subject changed their psychotherapy regimen since the last visit?
☐ Decreased ☐ Stopped ☐ Increased ☐ Same ☐ N/A

Did the subject use any "additional" Sleep aids since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 3 Follow-up Visit Form

SUBJECT STATUS CONTINUED

Did the subject use any "additional" anti-anxiolytics since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Have any additional depression related medications been *"added"* since the last study visit?
☐ YES→ *Update con-med log and report to Sponsor Immediately*
☐ NO

Does the subject believe they have been receiving active therapy?
☐ YES ☐ NO
*Why or why not? _____
_____

Does the PI believe they have been receiving active therapy?
☐ YES ☐ NO
*Why or why not? _____
_____

Please update the con-med log.

VISIT REQUIREMENTS

- ❑ MADRS (Video Taped)
- ❑ HRSD-17
- ❑ IDS
- ❑ QIDS-SR
- ❑ YMRS
- ❑ WSAS
- ❑ GAF
- ❑ QOL
- ❑ CGI
- ❑ PGI
- ❑ HAM-A
- ❑ C-SSRS
- ❑ HLQ
- ❑ SAFTEE-SI
- ❑ Programming by blinded programmer

🗓 Scheduled Date of Next Visit (1 month not 4 weeks): ___/___/_____

Example: if today's visit is on March 17th, the next visit would be April 17th

Coordinator Signature: _____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 4 Follow-up Visit Form

SUBJECT WELLBEING

Has the subject had contact with the case worker since the last visit?
☐ YES→ How many times? By Phone:_____ In person_____
☐ NO *(You do not need to fill out an unscheduled visit form)*

Have any unscheduled visits taken place since the last study visit?
☐ YES→ How many times? _____(complete form)
☐ NO

ADVERSE EVENTS

Have there been any adverse events since the last visit?
☐ YES→ *Record details on AE form*
☐ NO

Have there been any serious adverse events since the last visit?
☐ YES→ *Record details on AE form and report to sponsor and IRB*
☐ NO

SUBJECT STATUS

Have any "depression" related medications changed since the last study visit?
☐ YES→ *Update con-med log and report to Sponsor*
☐ NO

Has the subject changed their psychotherapy regimen since the last visit?
☐ Decreased ☐ Stopped ☐ Increased ☐ Same ☐ N/A

Did the subject use any "additional" Sleep aids since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Did the subject use any "additional" anti-anxiolytics since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Have any additional depression related medications been *"added"* since the last study visit?
☐ YES→ *Update con-med log and report to Sponsor Immediately*
☐ NO

Please update the con-med log.

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 4 Follow-up Visit Form

VISIT REQUIREMENTS

- ❑ MADRS
- ❑ IDS
- ❑ QIDS-SR
- ❑ WSAS
- ❑ GAF
- ❑ CGI
- ❑ PGI
- ❑ HAM-A
- ❑ C-SSRS
- ❑ Programming by blinded programmer

Scheduled Date of Next Visit (1 month not 4 weeks): ___/___/_____

Example: if today's visit is on March 17th, the next visit would be April 17th

Coordinator Signature: _____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 5 Follow-up Visit Form

SUBJECT WELLBEING

Has the subject had contact with the case worker since the last visit?
☐ YES→ How many times? By Phone: _____ In person_____
☐ NO *(You do not need to fill out an unscheduled visit form)*

Have any unscheduled visits taken place since the last study visit?
☐ YES→ How many times? _____ (complete form)
☐ NO

ADVERSE EVENTS

Have there been any adverse events since the last visit?
☐ YES→ *Record details on AE form*
☐ NO

Have there been any serious adverse events since the last visit?
☐ YES→ *Record details on AE form and report to sponsor and IRB*
☐ NO

SUBJECT STATUS

Have any "depression" related medications changed since the last study visit?
☐ YES→ *Update con-med log and report to Sponsor*
☐ NO

Has the subject changed their psychotherapy regimen since the last visit?
☐ Decreased ☐ Stopped ☐ Increased ☐ Same ☐ N/A

Did the subject use any "additional" Sleep aids since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Did the subject use any "additional" anti-anxiolytics since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Have any additional depression related medications been *"added"* since the last study visit?
☐ YES→ *Update con-med log and report to Sponsor Immediately*
☐ NO

Please update the con-med log.

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 5 Follow-up Visit Form

VISIT REQUIREMENTS

- ❑ MADRS
- ❑ IDS
- ❑ QIDS-SR
- ❑ WSAS
- ❑ GAF
- ❑ CGI
- ❑ PGI
- ❑ HAM-A
- ❑ C-SSRS
- ❑ Programming by blinded programmer

Scheduled Date of Next Visit (1 month not 4 weeks): ___/___/_____

Example: if today's visit is on March 17th, the next visit would be April 17th

Coordinator Signature: _____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 6 Follow-up Visit Form
Must Video Tape MADRS

SUBJECT WELLBEING

Has the subject had contact with the case worker since the last visit?
☐ YES→ How many times? By Phone:_____ In person_____
☐ NO *(You do not need to fill out an unscheduled visit form)*

Have any unscheduled visits taken place since the last study visit?
☐ YES→ How many times? _____(complete form)
☐ NO

ADVERSE EVENTS

Have there been any adverse events since the last visit?
☐ YES→ *Record details on AE form*
☐ NO

Have there been any serious adverse events since the last visit?
☐ YES→ *Record details on AE form and report to sponsor and IRB*
☐ NO

SUBJECT STATUS

Have any "depression" related medications changed since the last study visit?
☐ YES→ *Update con-med log and report to Sponsor*
☐ NO

Has the subject's living situation changed since baseline?
☐ No Change ☐ Lives with spouse and/or children
☐ Lives Alone ☐ Lives in boarding home
☐ Hospitalized ☐ Lives with other family
☐ Other:_____

Has the subject changed their psychotherapy regimen since the last visit?
☐ Decreased ☐ Stopped ☐ Increased ☐ Same ☐ N/A

Did the subject use any "additional" Sleep aids since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 6 Follow-up Visit Form

SUBJECT STATUS CONTINUED

Did the subject use any "additional" anti-anxiolytics since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Have any additional depression related medications been *"added"* since the last study visit?
☐ YES→ *Update con-med log and report to Sponsor Immediately*
☐ NO

Does the subject believe they have been receiving active therapy?
☐ YES ☐ NO
*Why or why not? _____
_____

Does the PI believe they have been receiving active therapy?
☐ YES ☐ NO
*Why or why not? _____
_____

Please update the con-med log.

VISIT REQUIREMENTS

- ❑ MADRS (Video Taped)
- ❑ HRSD-17
- ❑ IDS
- ❑ QIDS-SR
- ❑ YMRS
- ❑ WSAS
- ❑ GAF
- ❑ QOL
- ❑ CGI
- ❑ PGI
- ❑ HAM-A
- ❑ C-SSRS
- ❑ HLQ
- ❑ SAFTEE-SI
- ❑ Programming by blinded programmer
- ❑ Neuropsych Battery

🗓 Scheduled Date of Next Visit (1 month not 4 weeks): ___/___/_____

Example: if today's visit is on March 17th, the next visit would be April 17th

Coordinator Signature: _____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 6 Neuropsychological Examination

☐ **Hopkins Verbal Learning Test Revised (HVLT-R)** **Form # ____ (1-6)** **Initial: _____**

	Raw Score	**T-score**
Total recall	_____ (0-36)	_____ (20-80)
Delayed recall	_____ (0-12)	_____ (20-80)
Retention %	_____ (0-150+)	_____ (20-80)
Recognition Discrimination Index	_____ (<4-12)	_____ (20-80)

NOTES: _____

_____

☐ **Ruff 2& 7 Selective Attention Test** **Initial: _____**

	Raw Score	**T-score**
Automatic Detection Speed	_____ (0-300)	_____ (20-80)
Automatic Detection Accuracy	_____ (0-100)	_____ (20-80)
Controlled Search Speed	_____ (0-300)	_____ (20-80)
Controlled Search Accuracy	_____ (0-100)	_____ (20-80)
Total Speed	_____ (40-160)	_____ (20-80)
Total Accuracy	_____ (40-119)	_____ (20-80)

NOTES: _____

_____

☐ **Stroop Color Word Test (Golden version)** **Initial: _____**

	Raw Score	**T-score**
Word score (number correct responses)	_____ (max 150)	_____ (3-98)
Color score (number correct responses)	_____ (max 150)	_____ (3-98)
Color/Word score (# correct responses)	_____ (max 150)	_____ (3-98)
Interference	_____ (max 150)	_____ (20-80)

NOTES: _____

_____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 6 Neuropsychological Examination

☐ **Brief Visual Memory Test- Revised (BVMT-R) Form #_____ (1,2,3,4,5,6) Initial: _____**

	Raw Score	**T-score**
Trial 1	_____ (0-12)	_____ (38-80)
Trial 2	_____ (0-12)	_____ (38-80)
Trial 3	_____ (0-12)	_____ (38-80)
Total	_____ (0-36)	_____ (38-80)
Delayed Recall	_____ (0-12)	_____ (38-80)
Recognition Hits	_____ (0-6)	_____ NA
Recognition Discrimination	_____ (-6 to +6)	_____ NA

NOTES: _____

_____

☐ **Delis-Kaplan Executive Function Scale (D-KEFS) Form #_____ (1 or 2) Initial:_____**

	Raw Score	**Scaled Score**
Letter fluency	_____ (0-> 67)	_____ (0-19)
Category fluency	_____ (0-> 61)	_____ (0-19)
Switching fluency (2 scores)		
o Total correct	_____(0-> 21)	_____(0-19)
o Switching accuracy	_____(0->20)	_____(0-19)

NOTES:_____

_____

Initials _____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 6 Neuropsychological Examination

☐ **Wechsler Memory Scale – Third Edition Abbreviated (WMS-III-A)** **Initial: _____**

	Raw Score	**Age corrected scale score**
Letter number sequencing	_____	_____

NOTES:

_____

_____

☐ **Behavior Rating Inventory of Executive Functions (BRIEF-A)** **Initial: _____**

	Raw Score	**T-score**
Inhibit	_____ (0-24)	_____ (30-105)
Shift	_____ (0-18)	_____ (30-105)
Emotional Control	_____ (0-30)	_____ (30-105)
Self-Monitor	_____ (0-18)	_____ (30-105)
Behavioral Regulation Index	_____ (0-90)	_____ (30-105)
Initiate	_____ (0-24)	_____ (30-105)
	Raw Score	**T-score**
Working Memory	_____ (0-24)	_____ (30-105)
Plan/Organize	_____ (0-30)	_____ (30-105)
Task Monitor	_____ (0-18)	_____ (30-105)
Organization of Materials	_____ (0-24)	_____ (30-105)
Metacognition Index	_____ (0-120)	_____ (30-105)
Global Executive Composition	_____ (0-210)	_____ (30-105)

NOTES:

_____

_____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 7 Follow-up Visit Form

SUBJECT WELLBEING

Has the subject had contact with the case worker since the last visit?
☐ YES→ How many times? By Phone: _____ In person_____
☐ NO *(You do not need to fill out an unscheduled visit form)*

Have any unscheduled visits taken place since the last study visit?
☐ YES→ How many times? _____ (complete form)
☐ NO

ADVERSE EVENTS

Have there been any adverse events since the last visit?
☐ YES→ *Record details on AE form*
☐ NO

Have there been any serious adverse events since the last visit?
☐ YES→ *Record details on AE form and report to sponsor and IRB*
☐ NO

SUBJECT STATUS

Have any "depression" related medications changed since the last study visit?
☐ YES→ *Update con-med log*
☐ NO

Has the subject changed their psychotherapy regimen since the last visit?
☐ Decreased ☐ Stopped ☐ Increased ☐ Same ☐ N/A

Did the subject use any "additional" Sleep aids since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Did the subject use any "additional" anti-anxiolytics since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Please update the con-med log.

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 7 Follow-up Visit Form

VISIT REQUIREMENTS

- ❑ MADRS
- ❑ IDS
- ❑ QIDS-SR
- ❑ WSAS
- ❑ GAF
- ❑ CGI
- ❑ PGI
- ❑ HAM-A
- ❑ C-SSRS
- ❑ Programming by blinded programmer

Scheduled Date of Next Visit (1 month not 4 weeks): ___/___/_____

Example: if today's visit is on March 17th, the next visit would be April 17th

Coordinator Signature: _____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 8 Follow-up Visit Form

SUBJECT WELLBEING

Has the subject had contact with the case worker since the last visit?
☐ YES→ How many times? By Phone:_____ In person_____
☐ NO *(You do not need to fill out an unscheduled visit form)*

Have any unscheduled visits taken place since the last study visit?
☐ YES→ How many times? _____(complete form)
☐ NO

ADVERSE EVENTS

Have there been any adverse events since the last visit?
☐ YES→ *Record details on AE form*
☐ NO

Have there been any serious adverse events since the last visit?
☐ YES→ *Record details on AE form and report to sponsor and IRB*
☐ NO

SUBJECT STATUS

Have any "depression" related medications changed since the last study visit?
☐ YES→ *Update con-med log*
☐ NO

Has the subject changed their psychotherapy regimen since the last visit?
☐ Decreased ☐ Stopped ☐ Increased ☐ Same ☐ N/A

Did the subject use any "additional" Sleep aids since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Did the subject use any "additional" anti-anxiolytics since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Please update the con-med log.

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 8 Follow-up Visit Form

VISIT REQUIREMENTS

- ❑ MADRS
- ❑ IDS
- ❑ QIDS-SR
- ❑ WSAS
- ❑ GAF
- ❑ CGI
- ❑ PGI
- ❑ HAM-A
- ❑ C-SSRS
- ❑ Programming by blinded programmer

Scheduled Date of Next Visit (1 month not 4 weeks): ___/___/_____

Example: if today's visit is on March 17th, the next visit would be April 17th

Coordinator Signature: _____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 9 Follow-up Visit Form

SUBJECT WELLBEING

Has the subject had contact with the case worker since the last visit?
☐ YES→ How many times? By Phone: _____ In person_____
☐ NO *(You do not need to fill out an unscheduled visit form)*

Have any unscheduled visits taken place since the last study visit?
☐ YES→ How many times? _____ (complete form)
☐ NO

ADVERSE EVENTS

Have there been any adverse events since the last visit?
☐ YES→ *Record details on AE form*
☐ NO

Have there been any serious adverse events since the last visit?
☐ YES→ *Record details on AE form and report to sponsor and IRB*
☐ NO

SUBJECT STATUS

Have any "depression" related medications changed since the last study visit?
☐ YES→ *Update con-med log*
☐ NO

Has the subject changed their psychotherapy regimen since the last visit?
☐ Decreased ☐ Stopped ☐ Increased ☐ Same ☐ N/A

Did the subject use any "additional" Sleep aids since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Did the subject use any "additional" anti-anxiolytics since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Please update the con-med log.

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 9 Follow-up Visit Form

VISIT REQUIREMENTS

- ❑ MADRS
- ❑ IDS
- ❑ QIDS-SR
- ❑ YMRS
- ❑ WSAS
- ❑ GAF
- ❑ QOL
- ❑ CGI
- ❑ PGI
- ❑ HAM-A
- ❑ C-SSRS
- ❑ HLQ
- ❑ SAFTEE
- ❑ Programming by blinded programmer

Scheduled Date of Next Visit (1 month not 4 weeks): ___/___/_____

Example: if today's visit is on March 17th, the next visit would be April 17th

Coordinator Signature: _____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 10 Follow-up Visit Form

SUBJECT WELLBEING

Has the subject had contact with the case worker since the last visit?
☐ YES→ How many times? By Phone: _____ In person_____
☐ NO *(You do not need to fill out an unscheduled visit form)*

Have any unscheduled visits taken place since the last study visit?
☐ YES→ How many times? _____ (complete form)
☐ NO

ADVERSE EVENTS

Have there been any adverse events since the last visit?
☐ YES→ *Record details on AE form*
☐ NO

Have there been any serious adverse events since the last visit?
☐ YES→ *Record details on AE form and report to sponsor and IRB*
☐ NO

SUBJECT STATUS

Have any "depression" related medications changed since the last study visit?
☐ YES→ *Update con-med log*
☐ NO

Has the subject changed their psychotherapy regimen since the last visit?
☐ Decreased ☐ Stopped ☐ Increased ☐ Same ☐ N/A

Did the subject use any "additional" Sleep aids since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Did the subject use any "additional" anti-anxiolytics since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Please update the con-med log.

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 10 Follow-up Visit Form

VISIT REQUIREMENTS

- ❑ MADRS
- ❑ IDS
- ❑ QIDS-SR
- ❑ WSAS
- ❑ GAF
- ❑ CGI
- ❑ PGI
- ❑ HAM-A
- ❑ C-SSRS
- ❑ Programming by blinded programmer

Scheduled Date of Next Visit (1 month not 4 weeks): ___/___/_____

Example: if today's visit is on March 17th, the next visit would be April 17th

Coordinator Signature: _____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 11 Follow-up Visit Form

SUBJECT WELLBEING

Has the subject had contact with the case worker since the last visit?
☐ YES→ How many times? By Phone: _____ In person_____
☐ NO *(You do not need to fill out an unscheduled visit form)*

Have any unscheduled visits taken place since the last study visit?
☐ YES→ How many times? _____ (complete form)
☐ NO

ADVERSE EVENTS

Have there been any adverse events since the last visit?
☐ YES→ *Record details on AE form*
☐ NO

Have there been any serious adverse events since the last visit?
☐ YES→ *Record details on AE form and report to sponsor and IRB*
☐ NO

SUBJECT STATUS

Have any "depression" related medications changed since the last study visit?
☐ YES→ *Update con-med log*
☐ NO

Has the subject changed their psychotherapy regimen since the last visit?
☐ Decreased ☐ Stopped ☐ Increased ☐ Same ☐ N/A

Did the subject use any "additional" Sleep aids since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Did the subject use any "additional" anti-anxiolytics since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Please update the con-med log.

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 11 Follow-up Visit Form

VISIT REQUIREMENTS

- ❑ MADRS
- ❑ IDS
- ❑ QIDS-SR
- ❑ WSAS
- ❑ GAF
- ❑ CGI
- ❑ PGI
- ❑ HAM-A
- ❑ C-SSRS
- ❑ Programming by blinded programmer

Scheduled Date of Next Visit (1 month not 4 weeks): ___/___/_____

Example: if today's visit is on March 17th, the next visit would be April 17th

Coordinator Signature: _____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 12 Follow-up Visit Form
Must Video Tape MADRS

SUBJECT WELLBEING

Has the subject had contact with the case worker since the last visit?
☐ YES→ How many times? By Phone: _____ In person_____
☐ NO *(You do not need to fill out an unscheduled visit form)*

Have any unscheduled visits taken place since the last study visit?
☐ YES→ How many times? _____ (complete form)
☐ NO

ADVERSE EVENTS

Have there been any adverse events since the last visit?
☐ YES→ *Record details on AE form*
☐ NO

Have there been any serious adverse events since the last visit?
☐ YES→ *Record details on AE form and report to sponsor and IRB*
☐ NO

SUBJECT STATUS

Have any "depression" related medications changed since the last study visit?
☐ YES→ *Update con-med log*
☐ NO

Has the subject's living situation changed since baseline?
☐ No Change ☐ Lives with spouse and/or children
☐ Lives Alone ☐ Lives in boarding home
☐ Hospitalized ☐ Lives with other family
☐ Other:_____

Has the subject's marital status changed over the course of the study?
☐ YES → How? _____
☐ NO

Has the subject changed their psychotherapy regimen since the last visit?
☐ Decreased ☐ Stopped ☐ Increased ☐ Same ☐ N/A

Did the subject use any "additional" Sleep aids since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 12 Follow-up Visit Form

SUBJECT STATUS CONTINUED
Did the subject use any "additional" anti-anxiolytics since the last visit?
☐ YES→ Number of days used? _____ *Update Con-Med form*
☐ NO

Please update the con-med log.
Please complete the study exit form at this time.

VISIT REQUIREMENTS
- ❑ MADRS (Video Taped)
- ❑ HRSD-17
- ❑ IDS
- ❑ QIDS-SR
- ❑ YMRS
- ❑ WSAS
- ❑ GAF
- ❑ QOL
- ❑ CGI
- ❑ PGI
- ❑ HAM-A
- ❑ C-SSRS
- ❑ HLQ
- ❑ SAFTEE-SI
- ❑ Programming by blinded programmer
- ❑ Neuropsych Battery
- ❑ Exit form

Coordinator Signature: _____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 12 Neuropsychological Examination

☐ **Hopkins Verbal Learning Test Revised (HVLT-R)** **Form # ____ (1-6)** **Initial: _____**

	Raw Score	**T-score**
Total recall	_____ (0-36)	_____ (20-80)
Delayed recall	_____ (0-12)	_____ (20-80)
Retention %	_____ (0-150+)	_____ (20-80)
Recognition Discrimination Index	_____ (<4-12)	_____ (20-80)

NOTES: _____

_____

☐ **Ruff 2& 7 Selective Attention Test** **Initial: _____**

	Raw Score	**T-score**
Automatic Detection Speed	_____ (0-300)	_____ (20-80)
Automatic Detection Accuracy	_____ (0-100)	_____ (20-80)
Controlled Search Speed	_____ (0-300)	_____ (20-80)
Controlled Search Accuracy	_____ (0-100)	_____ (20-80)
Total Speed	_____ (40-160)	_____ (20-80)
Total Accuracy	_____ (40-119)	_____ (20-80)

NOTES: _____

_____

☐ **Stroop Color Word Test (Golden version)** **Initial: _____**

	Raw Score	**T-score**
Word score (number correct responses)	_____ (max 150)	_____ (3-98)
Color score (number correct responses)	_____ (max 150)	_____ (3-98)
Color/Word score (# correct responses)	_____ (max 150)	_____ (3-98)
Interference	_____ (max 150)	_____ (20-80)

NOTES: _____

_____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 12 Neuropsychological Examination

☐ **Brief Visual Memory Test- Revised (BVMT-R) Form #_____ (1,2,3,4,5,6) Initial: _____**

	Raw Score	**T-score**
Trial 1	_____ (0-12)	_____ (38-80)
Trial 2	_____ (0-12)	_____ (38-80)
Trial 3	_____ (0-12)	_____ (38-80)
Total	_____ (0-36)	_____ (38-80)
Delayed Recall	_____ (0-12)	_____ (38-80)
Recognition Hits	_____ (0-6)	_____ NA
Recognition Discrimination	_____ (-6 to +6)	_____ NA

NOTES: _____

_____

☐ **Delis-Kaplan Executive Function Scale (D-KEFS) Form #_____ (1 or 2) Initial:_____**

	Raw Score	**Scaled Score**
Letter fluency	_____ (0-> 67)	_____ (0-19)
Category fluency	_____ (0-> 61)	_____ (0-19)
Switching fluency (2 scores)		
o Total correct	_____(0-> 21)	_____(0-19)
o Switching accuracy	_____(0->20)	_____(0-19)

NOTES:_____

_____

Initials _____

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Month 12 Neuropsychological Examination

☐ **Wechsler Memory Scale – Third Edition Abbreviated (WMS-III-A)** **Initial: _____**

	Raw Score	**Age corrected scale score**
Letter number sequencing	_____	_____

NOTES:

_____

_____

☐ **Behavior Rating Inventory of Executive Functions (BRIEF-A)** **Initial: _____**

	Raw Score	**T-score**
Inhibit	_____ (0-24)	_____ (30-105)
Shift	_____ (0-18)	_____ (30-105)
Emotional Control	_____ (0-30)	_____ (30-105)
Self-Monitor	_____ (0-18)	_____ (30-105)
Behavioral Regulation Index	_____ (0-90)	_____ (30-105)
Initiate	_____ (0-24)	_____ (30-105)
	Raw Score	**T-score**
Working Memory	_____ (0-24)	_____ (30-105)
Plan/Organize	_____ (0-30)	_____ (30-105)
Task Monitor	_____ (0-18)	_____ (30-105)
Organization of Materials	_____ (0-24)	_____ (30-105)
Metacognition Index	_____ (0-120)	_____ (30-105)
Global Executive Composition	_____ (0-210)	_____ (30-105)

NOTES:

_____

_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

AE Start Date: ____/____/_____
Unanticipated (AE other than listed below) ☐ No ☐ Yes (Specify & Notify Sponsor)_____
Otherwise, please ***check only one*** of the following anticipated adverse events:

AE related to DBS surgical procedures:

- ☐ aphasia
- ☐ cerebrospinal fluid leakage
- ☐ death
- ☐ infection
- ☐ intracranial hemorrhage
- ☐ paralysis
- ☐ post-operative pain
- ☐ post-operative stress
- ☐ post-operative discomfort
- ☐ seizure or convulsion
- ☐ stroke
- ☐ subcutaneous hemorrhage or seroma

AE associated with use of the device

- ☐ allergic or rejection response to implanted materials
- ☐ anxiety (pre-existing)
- ☐ anxiety (new report)
- ☐ apathy
- ☐ asthenia, hemiplegia or hemiparesis
- ☐ ataxia
- ☐ attention deficit
- ☐ autonomic instability (change in vital signs)
- ☐ cerebrospinal fluid abnormality
- ☐ cognitive impairment, including confusion, abnormal thinking, hallucinations, alteration of mentation, amnesia, delusions, or dementia □ neuropathy
- ☐ diarrhea
- ☐ difficulty breathing
- ☐ disequilibrium
- ☐ drowsiness
- ☐ dysarthria
- ☐ dystonia
- ☐ DBS battery failure
- ☐ DBS system malfunction
- ☐ edema including periorbital
- ☐ eye disorder
- ☐ fever
- ☐ general erosion or local skin erosion over the pulse generator (IPG), burr hole cap, and/or extension
- ☐ headache
- ☐ hearing and visual disturbance
- ☐ hypomania
- ☐ increase in depressive symptoms
- ☐ increase in drug side effects
- ☐ increased salivation
- ☐ initial jolt or tingling during stimulation
- ☐ intracranial infarctions
- ☐ lead fracture
- ☐ lead migration
- ☐ loss of therapeutic benefit as a result of change in electrode positions, lead fracture, loose electrical connections, DBS system battery failure, DBS system malfunction, or inadvertent turning off of device
- ☐ mania
- ☐ myoclonus
- ☐ nausea and/or vomiting
- ☐ neuralgia
- ☐ neuropathy
- ☐ obsessive compulsive disorder (OCD) symptoms
- ☐ panic attacks
- ☐ paresis
- ☐ paresthesia
- ☐ persistent pain or redness at the IPG site or the surgery site/extension
- ☐ pneumonia
- ☐ pulling sensation along extension site
- ☐ psychosis
- ☐ rapid heart rate
- ☐ ruminativeness
- ☐ sensory deficit
- ☐ sleep disturbance
- ☐ skin disorder
- ☐ suicide or suicide attempt
- ☐ sweating
- ☐ symptomatic neumocephalus (intracranial air causing confusion requiring an extra day stay in the hospital)
- ☐ syncope
- ☐ system dislodgement
- ☐ undesirable changes in stimulation possibly related to cellular changes in tissue around the electrodes, changes in the electrode position, or loose electrical connections and/or lead fracture
- ☐ urinary incontinence
- ☐ venous air embolism (air entering the veins)
- ☐ venous infarctions

Subject Initials: _____
Subject Number: _____
Site Number: _____

AE Form Continued……

Is AE Device Related (check only one)?	☐ Not related ☐ Unlikely ☐ Possibly ☐ Probably ☐ Definitely
Is AE Surgery Related?	☐ Not related ☐ Unlikely ☐ Possibly ☐ Probably ☐ Definitely
Severity of AE:	☐ Mild ☐ Moderate ☐ Severe
System Intervention:	☐ None ☐ Patient Education ☐ Stimulation Discontinued ☐ System Revised ☐ System Explanted ☐ System Replaced ☐ Other: _____
Other Actions Taken:	☐ None ☐ Medication ☐ Patient Exited Study ☐ Other: _____
AE Outcome Date: ____/____/_____	☐ Resolved ☐ Improved ☐ Unchanged ☐ Worsened ☐ Death ☐ Insufficient follow up

Serious Adverse Event Information

An event is serious if any of the following are answered YES

Life threatening or fatal	☐ Yes	☐ No
Requires or prolongs hospitalization	☐ Yes	☐ No
The subject will be disabled	☐ Yes	☐ No

COMMENTS:_____
_____
_____
_____
_____
_____

SIGNATURE

I have reviewed all of the information for this Adverse Event and verify that it is correct.

_____ _____
Investigator Signature Date

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials:	_____
Subject Number:	_____
Site Number:	_____

Depression Exit/Early Withdrawal Form

COMPLETE THIS FORM IN CONJUNCTION WITH THE PATIENT'S LAST VISIT FOR THE STUDY

Were any of the following performed on the patient prior to EXIT from the study?

Revision to lead? ☐ No ☐ Yes (specify)_____

Revision to extension? ☐ No ☐ Yes (specify)_____

Revision to IPG? ☐ No ☐ Yes (specify)_____

Did Subject complete all study related visits?

☐ Yes

☐ No Reasons for not completing: (Subject could miss a visit but still complete all others)

- ☐ Subject's choice to withdraw
- ☐ Adverse Event (Complete AE form)
  - ☐ Suicide
  - ☐ Suicide Attempt
  - ☐ Worsening of depression
  - ☐ Failed rescue after increase in suicide ideations
  - ☐ Other: _____
- ☐ Subject is unwilling or unable to comply with study requirements
- ☐ Investigator decision to withdraw subject from study
- ☐ Lost to follow-up
- ☐ Other: _____

If the subject exited the study prior to 6 months, does the patient believe he/she was receiving active therapy?

☐ Yes

☐ No

Please Explain:

_____

_____

_____

If the subject exited the study prior to 6 months, does the PI believe he/she was receiving active therapy?

☐ Yes

☐ No

Please Explain:

_____

_____

_____

Was the system explanted? ☐ No ☐ Yes – Complete additional surgery form

Patient Satisfaction:

Based on your experience to date, would you choose to undergo the process to receive this DBS system again?

☐ Yes

☐ No

Please Explain:

_____

_____

_____

Would you recommend this DBS system to anyone else suffering form the same condition?

☐ Yes

☐ No

Please Explain:

_____

_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Will the subject enter the C-07-05 Long Term Follow-Up Study?

☐ Yes

☐ No

I certify that I have reviewed source documentation, case report forms and all other study related documents for this patient, and will verify all changes made to the documentation of study materials for this patient.

Principal Investigator

Signature: _____ Date: _____/_____/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

Additional Visit Form

Additional Visit Date: ___/___/____

Reason for this visit?

☐ Physician request ☐ Worsening of Depression Symptoms

☐ Pain at implant site ☐ DBS system malfunction

☐ Adverse Event (must fill out "AE Form") ☐ Other _____

Actions taken during this visit? (procedures and ratings):

☐ Reprogramming ☐ Medication adjusted (record on Con-Med page) ☐ Patient education

☐ Revision required ☐ No action taken ☐ Other _____

Any Adverse Events since last visit? ☐ No ☐ Yes – Record details on AE section

Any change in medications since last visit? ☐ No ☐ Yes – Record details on Con-Med page

Additional Visit Date: ___/___/____

Reason for this visit?

☐ Physician request ☐ Worsening of Depression Symptoms

☐ Pain at implant site ☐ DBS system malfunction

☐ Adverse Event (must fill out "AE Form") ☐ Other _____

Actions taken during this visit? (procedures and ratings):

☐ Reprogramming ☐ Medication adjusted (record on Con-Med page) ☐ Patient education

☐ Revision required ☐ No action taken ☐ Other _____

Any Adverse Events since last visit? ☐ No ☐ Yes – Record details on AE section

Any change in medications since last visit? ☐ No ☐ Yes – Record details on Con-Med page

ANS C-07-01
Date of Visit: ___/___/_____

Subject Initials: _____
Subject Number: _____
Site Number: _____

ADDITIONAL SURGERY FORM

Reason For Surgery:

☐ Lead migration ☐ Lead fracture ☐ Extension fracture

☐ Erosion at extension site ☐ Erosion at IPG site ☐ Erosion at Burr hole cap

☐ Infection of entire system ☐ Infection at IPG ☐ Infection at extension ☐ Infection at lead

☐ Battery failure ☐ Battery EOL ☐ IPG malfunction ☐ Unacceptable side effects

☐ Pain at IPG ☐ Lead initially not in target ☐ Loss of effectiveness

☐ Patient Req: (Reason)_____☐ Physician Req (Reason)_____

☐ Other (Specify)_____

Action Taken: (Check all that apply)

☐ Lead revised ☐ Extension revised ☐ IPG revised

☐ Lead replaced ☐ Extension replaced ☐ IPG replaced Serial #_____

☐ Lead explanted ☐ Extension explanted ☐ IPG explanted

☐ Entire system explanted ☐ Other (Specify)_____

Indicate all ANS components that were used for this surgery.

☐ Lead 6143DE-01 (30cm) ☐ Lead 6145DE-01 (40cm) ☐ IPG and Type: _____

☐ Extension 6346DE-01 (60cm) ☐ Extension 6345DE-01 (50cm)

☐ Stylet ☐ Connector strain relief ☐ Lead stop

☐ Torque Wrench ☐ Trial cable

☐ Tunneling tool (.156) ☐ Tunneling tool (.125) ☐ Burr hole ring and cap

Other:_____

ADVERSE EVENTS

Any Adverse Events during the surgery? ☐ No ☐ Yes – Record details on AE section

CONCOMITANT MEDICATION

Any change in medications since last visit? ☐ No ☐ Yes – Record details on Con-Med page

Initials _____

16.4 Appendix D: Study Visit Schedule

BROADEN STUDY QUICK REFERENCE

C-07-01 Assessment Schedule

	Baseline #1	Baseline #2	Baseline #3	Implant	2 Weeks	4 weeks	6 Weeks	8 Weeks	3 Months	4 Months	5 Months	6 Months	7 Months	8 Months	9 Months	10 Months	11 Months	12 Months
Clinical Evaluations																		
Montgomery and Asberg Depression Rating Scale (MADRS) (**Psychiatrist Rater ONLY**)	V	X	X		X	X	X	X	V	X	X	V	X	X	X	X	X	V
Hamiltion Rating Scale for Depression (HRSD-17)	X								X			X						X
Inventory of Depressive Symptomatology (IDS-C30)	X					X		X	X	X	X	X	X	X	X	X	X	X
Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR)	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X
The Mini-International Neuropsychiatric Interview PLUS (M.I.N.I. PLUS)	X																	
The Mini-Mental State Exam (MMSE)	X																	
Structural Clinical Interview for Personality Disorders (SCID II)	X																	
The Young Mania Rating Scale (YMRS)	X								X			X			X			X
Work and Social Adjustment Scale (WSAS)	X					X		X	X	X	X	X	X	X	X	X	X	X
Global Assessment of Functioning (GAF)	X					X		X	X	X	X	X	X	X	X	X	X	X
Quality of Life Enjoyment and Satisfaction (QOL)	X								X			X			X			X
Clinical Global Impression of Severity and Improvement (CGI)	X					X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Global Impression Index (PGI)	X					X	X	X	X	X	X	X	X	X	X	X	X	X
Hamiliton Anxiety Rating Scale (HAM-A)	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Columbia Suicide-Severity Rating Scale (C-SSRS) (**Psychiatrist Rater ONLY)**	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Health and Labor Questionnaire (HLQ)	X								X			X			X			X
Programming Form (un-blinded programmer)					X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Exit Form																		X
Cognitive Status/Safety Screens																		
Attention/Working Memory																		
Wechsler Memory Scale - Letter Numbering Squence			X									X						X
Stroop Color and Word Test (Golden, 1978)			X									X						X
Ruff 2&7 Selective Attention Test (Ruff & Allen, 1996)			X									X						X
Executive Functioning																		
Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency Test			X									X						X
Memory																		
Hopkins Verbal Learning Test - Revised (HVLT-R; Brandt & Benedict, 2001)			X									X						X
Brief Visual Memory Test - Revised (BVMT-R; Benedict, 1997)			X									X						X
Self and Informant Rating of Executive Functions																		
Behavior Rating Inventory of Exectuive Function - Adult Version (BRIEF-A; Roth et al., 2005)			X									X						X
Tolerability Screens																		
Andtidepressant Treatment History Form (ATHF)	X																	
Urine Pregnancy Test (if necessary)	X																	
MRI/CT (MRI to be captured after Baseline 3 and prior to implant, CT captured post implant)			X	X														
Brief physical exam	X																	
Brief Neurological exam	X																	
Systematic Assessment for Treatment Emergent Events (SAFTEE-SI)	X	X	X			X			X			X			X			X
Medical History	X																	
Demographics and prior history	X																	

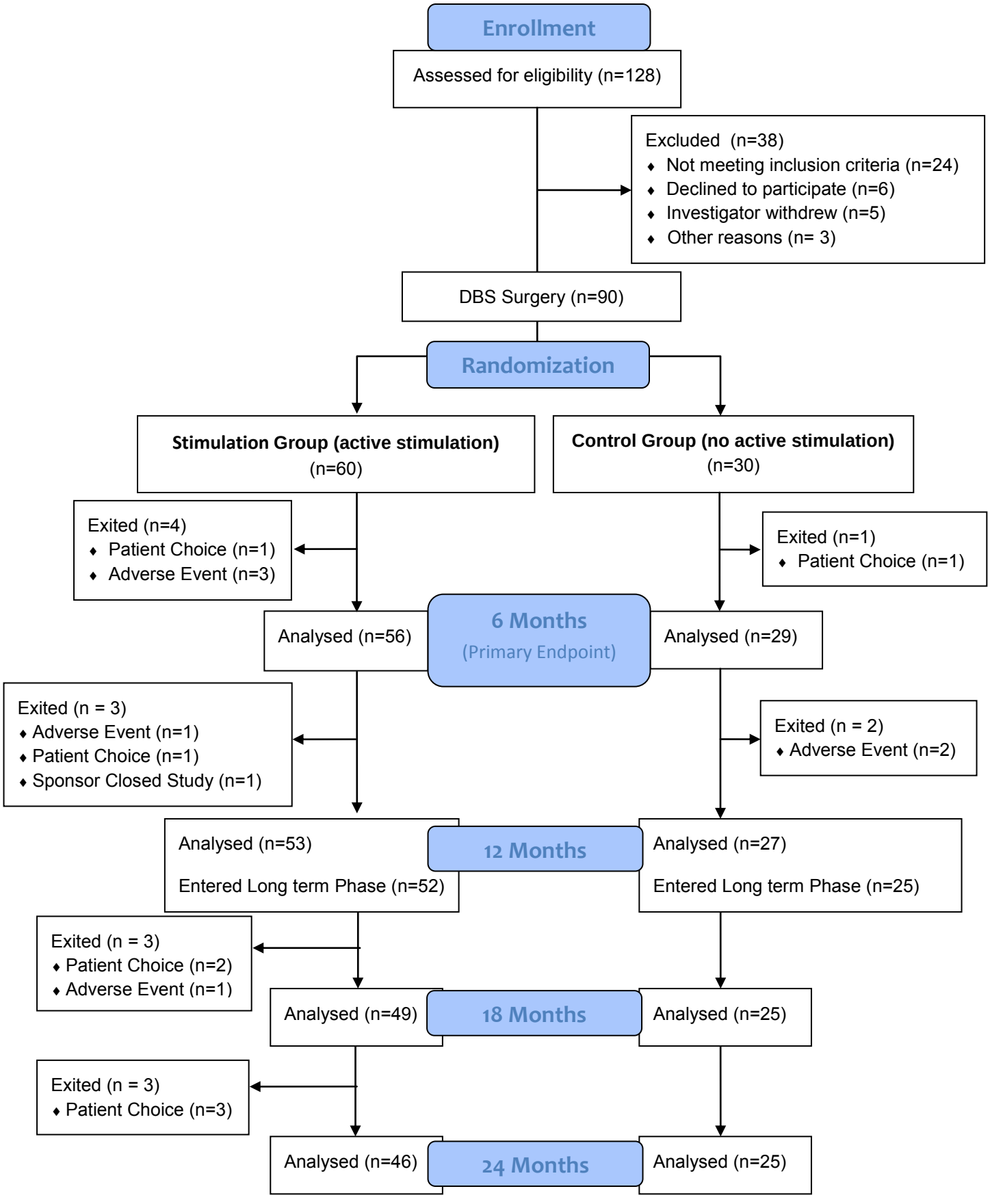
V = Denotes time points when the MADRS session is Videotaped

Window Visit Schedule for Baselines 1-3
Baseline 1 to Baseline 2 Window: ≥ 2 weeks & ≤ 4 weeks
Baseline 2 to Baseline 3 Window: ≥ 2 weeks & ≤ 6 weeks
Baseline 3 to Implant (Week 0) Window: ≥ 2 weeks & ≤ 4 weeks

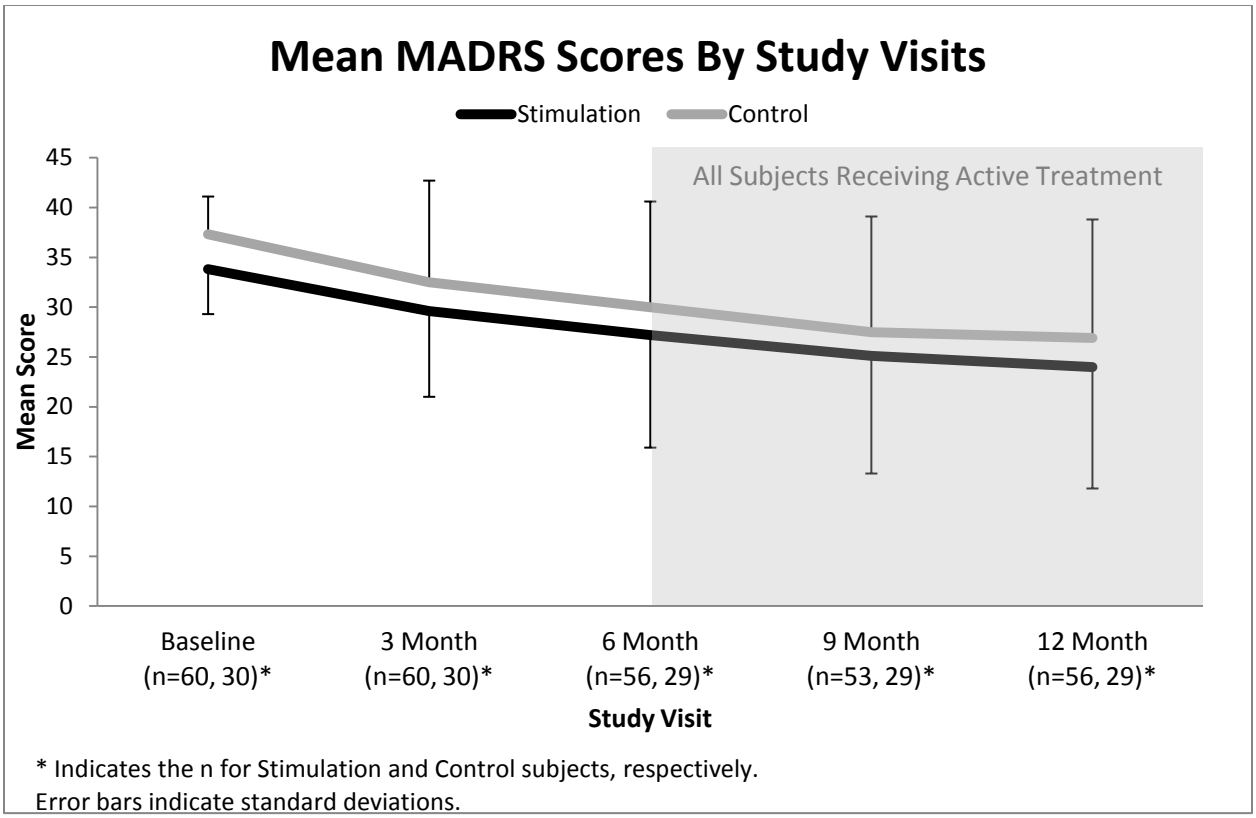
ST. JUDE MEDICAL

Figure

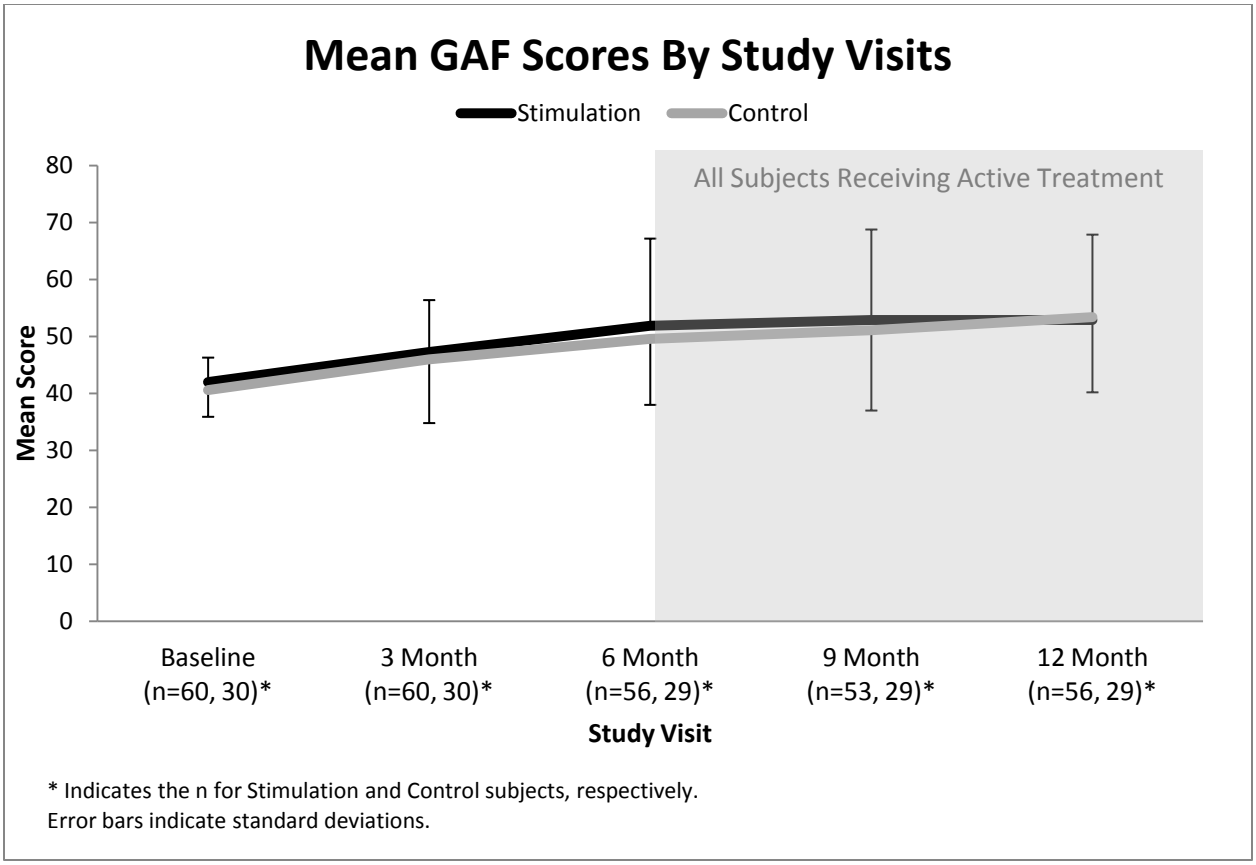
Figure 1. Participant disposition



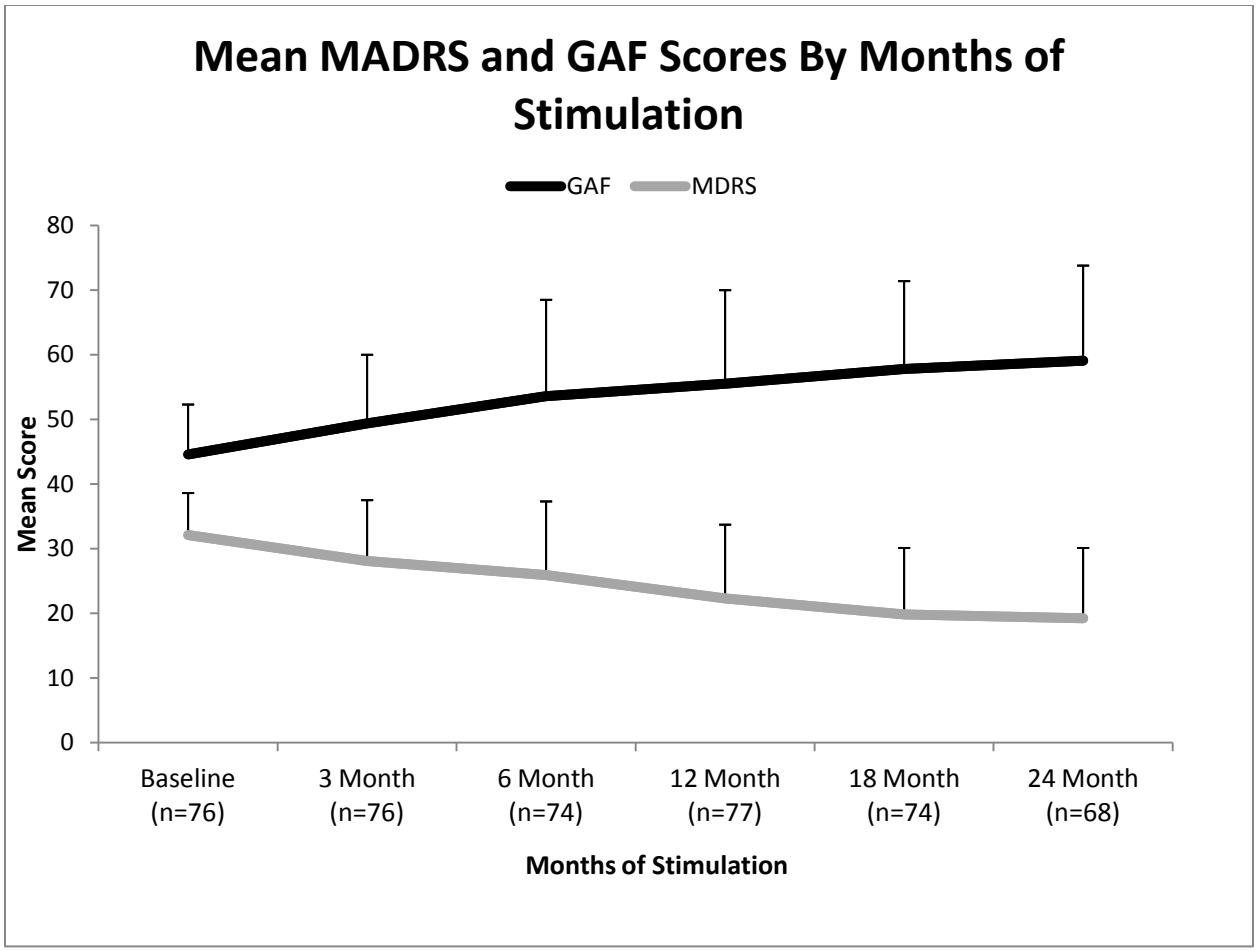
Figure


Mean MADRS Scores By Study Visits
Stimulation
Control
All Subjects Receiving Active Treatment
Mean Score
45
40
35
30
25
20
15
10
5
0
Baseline (n=60, 30)*
3 Month (n=60, 30)*
6 Month (n=56, 29)*
9 Month (n=53, 29)*
12 Month (n=56, 29)*
Study Visit
* Indicates the n for Stimulation and Control subjects, respectively.
Error bars indicate standard deviations.

Figure


Mean GAF Scores By Study Visits
Stimulation
Control
All Subjects Receiving Active Treatment
Mean Score
80
70
60
50
40
30
20
10
0
Baseline (n=60, 30)*
3 Month (n=60, 30)*
6 Month (n=56, 29)*
9 Month (n=53, 29)*
12 Month (n=56, 29)*
Study Visit
* Indicates the n for Stimulation and Control subjects, respectively.
Error bars indicate standard deviations.

Figure


Mean MADRS and GAF Scores By Months of Stimulation
GAF
MDRS
Mean Score
80
70
60
50
40
30
20
10
0
Baseline (n=76)
3 Month (n=76)
6 Month (n=74)
12 Month (n=77)
18 Month (n=74)
24 Month (n=68)
Months of Stimulation

Table

Table 1. Demographics and Clinical Characteristics

	Stimulation (N=60)	Control (N=30)
Female N(%)	30 (50%)	17 (57%)
Age (mean ± SD)	50.53 ± 9.73	48.70 ± 10.56
Race: Caucasian N(%)	58 (97%)	26 (87%)
Family history of mood disorder N(%)	41 (68%)	23 (77%)
Length of current depressive episode (years, mean± SD)	12.62 ± 8.15	9.67 ± 4.67
Lifetime number of episodes (mean ± SD)	4.95 ± 6.43	4.40 ± 3.56
Hospitalization for current episode: yes N(%)	18 (30%)	8 (27%)
Lifetime Hospitalization for MDD: yes N(%)	10 (17%)	10 (33%)
History of suicide attempt: yes N(%)	23 (38%)	9 (30%)
Lifetime number of adequate antidepressant treatments (Mean ± SD)	7.4 + 3.14	8.8 + 4.39
Total number of lifetime treatments for MDD (mean ± SD)	20.5 ± 8.16	22.0 ± 9.32
Prior ECT N (%)	52 (87%)	22 (73%)

No statistically significant differences were identified between groups on any demographic or clinical variable.

Table

Table 2. Depression severity over time - mean (SD)

	Baseline		3 Month		6 Month		9 Month*		12 Month*	
Measure	Stimulation N= 60	Control N=30	Stimulation N=60	Control N=30	Stimulation N=56	Control N=29	Stimulation N=53	Control N=29	Stimulation N=53	Control N=27
MADRS	33.8 (4.5)	37.3 (3.8)	29.6 (9.1)	32.5 (10.2)	27.2 (11.3)	30.0 (10.6)	25.1 (11.8)	27.5 (11.6)	23.2 (12.2)	26.7 (12.1)
GAF	42.0 (4.1)	40.2 (4.9)	48.1 (8.5)	46.6 (12.0)	52.8 (15.9)	50.0 (10.4)	54.5 (16.4)	52.3 (14.0)	53.6 (15.3)	55.2 (12.8)
QIDS-SR	17.4 (3.3)	19.5 (2.7)	15.0 (5.6)	16.4 (5.6)	14.1 (6.4)	16.3 (5.7)	13.8 (6.5)	15.2 (6.0)	12.8 (6.9)	14.1 (6.0)
HRSD-17	20.3 (3.8)	22.6 (4.4)	*	*	17.5 (7.6)	19 (7.9)	*	*	*	*
IDS	37.0 (7.4)	41.1 (38.2)	32.3 (11.4)	36.2 (12.4)	31.0 (12.9)	35.4 (13.4)	28.9 (12.4)	32.5 (12.3)	26.5 (13.9)	31.2 (14.3)

*Note that at months 9 and 12, the Control group was receiving active stimulation; therefore, for the Control group, 9 months refers to 3 months of active stimulation, and 12 months refers to 6 months of active stimulation.

Table

Table 3. Response/Remission by study visit.

	3 Month	Mean of Months 4, 5, & 6	6 Month	9 Month[a]	12 Month[a]	18 Month[a]	24 Month[a]	30 Month[a]
N (Active, Control):	60, 30	60 ,30	60, 30	60, 30	60, 30	52, 25	52, 25	52, 25
Responders [≥40% decrease in MADRS from baseline] – N (%)								
Stimulation Group	7 (12%)	12 (20%)	13 (21.7%)	17 (28.3%)	18 (30%)	28 (54%)	26 (50%)	25 (48%)
Control Group	*3 (10%)*	*5 (16.7%)*	*6 (20%)*	9 (30%)	8 (27%)	13 (52%)	12 (48%)	11 (44%)
Responders [≥50% decrease in MADRS from baseline] – N (%)								
Stimulation Group	4 (6.7%)	7 (11.7%)	10 (16.7%)	14 (23.3%)	16 (26.7%)	19 (36.5%)	22 (42.3%)	22 (42.3%)
Control Group	2 (6.7%)	3 (10%)	5 (16.7%)	6 (20%)	7 (23.3%)	8 (32%)	9 (36%)	9 (36%)
Remitters [MADRS ≤10] – N (%)								
Stimulation Group	1 (2%)	3 (5%)	6 (10%)	7 (12%)	11 (18%)	9 (17%)	16 (31%)	13 (25%)
Control Group	*2 (7%)*	*2 (7%)*	*2 (7%)*	2 (7%)	2 (7%)	5 (20%)	4 (16%)	3 (12%)

[a] Active stimulation was initiated in the control group at 6 months; therefore, for the control group, 9, 12, 18, 24, and 30 month time points reflect 3, 6, 12, 18 and 24 months of active stimulation.

Table

Table 4. Serious adverse events and non-serious adverse events by group.

Serious AEs	Stimulation Group (Implant to 6 Mo, n=60)		Control Group (Implant to 6 Mo, n=30)		Stimulation Group (6 months to 12 Months, n=60)		Control Group (6 Mo to 12 Mo, n=30)		All Patients (12 Mo, n = 77 to 24 Mo, n=68)	
	Number of events	Number of pts (%)	Number of events	Number of pts (%)	Number of events	Number of pts (%)	Number of events	Number of pts (%)	Number of events	Number of pts (%)
Increase in depressive symptoms	8	7 (12%)	1	1 (3%)	4	3 (10%)	1	1(3%)	13	9 (13%)
Infection	6	5 (8%)	1	1 (3%)	0	0	0	0		
Anxiety	3	3 (5%)	0	0	1	1 (3%)	0	0	0	0
Suicidal Ideation	1	1 (2%)	0	0	1	1 (3%)	0	0		
Suicide or suicide attempt	1	1 (2%)	0	0	1	1 (3%)	2	2 (7%)	1	1 (1%)
Seizure or convulsion	1	1 (2%)	1	1 (3%)	0	0	0	0	0	0
Headache	0	0	0	0	1	1 (3%)	0	0	0	0
Post-operative discomfort	1	1 (2%)	0	0	0	0	0	0	0	0
Hearing and visual disturbance	1	1 (2%)	0	0	0	0	0	0	0	0
General erosion or local skin erosion over the pulse generator (IPG?, burr hole cap, and/or extension	1	1 (2%)	0	0	0	0	0	0	0	0
Hospitalization (Elective Surgery for Bariatric, Back Surgery, Cervical Fusion, Hysterectomy, and anti-coagulant therapy)	0	0	0	0	0	0	1	1 (3%)	4	4 (6%)
Elective Admission (to eliminate burden on caregiver)	1	1 (2%)	0	0	2	1 (3%)	0	0	0	0
Death (Unknown cause)									1	1 (1%)
Non-Serious AEs*	Stimulation Group (Implant to 6 Mo, n=60)		Control Group (Implant to 6 Mo, n=30)		Stimulation Group (6 months to 12 Months, n=60)		Control Group (6 Mo to 12 Mo, n=30)		All Patients (12 Mo, n = 77 to 24 Mo, n=68)	
	Number of events	Number of pts (%)	Number of events	Number of pts (%)	Number of events	Number of pts (%)	Number of events	Number of pts (%)	Number of events	Number of pts (%)
Headache	12	11 (18%)	8	8 (27%)	7	7 (12%)	2	2 (7%)	4	4 (6%)
Post-operative discomfort/pain	11	11 (18%)	8	8 (27%)	0	0	0	0	1	1 (1%)
Persistent pain or redness at the IPG site or the surgery site/extension	9	9 (15%)	6	6 (20%)	1	1 (2%)	1	1 (3%)	2	2 (3%)
Anxiety	3	3 (5%)	5	5 (17%)	3	3 (5%)	3	2 (7%)	1	1 (1%)
Pulling sensation along extension site	6	6 (10%)	1	1 (3%)	0	0	0	0	3	3 (4%)
Hearing and visual disturbance	5	5 (8%)	0	0	4	4 (7%)	0	0	2	2 (3%)
Increase in depressive symptoms	3	3 (5%)	1	1 (3%)	1	1 (2%)	3	3(10%)	0	0
Nausea and/or vomiting	2	2 (3%)	3	3 (10%)	2	3 (3%)	1	1 (3%)	2	2 (3%)
Sleep Disturbance	2	2 (3%)	2	2 (7%)	2	2 (3%)	4	4 (13%)	2	2 (3%)
Paresthesia	2	2 (3%)	2	2 (7%)	0	0	4	4 (13%)	2	2 (3%)
Infection	2	2 (3%)	3	3 (10%)	0	0	0	0	1	1 (1%)
Disequilibrium	2	2 (3%)	1	1 (3%)	2	2 (3%)	0	0	1	1 (1%)
Skin Disorder	1	1 (2%)	2	2 (7%)	1	1 (2%)	1	1 (3%)	1	1 (1%)
Neuralgia	1	1 (2%)	0	0	4	4 (7%)	0	0	0	0

*Non-Serious AEs that occurred in 5 or more patients

Supplementary Tables. No significant difference between active stimulation (Stim) and sham stimulation (Control) groups was found for any of the below variables.

Table S1. Logistic regression analysis of 4-6 month response rate (≥40% reduction in MADRS from baseline) comparing Stimulation vs. Active groups controlling for baseline demographic/clinical variables. LR = logistic regression.

Source	DF	Chi-Square	Pr > ChiSq	Method
Treatment group	1	0.12	0.7274	LR
Sex	1	1.00	0.3164	LR
Site category	2	5.65	0.0593	LR
Average Baseline MADRS	1	0.39	0.5303	LR
Total number of lifetime antidepressant medications and acceptable medication augmentation strategies	1	0.68	0.4087	LR
Total number of lifetime antidepressant medications rated 3 or higher with at least good confidence	1	0.00	0.9686	LR
Total number of lifetime antidepressant treatments rated 3 or higher (can include psychotherapy, ECT, VNS, TMS)	1	0.19	0.6602	LR
Total number of lifetime treatments for depression (including all others listed on this document	1	1.81	0.1783	LR

Table S2. Hamilton Anxiety Scale (Ham-A). Note that 9 month and 12 month time points represent 3 and 6 months active stimulation for the control group.

	Baseline		3 Months		6 Months		9 Months		12 Months	
Group	Stim	Control	Stim	Control	Stim	Control	Stim	Control	Stim	Control
N	40	19	40	19	40	19			40	19
Mean (SD)	15.9 (6.52)	16.7 (4.81)	14.1 (7.00)	16.7 (6.67)	15.0 (7.54)	18.6 (8.70)	*	*	12.3 (7.99)	14.2 (7.97)

Table S3. Work and Social Adjustment Scale (WSAS). Note that 9 month and 12 month time points represent 3 and 6 months active stimulation for the control group.

	Baseline		3 Months		6 Months		9 Months		12 Months	
Group	Stim	Control	Stim	Control	Stim	Control	Stim	Control	Stim	Control
N	60	30	60	30	56	29	53	29	53	27
Mean (SD)	32.9 (4.66)	35.2 (3.06)	28.5 (8.35)	31.7 (9.42)	28.1 (8.52)	31.2 (9.51)	27.1 (10.67)	30.3 (9.58)	25.5 (11.46)	29.6 (9.45)

Table S4. Quality of Life (QOL) scale. Note that 9 month and 12 month time points represent 3 and 6 months active stimulation for the control group.

	Baseline		3 Months		6 Months		9 Months		12 Months	
Group	Stim	Control	Stim	Control	Stim	Control	Stim	Control	Stim	Control
N	58	28								
Mean (SD)	33.5 (6.08)	28.5 (5.87)	35.6 (8.33)	32.9 (9.99)	37.8 (8.93)	34.6 (8.18)	39.9 (10.18)	35.3 (8.80)	40.1 (10.72)	36.8 (11.35)

Table S5. Change in Young Mania Rating Scale (YMRS) score over time. Note that 9 month and 12 month time points represent 3 and 6 months active stimulation for the control group.

	3 Months		6 Months		9 Months		12 Months	
Group	Stim	Control	Stim	Control	Stim	Control	Stim	Control
N	60	30	56	29	53	29	53	27
Mean (SD)	0.2 (2.41)	-0.5 (2.0)	-0.1 (1.89)	-0.2 (2.01)	-0.2 (1.79)	-0.2 (3.17)	-0.3 (2.03)	-0.9 (2.19)

Table S6. Health and Labor Questionnaire. Note that 9 month and 12 month time points represent 3 and 6 months active stimulation for the control group.

	Baseline		3 Months		6 Months		9 Months		12 Months	
Group	Stim	Control	Stim	Control	Stim	Control	Stim	Control	Stim	Control
N	60	30	58	29	56	29	53	29	53	27
Paid Work	12	13	12	8	14	11	18	12	17	11
Manage a Household	5	0	5	2	4	1	3	1	4	1
Pension or Early Retirement	3	1	4	0	4	0	4	1	4	0
In School or a Student	3	0	0	0	1	0	2	0	2	0
Unable to Perform Paid Work Due to Health Problems	28	11	33	14	29	11	23	12	23	11
No Paid Work	8	4	2	5	3	5	2	3	4	4

Table S7. Columbia Suicide Severity Scale. Ns represent participants with a change in score over time. Note that 9 month and 12 month time points represent 3 and 6 months active stimulation for the control group.

	Baseline		**Month 3**		**Month 6**		**9 Month**		**Month 12**	
	Stim (N=39)	Control (N=19)	Stim (N=40)	Control (N=19)	Stim (N=39)	Control (N=18)	Stim (N=36)	Control (N=18)	Stim (N=38)	Control (N=17)
Suicidal Ideation(1-5)										
1) Wish to be dead	31	16	28	16	26	11	22	11	20	7
2) Non-specific active suicidal thoughts	26	14	14	7	13	7	13	7	10	3

3) Active suicidal ideation with any methods (not plan) without intent to act	17	12	10	4	8	7	7	5	6	3
4) Active suicidal ideation with some intent to act, without specific plan	7	7	0	1	4	1	3	0	2	1
5) Active suicidal ideation with specific plan and intent	5	5	1	0	0	1	0	1	0	1
Suicidal Behavior										
Actual attempt	13	5	0	0	0	0	0	0	0	1
Has subject engaged in non-suicidal self-injurious behavior?	4	4	0	0	0	1	0	0	0	1
Interrupted attempt	1	2	0	0	0	0	0	0	0	0
Aborted attempt	4	2	0	0	0	0	0	0	0	0
Completed suicide	N/A	N/A	0	0	0	0	0	0	0	1
Preparatory acts or behavior	6	4	0	0	0	0	0	0	0	1
Suicidal Behavior	1	0	1	1	0	0	0	0	0	0

Table S8. Clinical Global Impression-Severity (CGI-S) and Patient Global Impression-Severity (PGI-S). Note that 9 month and 12 month time points represent 3 and 6 months active stimulation for the control group.

	Baseline		**3 Months**		**6 Months**	
Group	Stimulation	Control	Stimulation	Control	Stimulation	Control
N	60	30	60	30	56	29
CGI-S	5.35	5.73	4.93	5.1	4.57	4.6
N	60	30	59	30	56	29
PGI-S	5.55	5.57	4.92	5.03	4.82	4.86