1. TITLE:
Cognitive Behavioral Treatments for Depression in Patients with Chronic Illness

2. PURPOSE OF STUDY (A.2. Rationale and Specific Aims)
Depression is a major public health problem.[1] Religion is a clinically relevant aspect of mental health that is not receiving adequate attention by the mental health community. Consideration of religious beliefs in therapy is preferred by many patients and may result in better patient outcomes. It is completely unknown whether religious cognitive-behavioral therapy (RCBT) is more likely than conventional CBT (CCBT) to (1) successfully treat depression in depressed **religious** patients with chronic, disabling medical illness, and (2) affect physiological systems altered by depression. Rationale and specific aims for Phases I and II of this **feasibility** study:

Phase I
Rationale: Prior to embarking on this feasibility trial, there is need to develop and refine religious cognitive behavior therapies, identify the best way of delivering them to those with chronic disabling medical illness (online via instant messaging vs. telephone vs. Skype), and verify that enough eligible chronically ill depressed patients can be recruited and make it through the protocol. An open trial format in 30 subjects will best accomplish the aims below.
Specific Aim #1. Develop an RCBT treatment manual, adapted to the particular cognitive distortions of chronically ill disabled religious patients, to guide a therapeutic intervention for depression in Christian patients, and then adapt it for Jewish, Muslim, Buddhist, Hindu patients.
Specific Aim #2. Determine whether adequate numbers of depressed religious persons with chronic illness can be identified, recruited, assessed and retained during the intervention.
Specific Aim #3. Determine if delivering CBT online via the Internet and/or by telephone or by Skype, is the most accessible and acceptable way of treating depressed persons with chronic disabling physical illness.
Specific Aim #4. Give therapists experience with online, telephone, or Skype methods of delivering CBT, and our versions of religious CBT in particular.

Phase II
Rationale: Religious beliefs are commonly used to cope with chronic disabling medical problems, and in epidemiological studies, predict a faster remission of depressive symptoms. CBT that utilizes the religious resources of religious patients in the treatment of depression should boost the effects of conventional CBT, and lead to a greater reversal of immune and endocrine changes association with depression. An RCT in 70 subjects is the design of choice.
Specific Aim #1. Determine if RCBT is more effective than CCBT in treating major depression in religious patients with chronic disabling illness, and examine whether religiosity is a moderator of this effect.
Specific Aim #2. Determine if the benefits of RCBT over CCBT can be explained by improvements in gratefulness, generosity, optimism, purpose in life, social and physical functioning, and/or a stronger therapeutic alliance. [we recognize that this aim is particularly under-powered]
Specific Aim #3. Determine if RCBT is more effective than CCBT in (1) reducing 12-hour urinary cortisol, norepinephrine, and epinephrine; (2) reducing pro-inflammatory cytokines

[1]See **Full Protocol,** pp 84-100, for citations documenting statements made in this document. Alphabetizing & numbering in parentheses ( ) refer to the Full Protocol.

(interferon-γ, interleukin [IL]-1β, IL-1ra, IL-2, IL-6, IL-17, tumor necrosis factor-α) and reducing another pro-inflammatory marker, C-reactive protein; and (3) increasing anti-inflammatory cytokines (IL-4, IL-10). In other words, is RCBT more effective than CCBT in optimizing the balance and modulation of endocrine and immune functions adversely affected by major depression.
Specific Aim #4. Determine if genetic polymorphisms that increase susceptibility to depression in the presence of stressful life events are more prevalent in deeply religious depressed subjects vs. those less religious. Of particular interest are the serotonin transporter-linked promoter region (5-HTTLPR) genotype SL/SS, the rs6295 5-HT1A receptor genotype CG/GG, and the MAOA-uVNTR promoter high-activity-allele carriers.
Specific Aim #5. Determine if RCBT is more effective than CCBT in the presence of one or more of these genetic polymorphisms, and if treatment efficacy is moderated by religiosity.

Importance (A.3)
We acknowledge that the feasibility study proposed here involves methodological challenges, which we have anticipated and discussed (see pp 34-39, **Full Protocol**). However, the findings from this research program could result in (1) the development of a new, more effective version of CBT for depressed religious patients that integrates religious resources (Christian, Jewish, Buddhist, Hindu, and Muslim) into therapy, (2) the identification of a delivery system particularly acceptable to depressed patients with chronic disabling medical illness that increases their access to treatment, (3) a better understanding of how religious beliefs and behaviors impact physical health through immune/endocrine mechanisms, and (4) genetic explanations (a) for why religious patients with chronic disabling illness are particularly vulnerable to (or protected from) depression and (b) for why a therapy that integrates religious resources into therapy is particularly effective in patients with strong religious beliefs.

3. BACKGROUND AND SIGNIFICANCE (B)

Depression is a Major Public Health Problem (B1-B3)

Based on a joint study conducted by the Harvard School of Public Health and the World Health Organization, depression was the leading cause of disability in the world (measured by years of life lived with disability) in 1990, and in 2020 is expected to be the world's second leading cause of disability, surpassed only by cardiovascular disease. The lifetime prevalence of depression in the U.S. is 20% in women and 10% in men. While the point prevalence of major depression in the United States is 7%, this figure increases to 10% to 45% in patients with medical illness depending on setting. Major depression is a potent risk factor for disease morbidity, as medical patients with depression have double the mortality of non-depressed patients matched by illness, age, and disease severity. The kinds of depression seen in primary care are often situation-related and due to changes in life that physical illness has brought on, including day-to-day problems with functioning at home and work. Thus, psychological approaches such as CBT have been particularly effective in treating depression in medical patients who need help coping with difficult circumstances.

Cultural Barriers to Psychotherapy and Role of Religion (B.4.)

Cultural factors interfere with patient acceptance and compliance with conventional forms of psychotherapy. There has been a long history of conflict between religion and mental health care. Negative attitudes toward religion by mental health professionals abound today, often

blinding clinicians to the possible benefits of using religious resources in psychotherapy. Likewise, religious professionals are often reluctant to refer members of their congregation to mental health professionals, especially for psychotherapy that seeks to alter beliefs and attitudes. Furthermore, if patients are members of a faith community and that community does not support (or counteracts) the changes made in psychotherapy, then those gains may not last [see **Full Protocol** for role of clergy in mental health care, p 13].

According to a January 2009 Gallup Poll, 65% of Americans indicated that religion is an important part of their daily life, a figure that increases to over 75% in the southeastern U.S. According to a Pew Foundation national survey of 35,000 Americans, 56% indicated that religion was "very important" in their lives, a figure that increases to 69% in North Carolina. This is especially true for medical patients, who often turn to religious beliefs to cope with illness. In a study at Duke Hospital, nearly 90% of medical patients used religion to cope, and of those who indicated this, nearly half (45%) reported that religion is *the most important factor* that keeps them going. We have also shown that religiosity predicts a faster resolution of depressive symptoms in medical patients over time.

Religious people, however, are not exempt from depression. In a study at Duke Hospital, 76% of medical patients over age 50 with major depression indicated that they prayed at least once daily. Many depressed patients who are religious may shy away from secular psychotherapy because they perceive it as unsympathetic to their religious beliefs. They may also avoid psychotherapy because they feel depression is shameful and that seeking therapy means they have abandoned their faith. Religious persons may feel guilty about being depressed, and thus fail to address it with their clergy and avoid seeking support within their faith community. Religious psychotherapy may help normalize depressed religious patients' need for psychotherapy and thus overcome this barrier to treatment.

The efficacy of religious psychotherapy – therapy that takes into account the religious beliefs and practices of patients and utilizes them in therapy – has yet to be examined in primary care medical settings. However, religious CBT has been shown in one study to increase the speed of remission in depressed religious patients above and beyond that achieved by conventional CBT. Likewise, a number of studies that took patients' religious beliefs into account in therapy have reported results superior to secular treatments or usual care, especially in religious patients. Furthermore, recent evidence indicates that 77% to 83% of adults aged 55 or older with depression and chronic medical illness would prefer to include religion in their therapy.

Barriers to Accessing Psychotherapy (B.5.)

Primary care patients with mobility problems or those who are home bound may have difficulty traveling to therapists' offices. Online or telephone approaches to delivering CBT have been effective and acceptable to medical patients with depression [see **Full Protocol** for discussion of these technologies, p 15]. Novel methods such as use of Skype have yet to be tested.

We have recently published in the Lancet the first report of a randomized controlled trial (RCT) of therapist-delivered online CBT for depressed medical patients demonstrating that CBT is more beneficial than usual care when delivered online by a therapist. Dropouts, however, have been a problem with online CBT (28% in recent Lancet study); thus, to minimize dropouts and boost effects, it has been recommended that a telephone component be added since telephone contact is known to increase compliance. Furthermore, structured CBT delivered by

telephone is both clinically effective and cost effective in medical patients with depression. Skype is novel technology that uses the computer and so represents another alternative.

Effects of Depression and Religion on Physiological Functions (B.6.)
Physiological alterations occur with depression. Religious beliefs and behaviors that facilitate coping could help to normalize those changes.

There is evidence that the alterations in immune and endocrine function associated with depression increase medical morbidity by increasing risk of infection, inflammatory disorders, and possibly malignancy. Depression has been associated with a host of immune, endocrine, and pro-inflammatory functions that could influence patients' recovery from medical illness. Depression is associated with an altered balance in the Th1/Th2 ratio, i.e., higher pro-inflammatory Th1 cytokines (IL-1, IL-12, INF-γ), higher pro-inflammatory monocytic cytokines (IL-6, TNF- α), and lower anti-inflammatory Th2 cytokines (IL-4, IL-10). Importantly, impaired immune functions associated with depression have been shown to normalize in response to psychological interventions (due in part to a return of the pro-/anti-inflammatory cytokine balance). See **Full Protocol** pp 16-18 for review.

There is evidence that religious involvement is associated with better immune and endocrine functions, including lower inflammatory markers (IL-6, INF-γ, pro-inflammatory/anti-inflammatory ratio), lower cortisol and catecholamine levels (see **Full Protocol**, pp 18-19, for a review of this research). No studies, however, have yet examined the effects of a religious psychotherapy on these functions.

Understanding the Genetic Basis for Religion's Association with Depression (B.7.)
While religiousness is often inversely related to depression and associated with faster recovery from depression, a number of studies suggest that depression may be more common in religious persons, perhaps due to greater emotional sensitivity (referred to as "neurosis" by Freud). Could underlying biological factors explain the link between religion and depression?

Genetic Polymorphisms and Risk of Depression. Certain gene forms or genetic phenotypes may increase vulnerability to depression, and there is some evidence that the capacity for spiritual or religious experience may be linked to such genes, increasing the religious person's risk for developing depression [see **Full Protocol**, pp 19-21 for review].

Religion/Spirituality and Genetic Polymorphisms. Preliminary evidence suggests a link between R/S and the genetic polymorphisms that confer increased risk of depression. The SS or SL 5HTTLPR genotypes have been associated with higher scores on the spiritual acceptance subscale of Cloninger's Temperament and Character Inventory and with other factors related to high spirituality. This is also true for the 5-HT1A receptor gene polymorphism (the so-called rs6295 marker) involving a C to G substitution resulting in CG and GG genotypes, a finding consistent with a functional magnetic resonance imaging study reporting lower brain serotonin receptor binding in those scoring high on spiritual acceptance [see **Full Protocol**, p 21, for an explanation of why a link between R/S may have developed during human evolution].

4. RESEARCH DESIGN AND PROCEDURES (D)

We plan to conduct a randomized proof of concept comparison of conventional CBT (CCBT) versus religious CBT (RCBT) that will demonstrate feasibility and then confirm the expected clinically meaningful difference on multiple outcomes. This study will take place in two phases.

Phase I (D.1.a.)

In Phase I (Rounsaville 1a) we will conduct an open trial to (1) assess the ease of subject recruitment (based on inclusion and exclusion criteria), (2) develop a system of obtaining, transporting, and analyzing biological specimens (blood and urine for immune/endocrine and genetic tests), (3) further refine a Christian RCBT manual (developing Jewish, Muslim, Hindu, and Buddhist versions) and study protocol, (4) develop a workable system of therapist supervision, (5) assess subject acceptability and compliance with therapy via online, telephone, or Skype, (6) decide whether telephone therapy or Skype should supplement or replace the online therapy entirely, depending on subject preference and ease of recruitment of those with necessary computer skills and equipment, (7) and enable therapists to gain experience with the RCBT and the method of delivery (online, telephone, Skype). Specifically, we will identify and enroll 15 subjects meeting eligibility criteria, administer the interventions (RCBT and CCBT), and run subjects through the study protocol (except 3-month f/u). We will then revise, and run 15 more subjects through the entire study protocol (except 3-month f/u) before finalizing it.

Phase II (D.1.b.)
In Phase II (Rounsaville 1b), we will conduct a randomized proof of concept comparison of CCBT vs. RCBT that will (1) further demonstrate feasibility of enrollment and subject compliance, and (2) confirm the expected clinically meaningful difference (effect size) in anticipation of developing a definitive R01 application.

In this head-to-head comparison, 70 religious persons ages 18-85 with a new episode of major depression (diagnosed by MINI Neuropsychiatric Interview), scores of 10-40 on the BDI, and at least one chronic medical illness will be randomized to either CCBT or RCBT (30 completing each intervention, anticipating a 15% dropout rate; if > 15%, will replace to ensure 30 in each arm). The trial will consist of ten 50 min sessions, administered by master's level therapists and delivered over 12 weeks. The primary endpoint will be continuous BDI score. Subjects will be assessed on the BDI at baseline, 4 weeks, 8 weeks, 12 weeks (end of treatment), and 24 weeks.

5. SELECTION OF SUBJECTS (D2)

For a complete description of inclusion and exclusion criteria (D.2.c.), see pp 31-34 of **Full Protocol**.

Inclusion Criteria: (1) at least one chronic illness, where “chronic illness” refers to the presence of least one chronic medical condition (6 months or longer in duration) (broadly defined), (2) ages 18-85 (medical outpatients or inpatients); (3) indicates that religion/spirituality is at least somewhat important (see below); (4) a DSM-IV diagnosis of major depression using the MINI Neuropsychiatric Inventory; and (7) moderate depression severity defined as a score of 10-40 on the Beck Depression Inventory (BDI). Having a history of depression, i.e., recurrent depression, will not exclude participants, but this will be noted and analyzed as a covariate since it may affect study outcomes.

Exclusion Criteria: (1) significant cognitive impairment (<14 on MSE) or inability to give informed consent; (2) currently receiving psychotherapy for depression (i.e., having received it within the past two months), (3) criteria on the MINI for psychotic disorder, alcohol or substance abuse, or PTSD (due to proposed immune and endocrine analyses) within the past year; (4) history of bipolar disorder (ever); (5) active suicidal thoughts that place participant at serious risk (during assessment); (6) diagnosis of HIV/AIDS, autoimmune diseases, dementia (moderate or severe), endocrine disorders likely to affect stress hormone levels, a prognosis of

less than 6 months, or taking immuno-suppressant drugs (again, due to proposed immune and endocrine analyses); (7) inability to communicate in written English; and (8) lack of telephone AND lack of access to a computer or the Internet or inability to type fluently (we may decide to do therapy by telephone exclusively, although will record whether patient has a landline telephone, a computer, access to Internet, able to type fluently, and what route of therapy the patient prefers, **even if patient is excluded**; this information will help determine the ultimate delivery method for therapy that we choose).

6. SUBJECT RECRUITMENT, RANDOMIZATION, AND COMPENSATION.

A detailed description of screening, baseline, and follow-up interviews (and the procedures for collecting immune/inflammatory, endocrine, and genetic specimens) is provided on pp 59-66 of **Full Protocol**. Initial drafts of all questionnaires are attached separately.

The sites for recruitment will be Duke Health Systems (DHS) (North Carolina) and Glendale Adventist Medical Center, Southern California. Two sites are necessary because in the larger, more definitive trial to follow (should we demonstrate feasibility and effects in this one), multiple sites will be necessary in order to recruit and enroll the number of subjects needed (up to 600); two sites on each side of the U.S. will also improve ability to generalize results and will increase diversity by increasing participation by Hispanics (for further justification of two sites, see D.2.b., p 31-33, **Full Protocol**).

We shall recruit depressed chronically ill patients in six ways: 1) identify eligible patients from primary care outpatient rosters and contact them by a letter signed by their physicians [see Letter]; 2) we will post and hand out flyers (see Flyer that explains study, with inclusion and exclusion criteria and examples of significant depressive symptoms) in clinics throughout the Health System and in hospital as allowed [see pp 31-33 of Full Protocol for a complete description of procedure], on Duke University and other local university campuses, in local mental health clinics such as ACCESS, and distribute to community groups such as churches and other community organizations who may have contact with persons at risk for depression; 3) referral from physicians and nurses staffing outpatient primary care clinics; 4) referral from hospital physicians or other hospital staff; 5) advertisements locally via print [see Advertisement], and if necessary, (6) by screening consecutively admitted patients to the medical-surgical services of the health systems above. A caregiver known to the patient will introduce the study and only if the patient is interested in hearing more will the study team approach; also, the patient will only be enrolled in the study with the prior approval of their physician. This applies to subjects who are referred to study by inpatient or outpatient providers; if subject contacts study coordinator independently, then subject will be encouraged to contact their physician (if they have a physician that usually provides their medical care) and let them know that they are in this study.

As a way of introducing study to potential patients in #3 and #4 above, we will ask patient's treating team (physicians or nurses) to give the Flyer to those who might benefit from study participation. Either a treatment team member or the patient can then contact the study coordinator. The study coordinator would then identify an interviewer to contact patient either by telephone or in-person for screening purposes. If by telephone, the interviewer will read a telephone script that explains the study [see Telephone Script] and obtain verbal consent from patient to proceed with the preliminary screening questions; if patient is still eligible based on this preliminary screen, then the interviewer will schedule a clinic visit when she will explain the full study, obtain written consent (enrollment consent), and continue with screening questions to

establish eligibility. If patient is eligible, then interviewer will complete the baseline assessment, and collected blood and urine specimens, as well as collect contact information on the patient and two alternative sources. Alternative sources of contact are needed in order to locate the patient in the event that they move, become hospitalized, or become too sick to respond.

Site coordinators will be given envelopes that include randomization numbers. After a patient completes baseline assessments including proper collection of laboratory specimens, the site coordinator will draw one envelope and open the envelope for the patient's randomization number. The site coordinator will then contact the Coordinating Center and give the patient's initials, study number, and randomization number. The Coordinating Center will find the treatment arm and therapist ID assigned to the randomization number in the Excel randomization database.

Utilizing the randomization program in Microsoft Excel, randomization numbers are randomly assigned to the treatment arm and therapist. A subject randomization number and a study treatment number will be provided. The study treatment number is linked to the treatment condition within the randomization database system. The Coordinating Center will provide a confirmation report of the randomization number and study treatment number assignment to help ensure that it is implemented accurately. Coordinating Study personnel will retain the confirmation reports. The recruitment site personnel at Duke and Glendale will remain blinded to patient group assignment, as they will be doing the follow-up evaluations of trial outcomes. Subjects will be reminded prior to assessments not to indicate what trial arm they are assigned to in order to maintain the blind.

The Coordinating Center will then arrange the first contact between patient and therapist, who together will set up the therapy schedule. The Coordinating Center will also send therapists, via secured e-mail, the following de-identified (patient ID only) baseline assessments of the study patient for a complete history of the patient prior to the therapy session: Demographics (Gender, Race, Marital Status, Education Level, Living Situation, Religious Denomination), Beck Depression Inventory, Cumulative Illness Rating Scale, RCOPE, Charlson Co-Morbidity Index, and a List of Medications. For further details on enrollment and randomization, see pp 39-40 **Full Protocol**.

We expect that subjects from all relevant demographic groups will be involved in this study. Based on prior studies at DHS and AHS of chronically ill and/or depressed patients, we expect our study group of 100 patients (50 from DHS and 50 from AHS) to be 68% female, 21% Hispanic/Latino, 24% Black/African, 5% Asian, and 48% White/Caucasian.

Subjects will be compensated for their time completing the baseline assessment, four follow-up assessments, and for providing blood and urine samples at baseline and two follow-up time points. They will receive $15-25 for each of these (up to $100), and will be paid at the end of the study after all assessments have been completed and specimens received.

7. CONSENT PROCESS (SEE SECTION 14 OF E-IRB)

8. SUBJECT'S CAPACITY TO GIVE LEGALLY EFFECTIVE CONSENT

Subjects will be over age 18. Subjects who do not have the capacity to give consent will be excluded. Capacity to give consent will be determined by subjects scoring 14 or higher (out of 18) on the abbreviated MMSE. If at any time interviewers suspect that capacity has diminished, then the abbreviated MMSE will be re-administered. If MMSE<14, then test will be repeated in 1 week; if still <14, then subject will be removed from study & referred for treatment.

9. STUDY INTERVENTIONS (D.5.)

An overview and session-by-session description of CCBT and RCBT is summarized on pp 40-48 of the **Full Protocol**.

Conventional CBT. CCBT helps clients recover from depression by helping them understand the links between thoughts, emotions and behavior. It uses guided discovery, Socratic questioning, and challenge of automatic negative thoughts to help clients identify and appraise cognitions and determine problematic behaviors. In this arm, therapists will be asked to avoid reference to the participant's religious beliefs. If religious issues come up, therapists will gently redirect the patient to more secular ways of approaching the issue, and if necessary, will address religious issues in the broadest conventional way possible, relating them to other cognitions/behaviors usually addressed in conventional CBT. In order to contrast the two approaches, therapists delivering CCBT will concentrate on the non-religious aspects of CBT.

Religious CBT. RCBT follows same process described for CCBT above. Our RCBT intervention will match CCBT step-by-step; the only difference will be a religious overlay on top of Beck's cognitive restructuring and behavior modification. For example, Session 5 on "dealing with loss" will be identical for both CCBT and RCBT, except for use of religious resources to make sense of losses in RCBT group. Session 6 will focus on managing negative beliefs/ emotions in CCBT group vs. managing negative religious beliefs/emotions in RCBT group. Faith issues will be considered only in terms of patients' beliefs and religious language. The treatment manual will be designed to incorporate the specific religious beliefs of participants. Prior to onset of therapy, time will be taken to identify subjects' religious language, symbols, and particular faith tradition; this information will guide integration of the participant's beliefs into the therapy. The RCBT manual will initially be developed within a Christian framework, and then adapted to the subject's faith tradition if not Christian.

Interfaith Council of Advisors. We will be developing versions of the Christian RCBT manual specific to the faith traditions of non-Christian participants in the study. Versions of the manual will be adapted to apply to Jewish (reform, conservative, and orthodox), Hindu, Buddhist, and Muslim (Sunni and Shia) patients. Members of the Council are described on pp 46-48 of **Full Protocol**.

Training and Supervision of Therapists. For a complete description of CCBT and RCBT training, supervisors, and qualifications of therapists delivering the interventions, see pp 49-51, & 76-78 of **Full Protocol**. For quality assurance (QA) procedures, See pp 51-54 of **Full Protocol** for description of QA procedures.

10. RISK/BENEFIT ASSESSMENT (E.3.-E.4.)

For detailed risk/benefit discussion, see pp 80-83 of **Full Proposal.** This section is summarized here.

Potential Risks. There is risk to confidentiality, risk from blood sampling, and suicide risk. To assure confidentiality of information, we will ensure that all specimens and data shipped between study sites and to consultants are both coded and de-identified. See Section 13 (Data Safety & Monitoring) below for specifics on risk and how handled.

There is a small risk to the subject during venipuncture of momentary discomfort and/or bruising. Infection, excessive bleeding, clotting, fainting or feeling light-headed, or hematoma is possible, although unlikely. Having multiple punctures to locate veins could be psychologically traumatic. All of these potential and theoretical risks will be described in the consent form. A total of no more than 3-5 cc of blood will be drawn from each patient for isolation of genomic DNA (in

addition to the 30 cc of blood for immune analyses and the 10 cc on every 6th or 7th subject for quality control). The consent form will discuss associated potential risks, but it is highly unlikely that the total amount taken (45 cc) will contribute to the patient's need for a blood transfusion. This sample volume is within guidelines for approval of the study as Minimal Risk under 45 CFR 46, Subpart D.

The most serious risk of this study involves subjects with depression developing serious suicidal ideation that increases the risk of self-harm. This may develop at any point in the study from initial baseline assessment to the 12-week intervention and then to the 12-week follow-up. We have a plan in place to address this risk.

Protection Against Risks (E.3.d.). As noted above, the greatest risk to subjects involves risk of suicide, the second greatest risk is breach of confidentiality (especially with regard to confidential questionnaire information and genotype information), and the third involves risk of blood sampling. With regard to the second risk, all data will remain absolutely confidential. In fact, genotype information will be housed separately from clinical data at the Coordinating Center and genotypes will only be merged with clinical data by our statistical geneticists in a file (with multiple layers of password protection and tracking) distinctly separate from the clinical database. Besides measures described above to ensure confidentiality, other measures to minimize risk include full disclosure of risk through informed consent and following a pre-established suicide protection plan.

Informed Consent. To insure that all subjects understand the procedures, all subjects will be informed about our need to collect sensitive questionnaire information at baseline and at four later times, as well as blood and urine samples at baseline and two additional time points. IRB approval will be obtained for the informed consent form from the DUHS and Glendale Adventist Medical Center IRBs. The descriptions given in the informed consent will conform to the guidelines provided in the Code of Federal Regulations.

Suicide Protection Plan. If at any time a study interviewer or study therapist believes that there is a significant suicide risk with a subject who is participating in the study, he or she will consult with Dr. Doug Nies (Glendale site) or Dr. Koenig (Duke site). Dr. Nies (a certified clinical psychologist) or Dr. Koenig (a board-certified psychiatrist) will then assess patient (and consult together as necessary). If they believe there is a significant risk, then they will immediately notify the patient's family and primary physician (if patient has a primary physician) with or without the subject's consent. However, if the situation is urgent, they will contact the family and physician without first assessing patient, again with or without the patient's consent. The informed consent will indicate that in the event of the subject expresses serious suicidal thoughts, study interviewers and therapists are duty bound to do whatever is necessary to ensure the subject's safety *with or without their consent.* In event that Dr. Nies cannot be immediately contacted at the Glendale site, then Dr. Koenig, study PI (who will carry a cell phone 24 hours/day during the study), will be notified and fulfill this responsibility, and Dr. Nies will be contacted if Dr. Koenig cannot be located; in the rate event that neither Dr. Koenig or Dr. Nies can be located, then Bruce Nelson (Coordinating Center administrator) will be contacted and/or one of the site PI's (Dr. Koenig or Dr. Yu) if necessary. (see pp 82-83 of **Full Protocol** for conditions under which this plan will be initiated).

Premature Withdrawal, End-of-Study Debriefing, Referral Options. In order to ensure the safety and adequate treatment of subjects who dropout or complete the study, we have developed a plan for early or end of study termination (see pp See p 57 of **Full Protocol**).

Potential Benefits. The benefits to subjects in this study are that they will receive free psychotherapy for their major depressive disorder from trained therapists experienced in CBT. The benefits to others will result from our learning whether integrating patients' religious beliefs/practices into therapy will result in faster and more complete remission of depression than that achieved with conventional CBT that does not typically utilize patients' religious resources in therapy. Others will also benefit from knowledge acquired from learning about the genetic basis of religiousness and depression, and how it affects response to psychotherapy. Finally, others will be benefited by knowledge of whether CBT can actually reverse some of the immune and endocrine changes seen in major depression, and whether religious CBT is any better than conventional CBT in this regard. Given our plans to protect against the risks, we believe the benefits outweigh risks.

11. COSTS TO SUBJECTS

There will be no costs to subjects. Subject reimbursement should be sufficient for any travel costs involved in participation. Subjects need to already have computes, online access, and landline telephone; if therapy by telephone, therapists will call subjects so no costs incurred. If we decide to do therapy via Skype, we will provide subjects with Skype cameras.

1**2. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS** (D.11.) (for Phase II)

Loma Linda University statisticians, led by doctoral-level statistician Dr. Noha Daher, will perform statistical analyses, prepare periodic reports for presentation to study investigators, and provide the statistical analysis sections for the manuscripts submitted from this project. A complete description of the hypothesis-by-hypothesis statistical analyses, power analyses and sample size considerations is provided on pp 70-75 of **Full Protocol**.

13. DATA AND SAFETY MONITORING (E)

The Clinical Trials Coordinating Center (CC) (GAMC's Quality Assurance & Monitoring Division) is responsible for database development, all data management and monitoring activities, including training and standardization, database development, database quality control, between-institution and study-wide tracking functions. A full description of these duties is contained on pp 67-70. **Full Protocol**. Also, for safety monitoring see pp 81-83 **Full Protocol**.

The most sensitive data involve the blood samples for genetics analysis, although confidentiality regarding personal information collected by questionnaires will also have to be carefully guarded. The DHS and AHS research teams and CC will be responsible for safeguarding the security of all study specimens, records and databases. Samples will be collected and stored at each respective sites until the samples are ready for batch shipment at the end of each phase of the study. Biological samples will be sent via Federal Express to Loma Linda Neuroimmunology Research Lab for endocrine/immune analyses and to Johns Hopkins CIDR for genetics analysis. All specimens will be labeled with a unique patient identification number (PIN). Samples will be batched sent to Johns Hopkins CIDR, where they will be stored using standard procedures and run as a batch. Once the DNA extraction and genotyping has been done, the results will be sent to the CC.

Only the DHS and AHS recruiting sites will hold the code (PIN with patient name) for the subjects they recruit and need to follow up (not the CC). Personal identifying information, such as name, address, driver's permit, Social Security Number, etc., will not be entered into the database. However, other identifying data fields, including date of birth, treatment group, and questionnaire

data will be recorded on the case report forms and will be transferred to the CC, which is highly experienced in keeping subject data secure and confidential. The control of access to databases will be managed centrally by the CC through user passwords linked to appropriate access privileges. This protects forms from unauthorized view and modifications and from inadvertent loss or damage. The CC has an extensive data security infrastructure with database servers are secured by a firewall as well as through controlled physical access.

The CC will ensure that each person accessing the database has the proper authority to perform the functions he or she requests of the data management system. Within the secondary SPSS databases, UNIX group access control will be used for maintaining similar security. The Sun workstation login will be secured by extensive user password facilities under UNIX. A Data Safety Monitoring Board is not required for this feasibility study. However, we will have an ombudsman assigned to study (Doug Nies, Ph.D., Glendale site) who together with Dr. Koenig (DHS site) will be available to make decisions regarding suicidal risk and will direct our suicide protection plan.

14. PRIVACY, DATA STORAGE & CONFIDENTIALITY (see Section 12, E-IRB form)