Reducing Suicidal Ideation through Insomnia Treatment

(REST-IT)

Clinical Protocol

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Project Summary

Epidemiologic reports have linked insomnia to suicidal ideation and suicide death. However, no studies have determined whether treating insomnia decreases the risk of suicidality. We have new data indicating that (1) the link between insomnia and suicidal ideation holds true in clinical trials of depressed insomniacs, (2) dysfunctional cognitions about sleep are related to suicidal ideas, and (3) treatment of insomnia with hypnotics leads to a reduction of suicidal ideation. We now propose to test whether cautious use of hypnotics in suicidal, depressed insomniacs may reduce suicide risk in a multi-site clinical trial, with the following Specific Aims:

Primary Aim: We will assess the effect of treating insomnia with hypnotic medication on the intensity of suicidal ideation in depressed outpatients with insomnia and suicidal ideation.
Hypothesis 1. Treatment of depressed, insomniac and suicidal outpatients with open-label selective serotonin reuptake inhibitors (SSRIs) and blinded zolpidem controlled release (ZOL) will reduce suicidal ideation more than treatment with SSRI and blinded placebo.

Secondary Aim: We will examine whether reduced suicidal ideation in depressed insomniacs is mediated through reduced dysfunctional beliefs about sleep, reduced hopelessness, or fewer nightmares.
Hypothesis 2a. Reduction in suicidal ideation will be mediated through reductions in dysfunctional beliefs about sleep.
Hypothesis 2b. Reduction in suicidal ideation will be mediated through reductions in hopelessness.
Hypothesis 2c. Reduction in suicidal ideation is mediated through fewer nightmares.

Tertiary Aim: We will confirm findings from our prior pilot studies that treatment of insomnia in depressed insomniacs leads to improvements in health-related quality of life, especially in women.

Exploratory Aim: We will archive actigraphy data to permit future examination to confirm our preliminary data that actigraphic activity decreases as suicidal ideation resolves.

Overview of the Need for and Management of a Collaborative Application The sample sizes required to satisfy the Aims are relatively large, necessitating the pooled recruiting resources of 3 sites. Georgia Regents University (GRU) will serve both as the coordinating/data management site, as well as a recruiting site, with Duke and Wisconsin as recruiting sites. Project management will be coordinated through an Executive Committee of site principal investigators, under the supervision of a Data and Safety Monitoring Board.

Impact on the Field This application has the potential to change providers' practice in the approach to treating insomnia in depressed patients with mild-moderate suicidal ideation. It may also reveal the mechanisms whereby insomnia increases the risk for suicidal ideation and behavior, and begin to examine whether there is an actigraphic "signature" for reductions in suicidal ideation. When these lessons are applied to the clinical world, they can be applied with low cost.

3. RESEARCH STRATEGY

3.a. Significance

Suicide is a leading cause of death across all ages and occurs at a rate of 10-11 cases per 100,000 persons per year in the United States.[1] It is the third-leading cause of death in those under 30 years of age.[1] Most suicides occur in the context of an active psychiatric disorder, most often a major depressive episode (MDE).[1]

The risk factors for suicide have been described, and include both unmodifiable and some potentially modifiable factors.[2-4] Examples of unmodifiable factors are advancing age, male gender, and Caucasian ethnicity. Potentially modifiable risk factors include symptoms of depression, hopelessness, social isolation, active alcohol/substance use, and severe sleep disturbance. As a predictor, insomnia is stronger than a specific suicide plan in predicting near-lethal suicide attempts,[5] yet insomnia is often overlooked in reviews of risk factors for suicide and suicide prevention.[6] The need to broaden the search for *modifiable* risk factors is epitomized by this recent statement: "nowhere is the lack of proven therapeutic methods greater than in the prevention of suicidal behavior."[7]

As we have reviewed elsewhere,[8-10] 60 research studies link insomnia to suicidal ideation, suicidal behavior, or suicide death, including 40 in adults. [9;11-43] Insomnia and nightmares were the most common sleep disturbances associated with suicide, even after adjusting for severity of depression. Five studies were prospective and showed that insomnia was a risk for completed suicide. [22-25;38] The clinical association of insomnia, nightmares, and suicidal ideation is paralleled by the physiologic finding that, among depressed outpatients, there is an inverse relationship between REM sleep latency and intensity of suicidal ideation.[43]

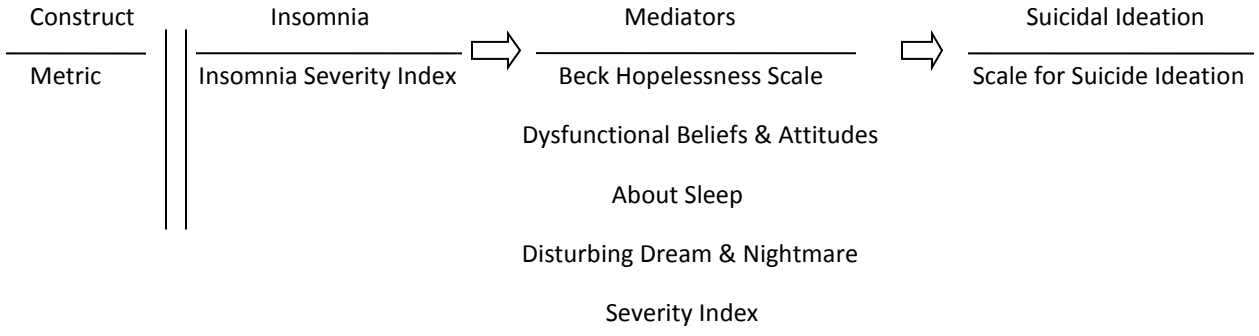
Despite these data, expert reviews of suicide risk factors and suicide prevention have generally overlooked insomnia.[3;6] A limited number of somatic therapies have evidence for a specific anti-suicide effect in mood disorders, including lithium and Electroconvulsive Therapy (ECT).[44;45] Notably, both lithium and ECT have favorable effects on sleep.[46;47]

3.b. The theoretical model

Hopelessness is common in MDE and is itself a potentially modifiable risk factor for suicide.[3] Interestingly, hopelessness is a key dysfunctional cognition that may perpetuate chronic insomnia, and hopelessness is reflected in the content of the Dysfunctional Beliefs and Attitudes about Sleep Scale, which includes items such as "When I sleep poorly one night, I know it will disturb my sleep schedule for the whole week".[48-50] These same dysfunctional beliefs regarding the hopelessness of sleep have been identified in depressed insomniacs.[51] Treatment of insomnia with cognitive behavior therapy for insomnia (CBT-I) reduces dysfunctional cognitions in primary insomnia, and resolves the insomnia syndrome.[50] Therefore, our theoretical model (Figure 1, below) is that treatment of insomnia leads to reductions in dysfunctional beliefs and attitudes about sleep, and thereby leads to reduced intensity of suicidal ideation.

Figure 1

Theoretical Model of Mediation of the Effect of Insomnia on Suicidal Ideation



Despite growing evidence for CBT's efficacy for both insomnia and depression, most patients with depression and insomnia receive pharmacologic treatment for insomnia. We reported that psychiatric disorders were the most common diagnoses associated with a prescription for a hypnotic medication.[52] This is explained in part by the fact that (1) serotonin reuptake inhibitors (SSRIs) do not immediately improve insomnia, (2) up to 40% of otherwise successfully treated MDE patients continue to have insomnia,[53] and (3) up to 10% actually experience worsened insomnia.[54] Thus, many taking SSRIs also receive a sleep aid medication,[55] but the effect of hypnotics on suicidal ideation has never been evaluated in clinical trials. Physicians treating depressed persons with insomnia are left with no guidance as to whether suicidal thinking would be decreased by using hypnotics to treat insomnia. More information is needed to resolve this conundrum.

The expert workshop on suicide prevention (led our DSMB chair, Dr. John Mann), concluded that "randomized controlled trials of psychopharmacology are needed in suicide prevention studies."[1] Targeted treatment of insomnia may represent one such avenue, although the use of hypnotic medications presents its own unique hazard. We show in our Preliminary Studies that (1) the relationship between insomnia and suicidal ideation holds true within the context of depression clinical trials, (2) dysfunctional beliefs about sleep may mediate risk for suicidal ideation in insomniacs, and (3) that depressed insomniacs who receive a hypnotic at bedtime will report lower, not higher, levels of suicidal ideation.

3.c. Innovation

Dr. McCall's group at Wake Forest completed the first clinical trial examining insomnia and suicide risk. Targeting insomnia as a modifiable risk factor for suicidal ideation is innovative. Despite dozens of reports of association between sleep insomnia and suicide, there are no psychopharmacology trials targeting insomnia for suicide risk reduction. Also, a plausible mechanism explaining the link between insomnia to suicide has not been explored. We will test the impact of insomnia therapy on suicidal thinking, and as part of our innovation, we will test whether improvement is mediated via reduction in distorted cognitions about sleep. We also have unpublished data, described below, showing (1) that suicidal ideation is related to dysfunctional beliefs about sleep, and (2) that early reductions in suicidal ideation is associated with a drop in actigraphy values from 4-6 PM. We will archive actigraphy data in this project for future analysis of biological signatures of early reductions in suicidal ideation.

3.d. How this project will improve knowledge and practice

Although some non-randomized studies have shown that hypnotic use is associated with less suicidal ideation,[38] other studies show the opposite,[56] leaving practitioners with little guidance as to the net value of hypnotics in depressed insomniacs with suicidal ideation. The results of the studies proposed in this application will inform this debate, and provide potential mechanisms (via actigraphy and dysfunctional beliefs about sleep) to explain the insomnia-suicide association. Further, this application is consistent with the August 2010 Report of the National Advisory Mental Health Council's Workgroup, "From Discovery to Cure", which emphasized the importance of advancing 'personalized treatment' and 'preemptive treatment' (page 3).[57] The emphasis of this Report is seen in our application as we identify insomnia as a symptom of particular relevance in some, but not all depressed patients, and deserving of targeted anti-insomnia intervention, leading to a preemptive reduction in suicidal ideation, and presumably, suicide. In Recommendation 2.4.1, the Report also calls for support for clinical trials which show that (a) "the adaptation [i.e., intervention] changes a factor [insomnia] that has been associated with ….partial response [suicidal ideation], and (b) clear explication of the mechanism [dysfunctional beliefs and cognitions about sleep] by which the moderator variable [insomnia] functions to disadvantage… a subgroup [insomniacs]. In Recommendation 1.3, the Report also calls for studies to 'identify biomarkers [actigraphy] predictive of treatment response." This application meets the needs expressed in the Report.

3.e. Approach

3.e.1 Preliminary Studies

Relationship between insomnia and suicidal ideation during a 10-week clinical trial conducted by Dr McCall

Eighty adults completed the first week of baseline assessment. Of these, 48 were free of all prescribed psychotropics at the initial screening, 10 were taking a hypnotic, 12 were taking an antidepressant, and 10 were taking both an antidepressant and a hypnotic without success. All 32 patients taking an antidepressant or hypnotic at screening were successfully tapered off those medications before the first visit, and were contacted daily by the research staff during the taper. After a week of baseline assessment, patients received one week of open-label fluoxetine (FLX) monotherapy, starting at 20 mg in the morning. Patients who were still experiencing insomnia after one week of FLX continued with 8 more weeks of open label FLX, and were randomly assigned to also receive either the hypnotic eszopiclone (ESZ) 3 mg or placebo given on a double-blind basis at bedtime. Patients who still had a 24-item Hamilton Rating Scale for Depression (HRSD24) [58] >15 at the end of 4 weeks of randomized treatment could choose to take 40 mg FLX for the next 4 weeks. Study endpoints included measures of sleep, mood, and suicidal ideation. Insomnia severity was graded by the Insomnia Severity Index (ISI).[59] Suicidal ideation was measured with the Scale for Suicide Ideation (SSI). [60-62]

Participants were 18-70 years old, with either (a) sleep latency > 30 minutes and sleep efficiency < 85% at least 4 nights per week, or (b) met Research Diagnostic Criteria (RDC) insomnia criteria for at least 4 nights per week. [63] All participants met a DSM-IV diagnosis of unipolar MDE per Structured Clinical Interview for DSM-IV (SCID), [64] with a Mini Mental State Exam (MMSE) score >24, [65] and a HRSD24 score $\geq$ 20. [58] All participants completed one night of baseline polysomnogram (PSG) which showed no clinically significant sleep apnea (Apnea/Hypopneas index >15) or Periodic Limb Movement Disorder (PLM arousal index >15), following standard measurement procedures described elsewhere. [66]

Sixty participants were randomized out of the original 80 consented patients, and 51 of these completed the final assessment during randomization. The average age of the randomized sample was 41.5 $\pm$ 12.5 years, and 66% were women, with 23.2% minorities. At baseline, the average HRSD24 score was 27.1 $\pm$ 3.9, and the average ISI score was 20.7 $\pm$ 4.0. Scale for Suicide Ideation (SSI) scores were analyzed using generalized linear mixed models for repeated measures with predictor variables being insomnia (ISI scores), the mood item, and the anhedonia item from the HRSD24. Baseline SSI was 3.7 $\pm$ 5.2, with 55% having a SSI score $\geq$1, and 37% of patients having a SSI score $\geq$ 3. If only the individuals with baseline SSI $\geq$ 1 are considered, then the average baseline SSI score was 6.8 $\pm$ 5.3.

The model with ISI as the predictor for SSI was significant with the regression coefficient corresponding to ISI being positive (β=0.055, SE=0.02, p<0.01). Other univariate models found that the depressed mood item was also a significant predictor of suicidal ideation (p<0.005), but anhedonia was not a predictor of suicidal ideation (p=0.9). A multivariate model simultaneously including both the insomnia and the depressed mood items found that both were independent predictors of suicidal ideation (both p<0.05). Our findings confirm that the intensity of insomnia predicts intensity of suicidal ideas during a clinical trial of MDE, even after adjusting for depressed mood and anhedonia.[9]

Actigraphic differences between suicidal and non-suicidal patients

Novel statistical methods based on functional data analysis were applied to averaged actigraphy data to compare circadian activity levels between the suicidal group (SSI>0) and non-suicidal group (SSI=0).[67] Functional data analysis smoothes raw actigraphy data into continuous curves, and the curves are placed into the context of the time of day when the data were collected. Statistical testing comparison of curves can then

be conducted across times. In Figure 2, diurnal patterning of activity at baseline is similar for suicidal and non-suicidal patients, with blue for SSI>0, red for SSI=0. However, one week of fluoxetine resulted in a significantly decreased activity level in the baseline-suicidal group between 4-6PM (Figure 3, $p<0.05$), previously reported as a peak time for suicide attempts.[68] The intensity of suicidal ideation also dropped during this week (Figure 4), suggesting that deceases in actigraphic activity may be a biomarker of early anti-suicide effect.

Figure 2

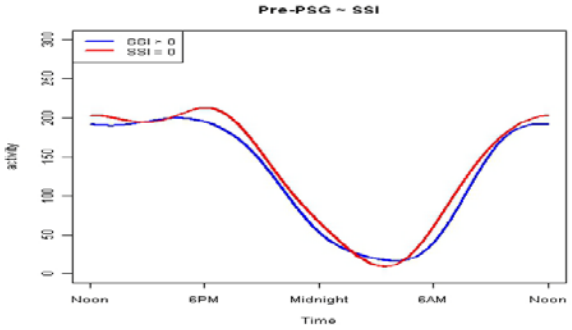


Figure 3

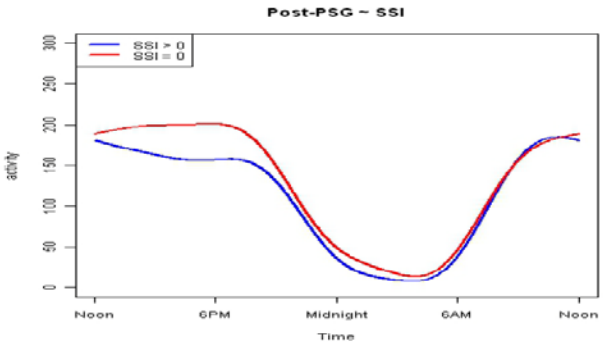
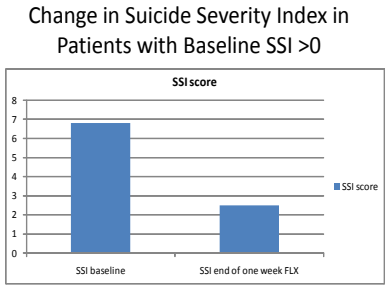


Figure 4



<u>Effect of Hypnotic Therapy on Suicidal Ideation</u>

SSI scores dropped in both the hypnotic and placebo groups during the trial, but were better in the end of treatment in those patients assigned to the hypnotic eszopiclone. If all randomized patients are considered, the adjusted standard deviation for post treatment SSI was 2.0 with an adjusted difference between treatment groups of 0.6, with the hypnotic group having lower (better) scores. Among the 55% of patients with baseline SSI $\geq$ 1, the unadjusted post treatment SSI means were 1.86 and 0.41 in the placebo and hypnotic groups, respectively, with an adjusted treatment difference of 1.3 (p=NS). We conclude that treatment of insomnia with hypnotics among depressed patients with suicidal ideation taking SSRIs has promise in reducing suicidal ideation.

Importantly, no patients made any suicide attempts. One participant became sufficiently suicidal that we removed that individual from randomized treatment and offered standard clinical management. In sum, our participant safety protocols, as described later, succeeded.

<u>Dysfunctional beliefs about sleep are related to suicidal ideation</u>

We hypothesize (Figure 1) that the relationship between insomnia and suicide was mediated through dysfunctional beliefs about sleep. We have collected new cross-sectional data on 50 adults (mean 55 y.o.) in various stages of active depression or recovery, including 16 psychiatric inpatients and 23 outpatients and 11 emergency psychiatry patients in the Wake Forest Emergency Department. Dysfunctional beliefs and attitudes about sleep (DBAS) were measured with the DBAS scale,[49;69] while the intensity of suicidal ideation was measured with SSI,[60-62] and hopelessness was measured with the Beck Hopelessness Scale (BHS).[70;71] There was no collinearity between BHS and DBAS (Pearson's r=0.05). DBAS was significantly related to SSI (r=0.49, $p<0.01$), and in a multivariate model, both hopelessness ($p<0.05$) and dysfunctional beliefs about sleep ($p<0.01$) made independent contributions to the prediction of suicidal ideation. These results support the premise that DBAS mediates insomnia as a risk factor for suicidal ideation. Using a receiver operating curve, we also found that emergency psychiatry patients are best discriminated from outpatients by a SSI score of 16.

Duke University Department of Psychiatry Procedures in Recruiting Depressed Outpatients

Duke has an extensive history in recruiting depressed insomniacs for clinical trials, and taking a leadership role in the analysis and reporting of the results.[72;73] All patients with major depression who contact Duke with an interest in participating in research or who are referred for clinical treatment are screened by a team with information about all ongoing trials. Those who are appropriate will be referred by the centralized assessment team to our study personnel, who will screen them for possible enrollment. This centralized service has dramatically increased enrollment in depression studies since its inception 4 months ago, processing over 15 new depressed patients every week. Further, the proposed trial will be referred all suicidal depressed subjects screened by the centralized assessment service as there are no current or anticipated studies at Duke enrolling suicidal patients with depression. Steps to decrease subject dropout and facilitate adherence to the study protocol include: reminder phone calls prior to visits; careful review of all study procedures with subjects; careful education about potential side-effects of treatments and what to do if side-effects occur; and compensating subjects ($50) for each visit and covering the costs of parking incurred during study participation. Dr. Krystal has consistently achieved his subject recruitment targets in prior trials in patients with insomnia and/or major depression.

University of Wisconsin (UW) Department of Psychiatry in Recruiting Depressed Outpatients

Subjects will be recruited via advertisements (newspaper, internet, newsletters, local postings), referrals from patient advocacy/support groups, and from the UW Sleep Disorders Center and Department of Psychiatry. Clinicians, including co-investigators in this study, may inform patients about the study, either verbally or with printed materials. The UW Department of Psychiatry sees at least 35 new patients per week with depression, and the Sleep Disorders Center sees approximately 10 patients per week with insomnia, 25% of who have concomitant mood disorders. UW has had significant success recruiting and retaining depressed subjects through clinical avenues and advertisements. In an ongoing study of sleep deprivation and depressed mood, UW recruited 57 depressed patients over 2 years, 40 of whom completed the trial. Like GHSU and Duke, UW will facilitate adherence to the protocol by reminder phone calls prior to visits; careful review of all procedures with subjects; careful education about potential side-effects of treatments and what to do if side-effects occur; and compensating subjects ($50) for each visit and covering the costs of parking.

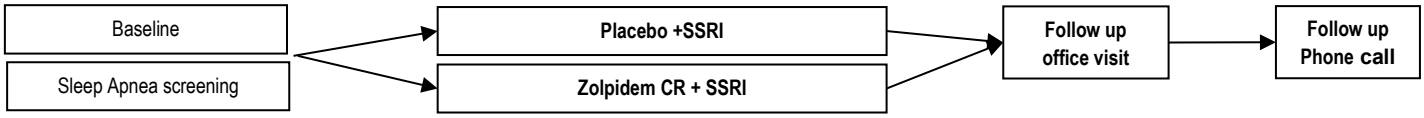
METHODS

3.e.2. OVERVIEW

This four-year, multi-site clinical trial will include 3 recruiting sites (GRU, Duke, University of Wisconsin-Madison) and one coordinating site (GRU). Each site will randomize 11.5 outpatients per year for 4 years, yielding a total of 138 participants (3X4X11.5=138). Participants must be English speaking and meet research criteria for both MDE and insomnia, and will also endorse *moderate* suicidal ideation with baseline Scale for Suicide Ideation (SSI) $\geq$ 3. After a one-week baseline which includes a screen for sleep apnea, participants who satisfy all inclusion and exclusion requirements will receive open label SSRI for 4 weeks, with an option to increase the dose of the SSRI for weeks 5-8. Persons with suicidal intent (SSI >15 and Columbia-Suicide Severity Rating Scale (C-SSRS) suicidal ideation level of 4 or 5 in the last week [74]) will be excluded. Participants will also be randomized to receive either ZOL 6.25 mg or placebo 15 minutes before bedtime each night while receiving open label SSRI in the morning for the first week Patients who still have insomnia, but no side effects at the end of the first week of treatment may have their ZOL increased to 12.5 mg Suicidal thinking, mood symptoms, insomnia, hopelessness, and dysfunctional beliefs about insomnia will be measured at baseline and weeks 1, 2, 4, 6 and 8 of randomized treatment. Participants will be contacted by telephone mid-week for weeks 1-2, and weekly for weeks 3, 5, and 7, and will be invited to come in for an additional face-to-face assessment if there are concerns about worsening suicidal ideas. A comprehensive safety plan is outlined in 6.d. ZOL/placebo will be stopped at the end of the treatment period as (1) sleep benefits may be continued in depressed insomniacs after a hypnotic is stopped,[75] and (2) most participants in our pilot study

preferred stopping their hypnotic after 8 weeks of randomized treatment.[76] Participants will be referred for standard outpatient management at the end of 8 weeks of randomized care, with the option of receiving a SSRI prescription at the end of the trial until they re-enter usual care. We will also provide two weekly follow-up visits after discontinuation of ZOL to assess transition and provide continuity of care until the first care-as-usual visit. Weekly phone calls will be made after the last visit until the patient has connected with their care provider.

Figure 5



Multi-site coordination and Data Management

The project will begin with an investigators' and project managers' meeting for reviewing the protocol and standardizing the delivery of the Hamilton Rating Scale for Depression (HRSD). HRSD ratings will be conducted by project managers, who will demonstrate agreement of 0.85 on criterion videotapes. All study investigators and study personnel will meet annually to review protocol elements and re-calibrate objective clinical ratings. Decisions regarding recruitment obstacles, unexpected protocol problems, etc, will be handled by the study Executive Committee (site PIs), chaired by Dr McCall, and the Executive Committee will have a monthly teleconference. A Steering Committee comprised of all principal and co-investigators will participate in the monthly teleconference. A Publications committee will approve all publications resulting from this project; and all principal investigators shall have access to all data.

A website will be created to facilitate communication and allow all study personnel to access a secure web-based data management system for data collection and participant tracking. The web-based system allows great flexibility in processing data management tasks including the ability to register participants and verify eligibility criteria prior to registration, real-time monitoring and reporting of accrual, retention and intervention adherence and participant follow-up tracking. The website will contain general information about depression, insomnia, and this study which will be available to the public, and a password-protected area for members of the study team (e.g., study protocol, MOP, and data collection forms). Using this system, research personnel can interact with data using web forms that mimic paper forms. The website will be designed with input from the research staff so that the workflow follows the protocol and is in line with trial conduct. Website activity will be monitored and audited for security purposes. Users may view detailed tracking and management information for each participant and/or by assessment time point or follow-up visit. When research staff accesses the website, upcoming participant assessments/visits are presented so that participant management is easily accessible. Once logged in, research staff may run reports, enter forms, review and edit data, and access trial-specific documents. As data are entered, validations rules are applied before data are saved. Inconsistencies are noted for staff to resolve. Research staff can resolve many queries immediately by comparing the screen to the form.

3.e.3. Participants

Participants will be outpatients recruited from local newspaper ads, posters, and normal clinical avenues. Potential participants will be pre-screened by telephone, and if eligible will be invited to the medical center for a face-to-face screening assessment. Participants will be 18-65 years of age, free of all psychotropic medications for one week before baseline assessment, except that prior FLX treatment will require 4 weeks of abstinence, and MAOIs will require 2 weeks of abstinence. The local project manager will confirm a DSM-IV-TR diagnosis of MDE by SCID, and a Research Diagnostic Criteria diagnosis of insomnia.[63] All participants will meet the following severity criteria: HRSD24$\geq$ 20, ISI >7, and reported habitual sleep latency $\geq$ 30 minutes or wake time in the middle of the night of $\geq$ 30 minutes, and sleep efficiency < 85%. Patients will not have a

clinical diagnosis of dementia, will have MMSE ≥ 24, and provide their own written, informed consent to participate. The difficulty in defining a sample of persons with suicidal ideation who have sufficient severity of suicidal ideation to be clinically relevant, yet not so severe as to constitute undue danger to their participation in a randomized trial, was the focus of a very recent editorial.[77] We have addressed this problem by defining participants as those with SSI score ≥ 3 but ≤15, and those with SSI > 15, but with C-SSRS suicidal ideation level less than 4 or 5.[74]. This defines patients with moderate suicidal ideation and no expressed intent to commit suicide. We justify this because suicidal emergency psychiatry patients are differentiated from psychiatric outpatients by a SSI score of 16, using received operating curves (AUC=0.95, p<0.0001).

Participants will be excluded if they have an active or past diagnosis of alcohol or substance abuse, bipolar disorder, schizophrenia per the SCID, or a prior sleep laboratory-confirmed diagnosis of a primary sleep disorder such as sleep apnea or periodic limb movement disorder. Clinical judgment, combining both historical information and urine drug screens, will be used to determine exclusion for alcohol or substance abuse. We will record the Epworth Sleepiness Scale Score, but it will not be a basis for exclusion.[78] We will exclude patients with BMI > 40 and during the one-week baseline participants will complete a screening test for sleep apnea, using a two channel recording of airflow and respiratory effort. Persons who screen positive for moderate-severe sleep apnea (AHI >10)[66] will be excluded and referred for clinical management of sleep disorders.

3.e.4. Treatment

We anticipate that >50% of participants will already be free of psychotropic medications at the first phone screen. If not, the research team will oversee a taper schedule for their current psychotropics, coupled with daily phone calls for safety, so that these patients also will be medication-free at their first visit. Participants who pass all screening and baseline-week assessments will immediately begin treatment with open-label SSRI according to the Table below, and will be randomized to ZOL controlled release (CR) versus placebo. Participants will receive only enough pills to last until the next scheduled research assessment. Research prescriptions will be written by a study psychiatrist and will be filled by a university research pharmacy.

Randomization to ZOL-CR or placebo

Randomized medication (ZOL-CR and placebo) will be prepared by the research pharmacy as identically-appearing capsules. Women and men randomized to ZOL-CR will begin their treatment with ZOL-CR 6.25 mg to be taken 15 minutes before bedtime. Both men and women will be advised that the FDA has expressed concerns about drowsiness after ZOL while driving or operating machinery, especially in the morning and especially in women. Participants will be instructed to call the study team immediately if they experience a side effect with study medications. Each post-randomization visit will include a standardized assessment of the presence or absence of drowsiness while driving or operating dangerous machinery, any accidents or injuries, and if any injuries or accidents occurred, then the time of day and relationship to the timing of the last ZOL dose. Patient adherence to waiting at least 8 hours after ZOL before driving or operating equipment will be confirmed.

At the end of the first week, if the patient (1) does not report drowsy driving or drowsy equipment use, nor accidents or injuries attributable to drowsiness, and if (2) the patient's insomnia has not resolved as evidenced by an insomnia severity index score > 7,[59] then the patient and study psychiatrist may elect to increase the ZOL-CR dose to 12.5 mg. If at any time during the study a patient is taking ZOL-CR 12.5 mg and experiences drowsy driving or drowsy use of dangerous equipment, or an injury or accident attributable to ZOL-CR 12.5 mg, then the dosage should be immediately reduced to 6.25 mg. A second dosage increase back to 12.5 mg may be allowed if it is clear that ZOL was not the source of prior side effects of sleepiness.

The study psychiatrist will be provided with that day's HRSD24 and SSI scores at each visit, and before writing prescriptions for the next interval. The SSI score will be used for further safety assessments, detailed later. At

the end of week 4, the study psychiatrist can increase the dose of the SSRI according to Table 1, if the HRSD24 score is >15 and if the participant concurs. Randomized treatment assignment will remain disguised at the end of treatment, but the study psychiatrist may continue to prescribe open-label SSRI until the first post-randomization usual-care visit. Treatment fidelity will be assessed by the project manager at each visit by pill counts of SSRI and ZOL/Placebo. Blinding fidelity will be assessed at the end of participation as the patient, project manager, and study psychiatrist each complete a 'best guess' questionnaire.

Table 1.
SSRI Dosing

SSRI	Dose for weeks 1-4 (mg)	Option Dose Increase for weeks 5-8 (mg)
Fluoxetine	20	40
Sertraline	50	100
Paroxetine	20	40
Citalopram	20	40

Protocol Deviations and Protocol Violations

Protocol deviations (PD) and protocol violations (PV) are similar in that both reflect a variation in the conduct of the study that is not consistent with the approved protocol and/or the Study Manual. However, PD and PV differ in that PD is said to occur when the patient fails to follow the protocol or Study Manual, while a PV is said to occur when the investigative team fails to follow the protocol or the Study Manual. In either instance, the CRF for PD/PV should be completed both as a paper CRF and on-line. By itself, the occurrence of a PD or PV does not automatically result in the dismissal of the patient from the study. If the local investigative site is considering dismissing a participant because of a PD or PV, then the study staff should first confer with Dr. McCall. Regardless of whether the patient is dismissed or retained after a PD or PV, the local investigative team should collect all scheduled data for the next scheduled visit.

3.e.5. General considerations regarding psychometric measurement

Each treatment visit by the patient will begin with the project manager. The project manager will interview the patient for the HRSD24 and SSI blinded to treatment, and will then oversee the patient's completion of the self-report ISI. The project manager will avoid soliciting side effects and adverse events that may contribute to their unblinding. The project manager will then bring the participant, along with the HRSD24 and SSI scores, to the study psychiatrist for safety assessments and writing prescriptions. The psychiatrist does not provide any assessments of mood, insomnia, or suicidal ideation.

3.e.6. Measurement of Suicidal Ideation and Behavior

The SSI consists of 19 items that evaluate active suicidal desire, specific plans for suicide, and passive suicidal desire.[60-62] Each item is rated on a 3-point scale from 0 to 2 for a maximum score of 38; a lower score indicates less severe suicidal ideation. The SSI will be collected by the project manager at baseline and at weeks 1, 2, 4, 6, and 8 of randomized treatment, and once by telephone one month after completing randomized treatment. An SSI score >2 predicts eventual suicide death over a period of years.[4] The SSI will be collected at the start of each visit, before the participant is seen by the study psychiatrist.

The Columbia-Suicide Severity Rating Scale (C-SSRS)[74] is based upon the Columbia Classification Algorithm of Suicide Assessment(C-CASA).[79] This C-SSRS is used by the FDA in clinical trials to assess suicide risk, and includes a structured assessment of past or recent suicidal behavior. It will be administered at each visit by a study psychiatrist blinded to treatment assignment. C-CASA has excellent inter-rater reliability in classifying suicide attempts, with an overall intra-class correlation coefficient of 0.89. Other pharmacologic clinical trials in samples of suicidal patients have excluded patients from participation on the basis of intent to

commit suicide,[80;81] and this is represented in the C-SSRS as a suicidal ideation score of 4 or 5 in the last week.

3.e.7. Measurement of Insomnia

The participants will complete the Insomnia Severity Index (ISI) at baseline and at weeks 1, 2, 4, 6, and 8 of randomized treatment, and at follow-up visits and phone calls after completing randomized treatment.[59] The ISI is a 7-item questionnaire, with each item scored 0-4, for a maximum of 28 points. Items are scaled according to the degree of dissatisfaction with sleep, in contrast to a sleep diary, which measures the dimension of time spent awake or asleep. Higher scores on the ISI represent more insomnia, and scores >7 indicate a clinically-relevant degree of insomnia. Successful treatment will be defined as final SSI <7. Participants will also complete a daily, morning sleep diary during randomized treatment, which to capture reported bed time, rise time, sleep latency, wake after sleep onset, number of awakenings, and total sleep time.

3.e.8. Measurement of Actigraphy

The participants will wear an actigraph on their non-dominant wrist for the duration of the randomized treatment. Estimates of sleep latency, wake after sleep onset, and total sleep time will be obtained from the medium sensitivity setting at 30-second epochs, as described in our prior research.[76] We have previously reported that actigraphy tracks polysomnography reasonably-well in depressed insomniacs.[82] Actigraphic data will also be archived for potential future additional data analysis (functional analysis) as described above.[67]

3.e.9. Measurement of Depression

Depression severity will be tracked by the observer-rated 24-item HRSD. [58;83] The HRSD24 will be administered by same project manager, blind to treatment assignment, at baseline and thereafter at weeks 1, 2, 4, 6, and 8 of randomized treatment, and once by telephone one month after completing randomized treatment. Research staff will demonstrate inter-rater reliability > 0.85 against a criterion-set of clinical videotapes. The HRSD24 has three sleep items and one suicide item. The HRSD will be recorded as the total score (HRSD24), and will also be analyzed without the three sleep items or the suicide item (HRSD20). The three insomnia items and the suicide item will be separately examined.

3.e.10. Dysfunctional Beliefs and Attitudes about Sleep

The Dysfunctional Beliefs and Attitudes Scale (DBAS) captures the most common distorted beliefs about sleep reported by insomniacs, with a set of 30 items. [84] Eighteen items tap themes of hopelessness related to insomnia, or fear of catastrophic outcomes from insomnia.[48-51] We hypothesize that the DBAS scale will be a mediator of insomnia's influence on suicidal ideation. The DBAS will be assessed at each visit.

3.e.11. Beck Hopelessness Scale

The Beck Hopelessness Scale is a 20-item scale that assesses pessimism and negative expectancies for the future with demonstrated validity across a wide age range.[71;85;85] Among adolescents and adults, it predicts future suicidal behavior.[70;86;87 86;87] This measure takes 5 minutes to administer, and is completed by the patient. Hopelessness will be considered as a potential exploratory mediating variable for understanding the effect of insomnia treatment on suicidal ideation. It will be assessed at each visit.

3.e.12. The Disturbing Dreams and Nightmare Severity Scale

The frequency and intensity of disturbing dreams and nightmares will be measured with the Disturbing Dreams and Nightmare Severity Scale (DDNSI). This scale is derivative of a simpler Nightmare Frequency Questionnaire that had a test-retest weighted kappa>0.85.[88] The revised DDNSI has good internal consistency with a Cohen's alpha >0.80.[16;18] Each participant will complete this self-report scale. Nightmares, like insomnia, have been linked in epidemiologic studies to suicidal ideation, yet an impact of hypnotics on pre-existing

nightmares has not been well described. It will be assessed at each visit.

3.e.13. Measurement of health related quality of life (HRQOL)
We have previously shown that depressed insomniacs taking eszopiclone have superior scores on the two HRQOL subscales of the Basis-32 (the daily living and role functioning (DLRF) subscale and relationship to self and others subscale (RSO) compared to placebo, and that women report superior HRQOL outcomes compared with men. The Basis-32 has good psychometric properties.[89;90] It will be assessed at each visit.

3.e.14 Clinical Global Impression – Severity (CGI-S) and Clinical Global Impression-Improvement (CGI-I)
The participants' overall clinical status and response to treatment will be assessed with the CGI-S and CGI-I. Both scales will be rated along a 7-point dimension. The CGI-S and CGI-I will be completed by a study psychiatrist. The CGI-S will be scored from "Normal" to "Among the most severely ill", while the CGI-S will be scored from "Very much improved" to "very much worse" The CGI-S will be completed at baseline and at all randomized treatment visits, while the CGI-I will be completed only during post-randomization treatment visits.

3.e.15 Reduced Morningness-Eveningness Questionnaire, and the Seasonal Pattern Assessment Questionnaire These two questionnaires are self-report instrument designed to assess how patient's sleep-wake propensity varies with time of day, and with season. Both forms will be self-administered at baseline and at the end of randomized treatment.

3.e.16 Treatment resistance
The participants' response or resistance to pharmacotherapy in the present episode of illness will be measured by a modification of the Antidepressant Treatment History Form (ATHF) and a Hypnotic Treatment History Form (HTHF)

3.e.17 Adverse events
Each post-randomization visit will include a standardized assessment of the presence or absence of drowsiness while driving or operating dangerous machinery, any accidents or injuries, and if any injuries or accidents occurred, then the time of day and relationship to the timing of the last ZOL dose. Patient adherence to waiting at least 8 hours after ZOL before driving or operating equipment will be confirmed. Additionally, the study psychiatrist will elicit spontaneous reports of adverse events (AEs) and serious adverse events (SAEs) at each treatment visit. In the unexpected event of potentially self-injurious behavior, the behavior will be coded as a suicide attempt according to the Columbia-Suicide Severity Rating Scale (C-SSRS)[74], which in turn is based upon the Columbia Classification Algorithm of Suicide Assessment(C-CASA) [79]. The C-CASA will be completed by the study psychiatrist and has excellent inter-rater reliability in classifying suicide attempts, with an overall intra-class correlation coefficient of 0.89.

STATISTICAL CONSIDERATIONS

3.f. Objectives
The primary aim of this double-blind, randomized clinical trial is to assess the effect of ZOL on suicidal ideation in patients who are experiencing suicidal ideation at baseline. It is expected that 67% of participants will be women. Patients who meet the eligibility criteria will be stratified by site, gender and history of prior suicide attempts, and then randomized to receive SSRI with either ZOL or a placebo with equal probability. The primary end point is suicidal ideation assessed repeatedly across 8 weeks after randomization with ZOL versus placebo. Secondary aims are to assess the effect of ZOL on hopelessness, dysfunctional beliefs and attitudes about sleep, and nightmares, and whether these measures mediated the reduction in suicidal ideation seen with ZOL. Tertiary aims will confirm our prior report that treatment of insomnia improves HRQOL while improving sleep and depression symptoms. Health-related quality of life will be measured with the Daily Living and Role Functioning (DLRF) Scale, with the change scores for DLRF contrasted by gender. Reported sleep will be measured by the ISI and sleep diaries, while actigraphy will provide an objective estimate of sleep.

Depression symptoms will be measured with the HRSD. Analysis of all outcome measures will be carried out based on an 'intent to treat' approach.

3.g. Study Design

A double-blind, randomized, parallel group design will be used to assess the effect of ZOL on the SSI. As discussed below, the primary analysis for assessing the main effect of ZOL on SSI will be a mixed model analysis of covariance with treatment and baseline SSI as fixed covariates. Under the assumption of compound symmetry, this test is equivalent to an analysis of covariance on the mean post-treatment SSI with the baseline level as the covariate. Thus, the sample sizes needed to detect clinically meaningful differences between treatment groups can be determined using formulae based on t-tests, where the standard deviation for the post-treatment mean is adjusted by its correlation with baseline levels. To ensure that the trial is not continued if one therapy is clearly superior, a three-stage group sequential design (i.e., two interim analyses and one final analysis) will be employed to allow interim monitoring of the data while the trial is ongoing using stopping boundaries that are intermediate to those proposed by Pocock and O'Brien and Fleming in the likelihood of stopping at the first stage (see Human Subjects for details). The S-Plus module S+SeqTrial 2 (2006) was used to determine the stopping boundaries and the sample size at each stage. Based on our preliminary data, the standard deviation (SD) for SSI for the patients meeting the eligibility criteria for this study was 3.1, somewhat higher than the 2.7 found in our previous randomized pilot study. Assuming conservatively that the SD will be 3.1 in the proposed study, and additionally assuming two interim looks and a drop-out rate of 20%, the total sample sizes to detect differences in SSI ranging from 1.5 to 2.0 between treatment groups with 80-95% power at the 5% two-sided level of significance are shown in Table 1.

Table 1. Total sample size needed to detect specified differences in SSI assuming 20% *dropout and two interim looks.*

Absolute Difference	*80% Power*	*90% Power*	*95% Power*
1.5	*183*	*244*	*302*
1.6	*162*	*215*	*265*
1.7	*143*	*190*	*235*
1.8	*127*	*170*	*210*
1.9	*114*	*152*	*188*
2.0	*103*	*138*	*170*

A total sample size of 138 patients will allow us to detect a difference of 2 units in SSI between the two groups with 90% power. In our previous pilot study, the adjusted treatment difference was 1.3, but the upper bound on the confidence interval was 3.5, so an effect of 2 units is consistent with the pilot data. Further differences in SSI >2 represent risk for future suicide death.[4]

3.h. Power for Secondary and Exploratory Outcome Measures

A secondary aim is to assess whether reductions in suicidal ideation in depressed insomniacs are mediated through reductions in hopelessness, dysfunctional beliefs about sleep, or nightmare intensity. Analyses are described below. We calculate the approximate power for detecting mediation effects according to methods provided by Vittinghoff et al.[91] The power depends on the sample size (assumed to be 110, or 80% of 138), effect of treatment (assumes as 2.0), the correlation between treatment and the mediation variable, the residual variance of the outcome (assumed as 3.0), and the proportion of the treatment effect explained (PTE) by the mediator. We do not know the correlation between treatment and the mediator, so we consider a range between .05 and .3 (the correlation between treatment and the outcome was approximately .2) and calculate power for PTE values between .1 and .8 (see Table 2). We have adequate power (>80%) for detecting mediation effects of .33 or higher as long as the correlation between treatment and the mediation variables are .2 or less.

Table 2. Power for detecting mediation effects.

	PTE							
Correlation	*.1*	*.2*	*.3*	*.4*	*.5*	*.6*	*.7*	*.8*

.05	*.94*	*>.99*	*>.99*	*>.99*	*>.99*	*>.99*	*>.99*	*>.99*
.10	*.41*	*.94*	*>.99*	*>.99*	*>.99*	*>.99*	*>.99*	*>.99*
.20	*.13*	*.40*	*.73*	*.93*	*.99*	*>.99*	*>.99*	*>.99*
.30	*.08*	*.20*	*.38*	*.60*	*.79*	*.92*	*.99*	*>.99*

Tertiary outcomes include health-related quality of life, reported sleep, actigraphically-measured sleep, and depression symptoms. Baseline means and standard deviations observed in our pilot study for these measures are shown in Table 3. Assuming conservatively that a t-test will be done to compare the post-treatment means between treatment groups, the absolute and relative differences detectable with 80% and 90% power are shown in Table 3. (We will actually have repeated measures and the SD will be adjusted for baseline values, both of which will increase our power.) With a sample size of approximately 55 evaluable patients per group (after 20% dropout), we can detect relative differences of less than 23% in each secondary outcome with at least 80% power. The power for detecting gender effects will be similar to the power for detecting treatment effects (as shown in Table 2), assuming the gender ratio is between 0.5 and 2.0. (For example, power is only reduced from 80% to 75% for a gender ratio of 2 compared to a ratio of 1.)

Table 3. Differences detectable in selected tertiary outcome measures with 80% and 90% power at the 5% two-sided level of significance.

		80% Power		*90% Power*	
Outcome	Mean (SD)	Absolute	Relative (%)*	Absolute	Relative (%)*
DLRF	2.0 (0.7)	0.38	19.0%	0.44	22.0%
RSO	1.9 (0.8)	0.43	22.6%	0.50	26.3%
ISI	20.7 (4.0)	2.16	10.4%	2.50	12.1%
HRSD24	27.1 (3.9)	2.10	7.7%	2.43	9.0%

* Relative to control group mean assuming no change in that group
DLRF= Daily living and role functioning; RSO=Relationship to self and others; ISI=Insomnia Severity Index; HRSD24=Hamilton Rating Scale for Depression, 24 item

3.i. Randomization

At baseline, all participants will be classified as either having a prior life-time suicide attempt or not, according to C-SSRS.[74] Participants will be stratified by site, sex, and prior history of suicide attempts and randomized within strata to receive ZOL or placebo with equal probability, using variably sized permuted block randomization to ensure approximately equal accrual to each treatment throughout the study. Block sizes of varying length will be determined randomly to ensure that future assignments cannot be inferred from past assignments. Treatment assignments will be generated using nQuery Advisor 6.0 and incorporated into a randomization table which can be accessed by the study coordinator via the study's website.

3.j. Statistical Analyses

SSI will be measured at baseline and weekly for 8 weeks. The primary analysis will be a mixed model analysis of covariance to assess treatment differences in mean post-treatment SSI and after adjusting for baseline SSI and design parameters such as clinic site and sex, and pretreatment patient characteristics such as age and weight. Adjustments will be made to ensure the analyses match the design, to correct for chance imbalances in important prognostic factors and to improve precision of group comparisons by accounting for variance from variability in patient characteristics. Regression diagnostics, residual plots, and exploratory analyses will be done to find appropriate transformations to satisfy the 1) linearity, 2) homogeneity of variances, and 3) normality assumptions. While we assume compound symmetry for the correlation among repeated measures, we will also consider other covariance patterns, and the appropriate covariate structure will be chosen based on likelihood ratio tests for nested models and the Akaike Information Criterion for non-nested models.

To measure the persistence of the treatment effect on insomnia (the ISI) and suicidal ideation (the SSI) 4 weeks after randomized treatment ends, ANCOVA will be used to assess intervention differences in primary and secondary outcomes. Covariates will include the value of the outcome at 8 weeks, an indicator for intervention group, an indicator variable defining the pre-randomization stratifying factors (e.g. clinical center), and possibly other pre-randomization values of factors known to be predictive of the outcomes or sustainability. Participants who failed to connect with their care-as-usual referral at the end of randomized treatment, or who are highly symptomatic or suicidal (SSI items $\geq$ 15) will be called back in to visit the research team for further assistance and bridging care until the care-as-usual referral is completed.

Despite best efforts, there are likely to be missing end point measurements due to missed visits or patients drop outs. Participants will be encouraged to remain in the trial, even if they need to reduce or discontinue their treatment; data also will be collected from individuals who refuse treatment. However, it is unlikely that we will obtain complete data. Thus, logistic regression models will be used to determine which covariates are predictive of missingness, and these covariates will be included in the outcome analyses to reduce the potential bias caused by dropouts. We will analyze the data using SAS Proc Mixed, a program that provides several computational methods for obtaining maximum likelihood estimates for repeated measures problems, allows for unbalanced designs, missing data at some times, structured or unstructured covariance matrices, and growth curve parameterizations of time effects. A maximum likelihood approach is appropriate if data are missing at random. If, however, the data are not missing at random, data analysis is more difficult and inferences must be made cautiously. Sensitivity analyses will be done to examine the effects that assumptions about missing data have on the results. These same analyses will be used to assess the effect of treatment on the tertiary outcome measures.

A secondary objective is to examine whether reduced suicidal ideation in depressed insomniacs is mediated through reduced dysfunctional beliefs about sleep, reduced hopelessness, or fewer nightmares. Scatterplots will be used to visualize the relationship between suicidal ideation and hopelessness, dysfunctional beliefs about sleep, and nightmares with different smoothed fits for the different interventions. Mediation analysis will be used to determine the degree to which hopelessness, dysfunctional beliefs about sleep and nightmares (separately and collectively) are responsible for (or mediate) the changes in suicidal ideation. Several methods have been proposed to overcome shortcomings in the original methods proposed by Baron and Kenny.[92] Several methods are compared by MacKinnon et al and summarized by Krause et al.[93;94] Several of these methods had similar operating characteristics and will be explored in our study, including assessing the product of the coefficients describing the relationship between treatment and the mediator and the mediator and the outcome,[95;96] and jointly testing the two coefficients.[97] In addition, we will explore the use of multi-level models and longitudinal mediation models, and consider lagged models which include previous measures of the mediation variables with future measures of suicidal ideation.
As an exploratory outcome, we will archive actigraphy data for future functional analysis to examine whether early decreases in actigraphy serves as a biomarker of an early anti-suicide effect.

3.k. WFBH Data Management / Statistical Center

Wake Forest Baptist Health, through the Department of Biostatistics in the Division of Public Health Sciences will be responsible for providing data management and statistical support for this study. WFBH will not see participants nor receive protected health information from the sites. Specifically, WFBH will:

1) Develop a web-site to store study documents and reports and to promote communication amongst project investigators.
2) Create web-based data entry forms that mimic the CRFs
3) Implement data validation error checks and generate error messages for site coordinators
4) Store study data; ensure security and confidentiality

5) Generate randomization and provide online randomization facility
6) Develop online reports for patient accrual and data completeness/quality
7) Generate interim reports for DSMB (described below)
8) Provide analyses and collaborate in manuscript development (described above)

Data handling and management.

The full electronic database will contain the participant's unique study identifier and some date elements (such as visit date), but will otherwise be clean of identifiers. A key at the sites will link the study identifier to participants' personal identifiers for participants recruited at that site. This key will be housed at each site with the consent forms in the study binder. Data entry will be performed at each site by trained research staff with valid confidentiality agreements.

The web-based data management system used for REST-IT will incorporate functionality we have developed for other research studies such as Look AHEAD, ACCORD, ACCORD MIND, LIFE, and SPRINT, among others. This system has substantial functionality in major areas such as security and authentication, user access management, calendar functionality, directory, document, and committee management and dynamic reporting. Electronic data being entered by research staff are immediately transmitted to a secure server at the Coordinating Center, where data will reside throughout the study. The web-based system allows great flexibility in processing data management tasks, including the ability to register participants and verify eligibility criteria before randomization; provide the randomization assignment; allow real-time monitoring and reporting of accrual, retention, and intervention adherence; and track participant phone calls and follow-ups. If needed, data can be securely downloaded directly by study team members for use in analyses. There will also be public areas of the website for posting of non-secured information available to the general public.

The web-based system allows research personnel to interact with data using web forms that mimic paper ones. The website will be designed with input from the research staff so that the workflow follows the protocol and is in line with how the trial will be conducted. Website activity will be monitored and audited for security purposes. Users may view detailed tracking and management information for each participant and/or by assessment time point or follow-up visit. When study team members access the website, a list of upcoming participant assessments is presented for them to view so that participant management is easily accessible. Once logged in, research staff may run reports, enter data into forms, review and edit data, and access trial-specific documents. As data are entered, validation rules are applied before data are saved. Inconsistencies are noted for staff to resolve. Research staff can resolve many queries immediately, comparing the screen to the source, often cleaning the entire database record on the spot. For queries not immediately resolvable, warnings are displayed whenever the data entry screen is recalled.

All access to the website will be logged and stored for auditing purposes. Restricted areas of the web site will be protected by user login. Prior to gaining access to the restricted area, the user will be required to enter a username and password that will be checked against a database. If the combination is correct, a "flag" will be set to allow the user to enter certain areas of the web site. This system allows precise assignments for access based on the person's role in the study. Once a user has successfully logged into the system, inactivity for a period of 30 minutes will automatically force the user to re-authenticate prior to using the system again.

A document describing each data element on the case report form and the location of its original source will be created, placed in the study regulatory binder, and posted on the study web site. CRFs will be used to obtain information from participants. Completed CRFs will be kept in the participant's study binder at each site. From the CRFs, data will be directly entered into electronic case report forms. The infrastructure will be a Windows server running Internet Information Server, with a middleware product (ColdFusion) to integrate database

content within the website. Data will be stored in a secure SQL server relational database. With this web infrastructure, data entered into the system are immediately available for review and reporting. All systems are backed up nightly to disk or tape and tapes are rotated off site several times a month.

Protection – General

Our security model for websites allows specification of access for each user to each area, allowing access to identifying information to be fully controlled. All research personnel are required to maintain current training in Protection of Human Subjects provided by WFSOM or the CITI web program. All systems are securely controlled in the Division of Public Health Sciences data center, which has limited access through badge access (with direct reporting to the Security office). The data center has environmental controls to monitor power, temperature, humidity and sound levels and triggers for notifying staff and engineering, who are on-call 24x7. Our core infrastructure consists of multiple servers, located in a secure network behind a firewall. Multiple intrusion detection systems monitor incoming and outgoing traffic patterns and signatures to identify and block potentially dangerous unauthorized attacks. Users are required to maintain secure passwords that expire every 90 days. Websites undergo a rigorous security scan by Wake Forest Baptist Health's Information Security department to ensure that users cannot be redirected to a third party site and to ensure that participant information is secure.

Protection - Disaster Recovery

Each night, data, programs, code, documents, etc. associated with the study are backed up to a DLT tape library. These tapes are kept indefinitely and are located in a fireproof cabinet that remains locked at all times. Periodically, copies of tapes are moved to an off-site location for storage. In the event that there is any loss of data, the information can be restored from tape in a matter of hours. The entire PHS computer facility is provided with conditioned power, UPS capability and environmental sensors with notification protocols.

3.I. Potential Pitfalls and Alternative Solutions

- Alternatives to generic SSRIs: we chose generic SSRIs because of our experience with them in prior trials, and their low cost. SSRIs have no inherent beneficial effect on sleep.[9899-109] 'Activation syndrome' with SSRIs occurs in <5% of SSRI-treated outpatients[110] and is not significantly associated with suicidal events.[111] Instead, SSRIs are commonly associated with a reduction in suicidal ideas.[57]
- Immediate starting of ZOL along with SSRI after a baseline week: In our prior research of depressed insomniacs, we designed a one-week wash-in of SSRI before starting insomnia therapy. No participants had resolution of their insomnia after one week of SSRI. Thus, there seemed no benefit to including a delayed start of hypnotic therapy in the present proposed trial.
- Recruitment of outpatients: We considered recruiting depressed inpatients into this trial, but concluded that the ethics of randomizing inpatients with suicidal ideation made their inclusion in the study unwise.
- We recognize the limitation of an 8-week study, but believe it is important to first establish acute effects of insomnia treatment in reducing suicidal thinking before pursuing longer-term studies.

Conclusions and Future Directions

Results from this application will immediately inform clinical practice, by answering whether hypnotic treatment of insomnia reduces the intensity of suicidal ideation. If so, it opens the possibility that other forms of insomnia treatment (i.e., CBT-I) may also have benefit, or that specific treatment of nightmares may have benefit. This application will also provide support for hypothetical mechanisms explaining the association between insomnia and suicidal ideation. Finally, we will archive actigraphy data to allow future novel functional data analysis that may distinguish suicidal and non-suicidal depressed insomniacs.

6. PROTECTION OF HUMAN SUBJECTS

6.a Subject selection procedures, and referral of excluded patients

The screening procedures for subject selection are intended to: (1) yield a sample with insomnia associated with depression, and (2) exclude patients who might be harmed by exposure to hypnotics, including pregnant women and patients with advanced sleep apnea and respiratory conditions. Three procedures will be used to qualify participants at the baseline assessment: body mass index (BMI), the Mini Mental State Exam (MMSE),[65] and a two-channel screening test for sleep apnea. A BMI > 40 is highly correlated with obstructive sleep apnea (OSA).[112] A MMSE score < 24 is statistically abnormal at any age and is consistent with global cognitive deficits such as seen in dementia.[113] A history of chronic sleep disturbance before the index MDE will neither be an inclusion or exclusion criteria. It is expected that many eligible participants will have a prior history of primary insomnia, since this is a risk factor for the later development of MDE.[114]
An apnea-hypopnea index >10 will be the threshold for screening positive for sleep apnea. Potential participants who are excluded because diagnosed sleep apnea will be referred to the Sleep Centers of the respective sites (under the leadership of the respective site principal investigators), while patients who are excluded because of absent suicidal ideation will be offered alternative care in the outpatient clinics of the respective sites. Persons excluded because of suicidal intent (SSI>15, and C-SSRS suicidal ideation level 4 or 5 in the last week) will be evaluated for safety and perhaps the need for psychiatric hospitalization at the inpatient unit of the respective sites. All women of child bearing age will complete a urine pregnancy test at the first face to face visit.

6.b. Recruitment and Consent Procedures

6.b.1. Recruitment Recruitment of depressed outpatients at each site will be facilitated by multiple methods, following upon the successful lessons learned in the pilot study. Recruitment methods will include: (1) internal communications to the clinicians within each department of psychiatry, (2) posters in pedestrian traffic areas in the hospitals, (3) presentations to the residents and faculty of primary care departments (internal medicine; family medicine) within each academic center, (4) presentations made to private practice providers in the respective communities, i.e., county psychiatric societies, and (5) newspaper ads. Historically, Dr. McCall's group has had no problem recruiting at least 20% minorities into depression clinical trials.

6.b.2. Consent procedures Initiation of the consent process begins when the Project Manager receives a phone call from the potential participant. At that time, the Project Manager will describe the overall study design, and will detail the time commitment required from the participant. The potential participant will be invited for the face-to-face screening, and the project manager provides a copy of the consent form, allowing enough time for the participant to read the consent form and ask questions, and sign the consent form.

6.b.3. Schedule of assessments

Figure 6

Telephone screening	Screening 1	Baseline	Baseline Follow-up
Consent		1	
Registration		2	
Demographics		3	
Vitals		4	
BMI		5	
Hamilton Rating Scale for Depression (HRSD)		6	
Insomnia Severity Index (ISI)		7	
Beck Hopelessness		8	
Beck Suicide Severity Index/SSI		9	
Research Diagnostic Criteria of Insomnia		10	
Patient report of latency, WASO and Sleep Efficiency Inclusion		11	
MMSE		12	
SCID		13	
Columbia-Suicide Severity Rating Scale-Baseline Screening		14	
Epworth Sleepiness Scale		15	
Dysfunctional Beliefs and Attitudes about Sleep		16	
Disturbing Dreams and Nightmare Severity Index		17	
BASIS-32		18	
Medical History		19	
Concomitant Medications		20	
CGI-S		21	
Antidepressant Treatment History Form (ATHF)		22	
Hypnotic Treatment History Form (HTHF)		23	
Urine Pregnancy Test/ Urine Drug Screening Test		24	
Sleep Apnea Screening			1
Inclusion Exclusion Summary			2
Seasonal Pattern Assessment Questionnaire (SPAQ)			3
Reduced Morningness-Eveningness Questionnaire (rMEQ)			4
Encounter Disposition Form- Baseline/Baseline Follow-up			5
Randomization			6
Study Medication Accountability			7
Study Medication Dispensation- Baseline			8

Outpatient Weeks 1-8

	Antidepressant and Nightly hypnotic/placebo Outpatient Weeks 1-8
Continued Visit Consent	1
Study Medication Accountability	2
Study Medication Dispensation-Randomized Treatment	3
Vitals	4
HRSD	5
Beck Suicide Severity Index/SSI	6
Columbia-Suicide Severity Rating Scale-Since Last Visit	7
Insomnia Severity Index	8
Beck Hopelessness	9
Dysfunctional Beliefs and Attitudes about Sleep	10
Disturbing Dreams and Nightmare Severity Index	11
Sleep Diary	12
BASIS-32	13
SPAQ (Week 8 only)	14
rMEQ (Week 8 only)	15
Actigraphy	16
Concomitant Medications	17
CGI-I	18
CGI-S	19
AE	20
Encounter Disposition Form- Randomized Treatment	21
Best Guess (End of study only)	22

Follow Up

	Follow Up
Insomnia Severity Index	**1**
Beck Suicide Severity Index/SSI	**2**
Encounter Disposition Form –Follow-up	**3**

6.c. Potential risks

The risks of participating in this project are related to (1) the open-label antidepressants, (2) randomized allocation to ZOL, (3) randomized allocation to placebo.

6.c.1. Risks of the open-label antidepressants

The risks associated with SSRIs include jitteriness, nausea and other gastrointestinal upsets that are typically time limited, pose minimal danger, and do not merit discontinuation unless the patient is overwhelmed by the side effect. Sexual dysfunction and changes in weight are more problematic several weeks into initiation of SSRIs. Contrary to common belief, SSRIs are rarely associated with worsening suicidality, and when an increase in suicidality does occur, it is not necessarily related to so called 'activation syndrome'.[57;110;111] SSRIs are not associated with high risk of teratogenicity,[115] but pregnancy tests will be obtained in women with the capacity to conceive. Pregnancy will be an exclusion criterion, and women will be instructed on birth control methods at the time of consent.

6.c.2. Risks of zolpidem

Some risks in previous placebo-controlled trials of hypnotics include daytime sedation, rebound insomnia upon discontinuation of the hypnotic, and memory impairment.[116;117] [117] Other risks that consistently appear in case-controlled epidemiologic studies include increased risk of falls and motor vehicle accidents.[118-120] [118-120] Each post-randomization visit will include a standardized assessment of the presence or absence of drowsiness while driving or operating dangerous machinery, any accidents or injuries, and if any injuries or accidents occurred, then the time of day and relationship to the timing of the last ZOL dose. Patient adherence to waiting at least 8 hours after ZOL before driving or operating equipment will be confirmed. Patients that endorse drowsy driving, near-miss accidents, or injuries related to sleepiness will have their dosage of ZOL reduced from 12.5 to 6.25 mg. Patients that endorse drowsy driving, near-miss accidents, or injuries related to sleepiness and who are already taking only 6.25 mg will be dropped from the study.

Finally, the possibility of tolerance, dependence, dose escalation, and abuse of hypnotics concern some physicians. However, community samples suggest that misuse/abuse rates for hypnotic medications are less than 1 in 300 patients.[121] Studies implicating increased rate of falls in older persons taking benzodiazepines cannot separate the risk of insomnia risks from the risk of insomnia treatment. Studies of untreated insomniacs show that, as a group, they have more falls and poorer cognitive efficiency compared with good sleepers.[122;123]

6.c.3. Risks of being allocated to placebo-hypnotic

Although placebo has no known inherent risk, our research premise is that treatment of insomnia may reduce risk of suicidal ideation. Therefore, placebo may be associated with higher rates of suicidal ideation.

6.d. Safeguards

The Star*D trial was among the first NIH-sponsored trials to follow the 2001 NIH guidelines for studies which included patients at risk of suicide. http://www.nimh.nih.gov/health/topics/suicide-prevention/issues-to-consider-in-intervention-research-with-persons-at-high-risk-for-suicidality.shtml [124] The guidelines have several stipulations, and we have responded accordingly:

1) "Provide specific inclusion criteria and their measurement with regards to suicidality"

   Response: Patients included in the study will have either: (1) a Scale for Suicidal Ideation (SSI) scores $\geq$3 but $\leq$15, or (2) SSI >15 and SSI suicidal ideation level less than of 4 in the week before baseline assessment. This range defines patients with mild and moderate suicidal ideation without suicidal intent. Depressed patients in a university emergency department who are so suicidal that they require admission for safety can be accurately discriminated from depressed outpatients by a SSI scores=16, using receiver operating characteristic curves (AUC=0.94, $p<0.0001$).

2) "Specify the criteria for withdrawal from the treatment trial with regard to increased suicidality, increased related symptoms, lack of treatment response, and treatment side effects, and what alternative treatment or referral will be offered."

   Response: The decision to withdraw the participant from blinded, randomized treatment will be based upon either the participant's view or the research psychiatrist's opinion that the patient is experiencing severe suffering, is at imminent risk for suicide, or is functionally decompensating. The clinician's opinion will be informed on the basis of the HRSD24 and the SSI, but the decision to withdraw a participant will be based upon a combination of psychometrics along with global clinical judgment. If a participant is withdrawn from the study, then he or she will be offered care-as-usual, or hospitalization if necessary. Participants will also be withdrawn from the study if they appear to have severe untoward reaction to bedtime study medication (i.e., repeated falls or ataxia).

3) "Consider and establish criteria for hospitalization, where the hospitalization will take place, and the procedures within the hospital that provide additional safety"

   Response: Hospitalization will be offered if the patient is *judged* at imminent risk of suicide, is functionally decompensated, or needs specialized treatment outside of the protocol (such as ECT), according to the global clinical judgment of the study psychiatrist. Hospitalization would take place in the inpatient units of each clinical site.

4) "Describe procedures in the protocol for managing increases in suicidality, and how research staff is trained and available to provide clinical management"

   Response: Managing increases in suicidality is predicated upon detection of such increases. Although we proposed to examine participants weekly for the first 2 weeks, we recognize that suicidal ideation may emerge suddenly and unpredictably. Therefore, research staff will make at least one mid-week phone call to each participant for the first 2 weeks, and weekly for the second two weeks, to check on their well-being

and assure them that the study staff is available. At each scheduled study visit, the protocol will quantify suicidality 2 ways. First the participant will complete the Beck SSI; second, the research staff will administer the HRSD24. This information flows from the research staff to study psychiatrists at the time of the visit. Participants who have an increase in SSI score of $\geq$ 6 point items will have a thorough review for the presence of any self-injurious behavior since the last visit or the development of any preparatory suicidal planning, as categorized by the C-SSRS.[74] Six-points has been determined as the definition of emergent increase in suicidal ideation, as this value represents one standard deviation in SSI in depressed outpatients seen in Dr McCall's outpatient clinic. Patients judged by the study psychiatrist to be at increased risk of suicide will have an increased frequency of research visits, have smaller supplies of research medication, or may be withdrawn from the study and possibly hospitalized.

5) "Have a procedure for emergency coverage that is clearly understood by the clinical research staff, study participants, and families"

   Response: At the time of consent, participants will receive clear instructions for how to reach study staff during the daytime, and how to access after-hours coverage as provided through each site'. Psychiatry residents-in–training who receive emergency calls from participants after-hours will be instructed to call the local principal investigator immediately, regardless of the time of day. The PI or designated co-I will be continuously available to the respective on-call residents to guide crisis management and assess for the primary suicidal endpoints, if necessary by phone.

6) "As part of the consent process, consider having explicit discussion with relevant family members, guardians, or friends that includes the risks inherent when study participants are suicidal (risk of death, side effects of treatment)"

   Response: Involvement of the participant's family will be encouraged, starting by asking potential participants to bring their families to the first face-to-face screening visit.

7) "Consider and identify the limits of confidentiality with respect to suicidality, as well as other circumstances"

   Response: When a participant has emergent suicidality defined as an increase of 6-points (one standard deviation of SSI scores in Dr McCall's outpatients), we will inform the participant of our intent to share this with the relevant family, and the consent form will reflect this.

8) "Consider the impact of suicidality on the study participant's capacity to give informed consent"

   Response: Consent will be obtained only from persons who normally would not meet criteria for emergent psychiatric hospitalization, i.e., SSI scores will be $\leq$15.

9) "Determine whether additional safeguards are needed to ensure the safety of the study participants"

   Response: A web page will be created to instruct participants on study progress and tell them how to contact the research team at any time. Patients or families without Internet access will receive paper copies of this information.

10) “Consider situations in which a trial would be terminated prematurely”

Response: The trial may be prematurely terminated by the DSMB as described in section E.8 .

6.e. Confidentiality of subjects’ responses

All participants are assured of confidentiality of the information obtained during their participation, with the exception of the expression of imminent suicidality. We will make every attempt to secure the participant’s permission to share a high risk of suicide with the participant’s family. All participants are assigned a subject number for the internal purposes of the research, and the patients’ identity on Case Report Forms is indicated only by their subject number and initials. Case Report Forms are locked in the research offices of the principal investigators. Original source documents relevant to the delivery of clinical care are kept in the patient file office of the Departments of Psychiatry which is continuously staffed or locked, and these clinic files do not circulate beyond the Departments of Psychiatry. Participants will be advised that confidentiality could be breached in the event of an audit by the parent institution or the sponsor.

All access to the website will be logged and stored for reporting uses. Restricted areas of the web site will be protected by user login. Prior to gaining access to the restricted area, the user will be required to enter a username and password that will be checked against a database. If the combination is correct, a "flag" will be set to allow the user to enter certain areas of the web site. This system gives us the ability to designate which areas and functionality the person can access. Once a user has successfully logged into the system, any inactivity for 30 minutes will automatically force the user to re-authenticate (enter user name and password) before using the system again.

All research personnel will be required to maintain current training in Protection of Human Subjects provided by the respective sites or the CITI web program. All systems are securely controlled in the Wake Forest University Division of Public Health Sciences data center, which has limited access through badge access (with direct reporting to the Security Office). The data center has environmental controls to monitor power, temperature, humidity and sound levels and triggers for notifying staff and engineering, which are on-call 24x7. Our core infrastructure consists of multiple servers, located in a secure network behind a firewall. Multiple intrusion detection systems monitor incoming and outgoing traffic patterns and signatures to identify and block potentially dangerous unauthorized attacks. Users of the data entry website at all recruiting sites are required to maintain secure passwords that expire every 90 days. Websites undergo a rigorous security scan by the institution’s IS department to ensure that users cannot be redirected to a third party site and to ensure that personal health information is secure.

6.f. Research procedures

Risks of teratogenicity will be limited by obtaining a pregnancy test from each women of childbearing potential before exposure to the first week of outpatient treatment and by counseling on the need for birth control. Pregnancy will be an exclusion criterion for study entry or for continued study participation. The research procedures include weekly assessment of suicidal ideation (the SSI) and side effects related to medication, including inquiry regarding gait or cognitive side effects (re: hypnotic), and sensory abnormalities (re: hypnotic). A study psychiatrist will examine each participant weekly during routine study visits and will clinically assess the risk of suicide. Participants judged to be at imminent risk of suicide will be managed as described above. Participants will only be given enough study medication to last until their next research visit. If unblinding is necessary, we will have a web-based facility that will allow unblinding of individual patients without unblinding the entire study. A log will be kept of who accesses the unblinding table and which patients were unblinded.

The principal investigators or designated co-Is will be available 24-hours per day by phone and beeper in the event of a participant's medical emergency for the entire duration of the trial. Subjects will be provided with a business sized card to carry in their wallets. This card will include contact information for the physicians and staff members. In addition, it will include a 24-hour number to call in case of emergency. This number will put the subject in touch with the Resident-On-Call provided by the Departments of Psychiatry. The Resident will be able to put the subject in touch with the PI if needed.

6.g. Limited access to hypnotics

We will dispense no more than a week's supply of ZOL/placebo at each visit in the first 2 weeks. A 2-week supply will be allowed in the following 6 weeks only if the participant's most recent SSI did not increase 6 points over baseline (i.e., one standard deviation of SSI scores in stable outpatients). Pill counts will be conducted before dispensing additional hypnotic/placebo. A week's supply of hypnotic, taken as a sole agent in an intentional overdose, is highly unlikely to be fatal.[125]

6.h. Data and safety monitoring board (DSMB)

The external data safety monitoring committee (DSMB) will be under the leadership of John Mann, MD, a suicidology expert at Columbia University. Also on the DSMB will be Maurizio Fava, MD, a depression psychopharmacology clinical trials expert from Harvard, John Winkelman, MD, a hypnotic and insomnia expert from Harvard, Ana Iltis, PhD, a bioethicist from the Graduate School campus of Wake Forest, Dusan Hadzi-Pavlovic, PhD, a biostatistician from the University of New South Wales, and Mr. Andy Hagler, a patient advocate. Dr. Mann will receive quarterly, written reports of unblinded data regarding patient safety, recruitment statistics, any protocol violations, compliance, and completion rate. Serious Adverse Events (SAEs) will be reported in real-time. The DSMB can determine if the trial should be terminated prematurely because of excessive SAEs in any arm of the trial. SAEs of primary concern will be death, hospitalizations, suicide attempts, and falls. In addition, the DSMB will convene a teleconference with the investigators no less than every 6 months, and an independent, formal report will be prepared by the DSMB to be forwarded to the investigators, the site IRBs, and the NIMH Program staff.

Additionally, after 1/3 and 2/3 of the patients have completed the study, the study statistician (Dr. Case) will perform an interim analysis of the data, to determine whether early stopping of the study is necessary. The results of the analysis will be provided to the DSMB at their next teleconference, which should be convened no less than 2 months after the interim analysis is provided to the DSMB, and the DSMB will have final say over the implications of the interim results. The stopping rules are as follows:

1) Accrue 46 patients and test H_0 (no difference in SSI between the two arms). If the two-sided p-value < .0126 then stop the study and reject H_0; otherwise continue to accrue patients.

2) Accrue 46 additional patients (92 total) and test H_0. If the two-sided p-value < .0228 then stop the study and reject H_0; otherwise continue to accrue patients.

3) Accrue 46 additional patients (138 total) and test H_0. If the two-sided p-value < .0308, then reject H_0; otherwise fail to reject H_0.

6.i. Risk/benefit ratio

6.i.1. Risks

Emergent suicidal ideation or behavior is a risk of major depression. We have operationalize emergent suicidal ideation as a 6-point increase, as this represents on standard deviation of SSI scores seen in stable, depressed outpatients seen in the Wake Forest clinic. These risks will be discussed with the participant as part of the consent process. The risk of a fatal outcome from a suicide attempt is mitigated by limiting access to study medication. The likelihood of side effects related to ZOL increases if the patient ingests the medication and then fails to go to bed within 15 minutes, or if the ingestion occurs too late in the night to allow sufficient time before the morning rise time. Patients will be instructed appropriately to go to bed within 15 minutes of ingesting the hypnotic study drug, and to remain in bed (except for bathroom trips) for approximately 8 hours. Patients will be advised to guard against falls during nocturnal bathroom trips. If an adverse event (ataxia, falls, amnesia, dissociative reactions, hallucinations, residual sleepiness, delayed psychomotor reaction times) occurs despite participant adherence to recommended precautions, then participants will be advised to contact the principal investigator immediately to discuss possible ZOL dosage reduction or termination in the study.

6.i.2. Benefits

Benefits of participation include a detailed and accurate psychiatric assessment with the SCID and standard-of-care antidepressant therapy at no cost to the patient. Treatment of depression and insomnia should bring lessened psychic distress, improved quality of life, improved psychosocial function, and perhaps lessen suicidal risk. The frequency and intensity of patient monitoring for depression symptoms and suicidal thinking is greater than that seen in routine care, and is an additional benefit. The overall benefit/risk ratio in this clinical trial is highly favorable, with a large potential impact upon public health policy in the management of depression with insomnia.

6.j Gender and minority recruitment

It is expected that women will constitute approximately 67% of the sample, since women represent both the majority of persons suffering with either depression or insomnia. The prior experience at all sites in recruiting depressed patients met this expectation. Minorities, chiefly African-Americans, will comprise approximately 15% of the total sample. More minorities will be recruited from GHSU and Duke (approximately 20-25% at these sites), consistent with the pilot study for this proposal. Wisconsin will have lower minority recruitment, reflecting its overall demographic composition.

6.k Targeted/Planned Enrollment

Table 3.
Targeted/Planned Enrollment

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	5	2	7
Not Hispanic or Latino	87	44	131
Ethnic Category Total of All Subjects*	92	46	138
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	14	7	21
White	78	39	117
Racial Categories: Total of All Subjects *	92	46	138

6.l. Children and adolescents

Children under 18 years old will be excluded since the safety of zolpidem has not been established in this group.

7. Vertebrate Animals N/A

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