PROPOSAL

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Cognitive Behavioral Treatments for Depression in Patients with Chronic Illness

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A. OVERVIEW AND SPECIFIC AIMS

A.1. Summary

This project is the initial first step in developing a research program and bringing together a team of investigators capable of conducting future studies to uncover the biological mechanisms that explain why religion affects physical health and longevity. Our target here is depression – a prototype disorder that is (1) widespread, (2) causes tremendous functional disability, (3) produces adverse immune and endocrine changes with clinical implications, (4) has genetic roots, and (5) is influenced both in its development and course by religious involvement.

Major depression is a common, painful, physically impairing, and financially costly illness with a lifetime prevalence of nearly 15%, the world's second most disabling condition (behind heart disease). Depression has negative effects on physical health and medical outcomes by destroying the motivation necessary to recover and by adversely affecting vital immune and endocrine functions. Religion is widely prevalent and often turned to as a coping behavior in response to stressors related to physical illness, disability, and loss. A psychological therapy that takes advantage of patients' religious resources ought to improve depression more quickly than one that ignores them, and be more effective in reversing depression-induced physiological changes.

Duke University Medical Center, in partnership with University of London and Glendale Adventist Medical Center Department of Clinical Research's Quality Assurance & Monitoring Division propose a randomized clinical trial of conventional cognitive behavior therapy (CCBT) vs. religious cognitive behavior therapy (RCBT) for major depression in medical patients with chronic disabling illness. Therapists will deliver the treatment in real time over the Internet and/or by telephone. In Phase I (Rounsaville 1a) we will conduct an open trial of 30 patients to assess subject recruitment, refine RCBT and CCBT manuals and protocol, assess compliance with treatment, acceptability of treatment and delivery system (online vs. telephone), and allow therapists to gain experience in the delivery system and RCBT.

In Phase II (Rounsaville 1b) we will conduct a randomized proof of concept comparison of CCBT vs. RCBT that will demonstrate feasibility and confirm the expected clinically meaningful difference for a definitive R01 application. In Phase II, 70 religious patients ages 18-85 with an episode of major depression (MINI), scores of 10-40 on the Beck Depression Inventory (BDI), and at least one chronic disabling medical illness will be randomized to either CCBT or RCBT. 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 BDI score at baseline, 4, 8, 12, and 24-week follow-up. Christian, Jewish, Hindu, Buddhist, and Muslim versions of the RCBT manual will be developed, and CBT experts in each of these traditions will supervise therapists for these patients. Of particular importance, we will examine the effects of genetic variation at candidate genes (serotonin transporter, 5-HT1A receptor, and monoamine oxidase A promoter) on treatment response, and compare the effects of RCBT vs. CCBT on endocrine and immune measures in blood and urine.

The purpose of this study is to determine feasibility and effect sizes for a future, fully powered immune, endocrine, genetic, and treatment study. The significance of this research program is that it may help to uncover key physiological mechanisms that explain the religion-health relationship.

A.2. Rationale and Specific Aims

Depression is a major public health problem. 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. Whether or not religious CBT is more likely than secular treatments to successfully treat depression in depressed religious chronically ill medical patients is completely unknown. Our rationale, specific aims, and hypotheses for Phase I and for Phase II of this planning grant follow:

Phase I

Rationale: Prior to embarking on a large clinical trial, there is need to develop and refine religious cognitive behavior therapies, identify the best way of delivering them (via online and/or telephone), and verify that an appropriate number of eligible chronically ill depressed patients can be recruited and make it through the protocol. An open trial format will best accomplish the aims below.

Specific Aim #1. Develop RCBT treatment manuals, adapted to the particular cognitive distortions of chronically ill disabled religious patients, to guide a therapeutic intervention for depression in Christian, Jewish, Muslim, Buddhist, and 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 is the most accessible and acceptable way of treating depressed persons with chronic disabling physical illness.

Specific Aim #4. Give therapists experience with online and telephone methods of delivering CBT and with administering RCBT.

Phase II

Rationale: Religious beliefs and behaviors are commonly used to cope with chronic disabling medical problems, and in epidemiological studies, predict a faster remission of depressive disorder. CBT that utilizes the religious resources of patients in the treatment of depression should boost the effects of conventional CBT, especially in religious patients with situational stressors. This should also result in a greater reversal of the immune and endocrine changes association with depression. An RCT 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.[1]

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 (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.

A.3. Importance of Study

We acknowledge that the proposed feasibility study involves methodological challenges, which we have anticipated and discussed (Section D3). 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 for why religious patients with chronic disabling illness are particularly vulnerable to (or protected from) depression and for why a therapy that integrates religious resources into therapy is particularly effective in patients with strong religious beliefs. *The potential of this study is that it will help test several of the major mechanisms by which religion could influence physical health and longevity.*

[1] Although we do not expect to have adequate power for any of the hypotheses listed in Phase II, with a final N of only 60, identifying multiple pathways explaining the effect will particularly suffer from a lack of power. We should, however, at least be able to identify trends for confirmation in a future larger trial.

B. BACKGROUND AND SIGNIFICANCE

B.1. Depression is a Major Public Health Problem

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[1] and in 2020, is expected to be the world's second leading cause of disability, surpassed only by cardiovascular disease.[2] The lifetime prevalence of depression in the U.S. is 20% in women and 10% in men.[3]

B.2. Depression is Widespread in Patients with Chronic Disabling Medical Illness

While the point prevalence of major depression in the United States is 7%,[4] this figure increases to 10% to 45% in patients with medical illness depending on setting.[5,6,7,8] Not surprising, the use of antidepressants by primary care physicians has increased dramatically in recent years.[9] Treating with antidepressants, however, increases risk of side effects in medically frail patients and increases the risk of drug interactions with medications prescribed for other reasons.[10] Major depression is already a potent risk factor for disease morbidity, as medical patients with depression have double the mortality of non-depressed persons.[11,12] Furthermore, medications are expensive, even without considering the costs from managing side effects and drug interactions.

B.3. Psychotherapy is Beneficial for Depressed Medically Ill Patients

The kinds of depression seen in primary care are often situation-specific and due to changes in life that physical illness has brought on, including day-to-day problems with functioning at home and work. Thus, depressed patients seen in primary care settings are often benefit from psychotherapeutic approaches that focus on adjustments to real life circumstances. Not surprising, psychological approaches such as CBT have been particularly effective in treating depression in medical patients who need help coping with difficult circumstances, and especially, by addressing maladaptive beliefs and thoughts that initiate and maintain depression.[13,14,15,16]

B.4. Barriers Involve Referral, Compliance, Follow-up, and Attitudes

Although physical barriers to psychotherapy for medically ill disabled patients are formidable (see below), cultural factors also interfere with patient acceptance and compliance with conventional forms of therapy. There has been a long history of conflict between religion and mental health care, beginning with Freud's description of religion as "the universal obsessional neurosis."[17] There is open resistance to consideration of religious beliefs in mental health care, resistance that became clear in a recent discussion among British psychiatrists (see e-letters in response to two recent articles in The Psychiatrist).[18,19] Negative attitudes toward religion by mental health professionals are not limited to Great Britain. A systematic review of the religious content of DSM-III-R found that nearly one-quarter of all cases of mental illness included religious descriptions.[20] More recent publications by mental health professionals continue to reinforce the lack of concern for patients' religious beliefs,[21,22] and a recent national survey of U.S. psychiatrists found that 56% never, rarely, or only sometimes inquire about religious/spiritual issues in patients with depression or anxiety.[23]

Based on this generally neglectful (and at times disparaging) attitude of many mental health professionals toward religion, 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. Failure of clergy to refer, given that clergy represent a major first line treatment for depression in the community,[24] may prevent many patients from receiving adequate treatment (see below). Furthermore, if patients are members of a faith community and that community does not support (or counteracts) the gains made in psychotherapy, then those gains may not last.

Referral and Follow-up by Clergy is a Missed Opportunity to Increase Access to Psychotherapy

There is a community-based form of counseling that is nearly as prevalent as professional forms of therapy. Clergy serve as front-line mental health providers in communities across the U.S., providing nearly as many hours of counseling as does the entire membership of the American Psychological Association. Consider that clergy spend on average 15% of their time in counseling activities, providing over 140 million hours of mental health services each year, not including the activities of nearly 100,000 full-time nuns or chaplains.[25] Furthermore, they do not charge for their services, and there is no stigma associated with this type of counseling. Thus, depressed religious persons often receive their first treatment by clergy or other counselors within the faith community

However, given the long history of antagonism between religion and mental health professionals, referrals by clergy of religious patients for professional counseling (such as CBT) are infrequent, which may ultimately jeopardize a patient's recovery. Moreover, there is little information on the kind of follow-up that religious patients in professional psychotherapy receive within their religious communities after formal therapy has ended.

Religion is a Clinically Relevant Aspect of Mental Health

Religious involvement is important to many in the U.S.[26] According to a January 2009 Gallup Poll, 65% of Americans indicated that religion is an important part of their daily life, a figure which increases to over 75% in the southeastern U.S.[27] According to the Pew Foundation's 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 (especially those in ethnic minority groups).

Hundreds of qualitative and quantitative studies document high rates of religious coping behaviors in Americans with medical illness.[28,29] In some areas of the U.S., nearly 90% of medical inpatients use religion to cope, and of those who do, nearly half (45%) report that religion is *the most important factor* that keeps them going.[30] Furthermore, religious involvement has been associated with positive emotions such as optimism and purpose in life,[31] and consequently, religiosity also predicts a faster resolution of depressive symptoms in medical patients over time (increasing speed of remission by 50 to 70 percent).[32,33,34,35]

Religious beliefs and practices may also reduce depression by enhancing gratefulness, generosity and altruism. While research on the human virtues is still in the early stages, there is growing evidence that religious involvement is associated with higher levels of gratitude, altruism, and attention to the needs of others.[36,37,38] These characteristics, then, may enhance well-being and counter depressive cognitions and feelings.[39]

Religious people, however, are not exempt from depression, especially when severe or chronic medical illness strikes. In a study at Duke Hospital, 64% of patients on the medical services over age 50 with major depression (diagnosed using the Structured Clinical Interview for Depression [SCID]) indicated that they were both spiritual and religious and 76% prayed at least once daily.[40] Many depressed patients who are religious, however, may shy away from secular psychotherapy because they perceive it as unsympathetic to their religious beliefs (see above).[41] 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.

Consideration of Religious Beliefs in Therapy May Result in Better Outcomes
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 to increase the speed of remission in depressed religious patients above and beyond that achieved by conventional CBT.[42,43] 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.[44,45,46,47,48] Furthermore, recent evidence suggests that 77% to 83% of adults aged 55 or older with depression and co-morbid chronic medical illness prefer to include religion in their psychotherapy.[49]

The benefits of addressing religious beliefs in therapy with religious patients may stem partly from redirecting attention from a focus on losses and preoccupation with self to cognitions that focus on gratitude, altruism, and generosity. Positive cognitions such as gratitude and generosity have been shown to predict lower rates of depressive symptoms.[50,51,52,53] Positive cognitions related to gratitude and generosity, together with healthy religious beliefs, may also promote positive emotions associated with having purpose and meaning in life and having a hopeful and optimistic attitude toward circumstances. This may, in turn, serve to counter the negative cognitions and emotions of depression. Dozens of studies have reported a link between positive emotions such as optimism and purpose in life, religious involvement, and fewer depressive symptoms.[54] Finally, having a common worldview and explanatory model that gives meaning and purpose to negative life events may strengthen the therapeutic alliance between patient and therapist, which may contribute to treatment efficacy.[55] As an aspect of culturally competent therapy, this may be particularly true for minority populations who often suffer from disparities in psychiatric care and tend to be quite religious.

B.5. Technology Can Overcome Physical Barriers to Accessing Psychotherapy
Medical patients with mobility problems or those who are home bound may have considerable difficulty obtaining access to psychotherapy (i.e., traveling to therapists' offices, sitting in waiting rooms, etc.). Online or telephone approaches to delivering CBT have been shown to be effective and acceptable to medically ill patients with depression.[56, 57]

Online Communications
Online communications are now widespread in the United States and around the world. Of 6.8 billion people, 25% (1.7 billion) use the Internet.[58] Of the 341 million people in North America, nearly 75% (252 million) use the Internet. In 2005, close to 75 million Americans used e-mail and search engines on an average day (29% over age 50),[59,60] and that number has increased considerably since then, not to mention the millions who now have a MySpace or Facebook account (74% of all Americans ages 18 to 34, and 25% of those ages 55 or older) or the estimated 15 million who use Twitter.[61] One of the fastest growing groups of Internet users are persons over age 55, 77% of whom use the Internet to search for healthcare information.[62]

Online CBT
Individual cognitive-behavior therapy (CBT) can be offered online by a therapist using instant messaging, during which client and therapist communicate in real time with typewritten responses. Possible benefits from this approach include flexibility and optimal use of patient and therapist time; reaching client groups for whom travel to treatment centers is difficult for reasons of geography or disability; and accessing foreign language therapists. Furthermore, this approach is acceptable to depressed patients and therapy without face-to-face contact may encourage greater disclosure.[63] There is also evidence that writing about traumatic events by itself can lead to improvements in mental health.[64,65]

We have recently published[66] 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. Those benefits were maintained over 8 months and were present in those with moderately severe symptoms of depression. This convenient form of delivery means that we will now be able to test different forms of CBT quite readily across a range of communities. It also means that a relatively small number of therapists can cover a wide geographical area and be available to patients at a range of times.

Writing about Traumatic Experiences from a Religious View Improves Outcomes
Besides being sensitive to and utilizing the religious beliefs of patients in therapy, the way that patients express their feelings may also impact treatment effectiveness. At least two separate studies have reported that *writing* about distressing circumstances from a religious perspective helps to resolve symptoms more quickly than writing about events from a secular perspective.[67,68] For example, Chen examined 177 college students randomly assigned to either a conventional trauma writing condition or to a religious trauma writing condition.[69] Participants in the conventional writing condition were

instructed to write about a traumatic experience, but without any specific directions on what approach to take. Participants in the religious writing condition were instructed to write about the trauma from a religious/spiritual perspective. Conventional writing was more effective in reducing PTSD symptoms only for participants reporting low trauma severity, whereas religious writing was effective regardless of trauma severity. Thus, as patients discuss their medical stresses and losses from a religious perspective by typing them during online therapy sessions, this may add to the effectiveness of this treatment modality.

Telephone CBT
However, an issue with online CBT -- particularly when delivered alone without therapist guidance -- has been dropouts during treatment.[70] Even with *therapist-delivered* online CBT, this remains a problem (28% in our recent Lancet study). To minimize dropouts and boost effects, it has been recommended that a telephone component be added[71] since telephone therapy is known to increase compliance.[72] Furthermore, structured CBT delivered by telephone has been shown both clinically effective and cost effective in treating medical patients with depression.[73] Our research team has direct experience using the above technologies.

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

Physiological Effects (or Correlates) of Depression
Depression has been associated with endocrine and immune changes that increase risk of medical illness and adversely affect medical outcomes. Treatment of depression, in turn, has been shown to normalize these physiological changes.

Depression is Associated with Changes in Immune/Endocrine Functions. There is evidence that the alterations in immune and endocrine function associated with depression increase medical morbidity by increasing risk of infection,[74] inflammatory disorders,[75] and possibly malignancy.[76,77,78] The etiological relationship, however, is a complex one that is likely bi-directional in nature.[79] Furthermore, depression is known to stimulate some components of the immune system and suppress others. Likewise certain immune elements (such as pro-inflammatory cytokines) can lead to sickness behaviors that resemble depression, which has led to a consideration of on how altered immune and endocrine functions influence the pathophysiology of depression, especially when depression develops in a setting of chronic stress.[80]

Regardless of direction of effect, major depression has been associated with a host of immune,[81] endocrine,[82] and pro-inflammatory functions[83] that could affect patients' ability to respond to medical treatments. 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), [84,85,86] and lower anti-inflammatory Th2 cytokines (IL-4, IL-10).[87] Depressed patients also have reduced natural killer [NK] cell cytotoxicity[88,89,90,91,92,93], and diminished lymphocyte responses

to phytohemagglutinin and concanavalin A.[94,95] Importantly, impaired immune functions associated with depression have been shown to normalize in response to treatment: electroconvulsive therapy (serum TNFα),[96] antidepressant drug therapy (serum TNFα and CRP),[97] and psychological interventions (due in part to a return of the pro-/anti-inflammatory cytokine balance).[98]

With regard to the effects of psychotherapy (or other interventions that reduce negative or increase positive emotions), at least six randomized clinical trials have reported improvement in immune and/or endocrine functions. Antoni and colleagues conducted a 10-week CBT stress-management program in human immunodeficiency virus (HIV)-infected men.[99] The intervention resulted in a significant increase (40%) in naïve CD4+ T cells in blood over a 12-month follow-up among those in the CBT group (n=16) compared to controls (n=9). This effect was mediated by a reduction in depressive symptoms and a decrease in urinary cortisol levels. Similarly, another RCT examined the effects of 8 weeks of CBT on NK cell cytotoxicity (by ^{51}Cr-release assay), IL-6, and CRP in 15 depressed women following coronary artery bypass surgery (87% with major depression).[100] Subjects receiving CBT (n=7) experienced a 2% increase in NK cell cytotoxicity (vs. 4% decrease for controls) (effect size=0.67), an 11 pg/mL decline in IL-6 (vs. 3 pg/mL decline for controls) (effect size=0.61), and a 12 pg/ml decline in CRP (vs. 6 pg/mL decline for controls) (effect size=0.85).

A more recent study by Antoni and colleagues examined the effects of a 10-week cognitive behavioral stress management program on endocrine and immune functions in 128 women with breast cancer, finding that the intervention significantly lowered serum cortisol, increased Th_1 pro-inflammatory cytokines (IL-2 and INF-γ), and increased IL-2:IL-4 ratio;[101] note, however, that subjects were not all depressed and all were women, which may explain the increase in proinflammatory Th1 cytokines due to gender effects.[102] In a fourth study, Van Middendorp and colleagues conducted an emotional disclosure intervention (4 weekly sessions) in 68 non-depressed patients with rheumatoid arthritis, finding a reduction in urinary cortisol, a reduction of serum INF-γ, and trend toward reduction in IL-6 (p=0.07), although no effect on IL-10 or urinary norepinephrine was reported.[103] Also, a recent intervention by Lee Berk and colleagues to increase positive emotions (via mirthful laughter) in 20 high-risk diabetic patients with hypertension and hyperlipidemia found that the intervention lowered serum epinephrine, norepinephrine, INF-γ, CRP, TNF-α, and IL-6.[104] Finally, and quite interestingly, Roberts and colleagues found that the hypocortisolism in 41 subjects with chronic fatigue syndrome (a depression-like syndrome) was improved following 15 sessions with CBT;[105] thus, whether cortisol is pathologically high or low, psychological therapies may help normalize levels.

In summary, psychotherapeutic treatments that increase positive emotions (particularly CBT) appear to be effective in increasing naïve CD4+ cells, increasing NK cell cytotoxicity, reducing IL-6, reducing TNF-α, reducing CRP, reducing INF-γ (sometimes increasing in non-depressed female patients), decreasing catecholamines, and normalizing (decreasing or increasing) cortisol in samples ranging from 15 to 128 subjects. Given the role religion plays as a coping behavior, including religious resources

in therapy may help to speed the resolution of depression, and thus, help to normalize endocrine and immune dysfunctions (more so than conventional treatments).[106]

Religious Beliefs and Behaviors May Improve Immune and Endocrine Functions Impacted by Depression

Religious involvement has been associated with better mental and physical health, and greater longevity.[107,108] The mechanisms that explain this association are unclear, but likely involve behavioral and psychosocial factors operating at least partly through immune/endocrine pathways related to stress.[109,110,111]

Religion and Immune/Endocrine Functions. There is evidence that religious involvement is associated with better immune and endocrine functions, although no studies have yet examined the effects of a religious psychotherapy on these functions.

Sephton and colleagues examined the relationship between religious involvement and immune function in 112 women with metastatic breast cancer.[112] Religious expression was positively related to the total number of circulating T cells ($r=0.24$, $p=0.01$) and helper T cells ($r=0.23$, $p=0.01$); social network size, disease, and medical treatment variables could not explain these relationships and had little effect on reducing the strength of the correlations. Investigators also found positive associations between religious expression and cytotoxic T cells ($r=0.18$, $p<0.05$) and a trend for greater NK cell numbers ($r=0.14$, $p=0.07$).

Ironson and colleagues examined the effects of changes in spirituality/ religiousness (S/R) following the diagnosis of HIV on CD4 cell levels and viral load during 4 years of follow-up.[113] Hierarchical linear modeling was used to examine the effects of changes in S/R over time with the outcome being slopes of change in CD4 cells and viral load during follow-up. Patients who reported an increase in S/R after diagnosis experienced significantly less decrease in CD4 counts and less increase in viral load during the 4-year follow-up. Results were independent of church attendance and initial disease status, medication use at every time point, age, gender, race, education, health behaviors, depression, hopelessness, optimism coping, and social support. In fact, among all other predictors of CD4 cell count and viral load, change in S/R was the most powerful predictor. A number of other studies have found similar connections between religious involvement and other immune functions (T cells, in particular), [114,115,116] pro-inflammatory indicators (IL-6),[117,118,119] and endocrine measures (specifically cortisol).[120,121,122,123,124]

There have been far fewer intervention studies. However, one study in non-depressed HIV+ patients reported that a stress management intervention designed to increase spiritual growth led to an increase in lymphocyte proliferation and a 3-fold increase of INF-γ.[125] Likewise, Eastern spiritual meditation has been shown to increase antibody response to influenza vaccine,[126] alter the ratio of pro-/anti-inflammatory cytokines,[127,128] increase NK cell activity,[129] reduce cortisol,[130,131,132,133,134,135] and decrease catecholamine[136,137] levels (and in one study, there was a trend toward superiority over conventional CBT[138]).

Whether or not religious psychotherapy might be more likely than secular treatments to optimize the balance of immune and endocrine measures in depressed religious medical patients is completely unknown. This proposal is designed to address this gap in the literature. Such a possibility is suggested by a study showing that patients receiving conventional CBT responded more quickly to the therapy if they indicated that religion was important to them.[139] CBT adapted to the religious beliefs of patients, then, might be even more effective in relieving symptoms and consequently impacting immune and endocrine functions.

B.7. Understanding the Genetic Basis for Religion's Association with Depression

While religiousness is often inversely related to depression and associated with faster recovery from depression, a number of studies also suggest that depression may be more common in religious persons, [140,141,142,143] perhaps due to greater emotional sensitivity (referred to as "neurosis" by Freud[144]). Could there be underlying biological factors that explain the link between religion and depression? Common genetic predispositions could be one explanation.

There is evidence that similar polymorphic genes may influence both the likelihood of depression and the development of R/S. Using a candidate gene approach, we hope to identify genetic polymorphisms/mutations responsible for the relationship between religion and depression using rigorous phenotypic characterization and controls for confounding. The ultimate success of this study is related to our choice of the candidate gene SNPs (single nucleotide polymorphisms). At each SNP site, we will compare the frequencies (both individually and in combination) in deeply religious and less religious subjects, and examine their impact on treatment response. This research will be done in collaboration with internationally renowned psychiatric geneticists from the University of Granada. Identifying common genes, if they exist, will help us to better understand the underlying biological mechanism by which R/S is related to 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 or decreasing the religious person's risk for developing depression.

Among individuals with the 5-HTTLPR genotype SS or SL at the serotonin transporter gene (5-HTT), number of stressful life events predicts the development of major depression. [145] This effect is absent in those with the LL genotype. While this association has recently been challenged by a meta-analysis,[146] a critique of that critique has pointed out flaws in their review.[147] The latest report concluded that further work was needed to understand how 5-HTT allelic variations affect response to stressors. Few studies have examined the relationship of 5-HTTLPR polymorphisms and depression in primary care medical settings, where health-related stressors abound, and no studies have examined the influence of gene-environment interactions on response to psychotherapy.

Our group (King, Cervilla, Gutiérrez) has begun to investigate this relationship in medical outpatients, finding that depressive episodes were significantly (50% to 79%) more frequent among those with the SS genotype, an association that increased in strength as depression severity increased.[148] Furthermore, the SS genotype interacted with number of stressful life events (SLE) in that study, such that those with the SS genotype required only minimal exposure to SLE to increase their risk for depression, compared to SL or LL genotypes that required much higher levels of stress to increase risk.[149] We have also identified other genetic variants (such as high activity uMAOA alleles at the promoter region of the MAOA gene [121] or C allele at the 5HT1A gene[121bis])[150] associated with a higher risk of depression in primary care patients.[151] Our group, however, is not the only research team examining this topic in medical patients.. Otte and colleagues recently reported that those who carried the S allele of the 5-HTTLPR polymorphism were more vulnerable to depression, perceived stress, and high norepinephrine secretion in 557 outpatients with coronary artery disease.[152]

The S allele of the 5-HTTLPR polymorphism at the serotonin transporter gene is thought to cause greater emotional sensitivity to life events or environmental stressors because this form of the gene produces less of the serotonin transporter protein. Furthermore, response to treatment may also be affected (decreased) by the presence of the 5-HTTLPR low functioning alleles.[153,154] Finally, cognitive defects such as greater negative schematic processing following negative life events, have been documented in those with the S allele of the 5-HTTLPR.[155] If life events such as medical stressors increase the risk of depression in subjects with the SS or SL genotype, then these individuals might be more sensitive to the effects of psychotherapy (an environmental influence), especially CBT.

Such relationships, however, are not simple, but rather heavily moderated by both race and gender. While 50% of Caucasians have the S-allele, only 30% of African-Americans do,[156] and effects may be the opposite in African-Americans (L-allele confers increased risk, rather than S-allele) compared to whites.[157] While prevalence of S-allele may not be different between men and women, sensitivity to stress may be greater for women with the S-allele than for men.[158] The clinical trial proposed in this study may add data to further clarify these findings.

Religion/Spirituality and Genetic Polymorphisms

Preliminary evidence suggests a link between spirituality 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[159] and with other factors related to high spirituality.[160] 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,[161] a finding which is consistent with a functional magnetic resonance imaging study reporting lower brain serotonin receptor binding in those scoring high on spiritual acceptance.[162]

Why might religiousness/spirituality be associated with genes that increase sensitivity to negative life events or risk of depression? Depression may serve as an evolutionary force that removes "less fit" persons from the population, increasing their risk of suicide and affecting vulnerability to physical disease (for reasons described above). Religious involvement, however, may act counter to this evolutionary force by providing beliefs that facilitate coping with negative life events and a faith community that supports and cares for those who are vulnerable, enabling depressed religious persons to survive and pass on their genes to the next generation. Thus, genes associated with sensitivity to negative life events (and depression) and with receptivity to religious/ spiritual experiences may be preserved within the population. Although such ideas are highly speculative, they help to explain why such a genetic link might exist.

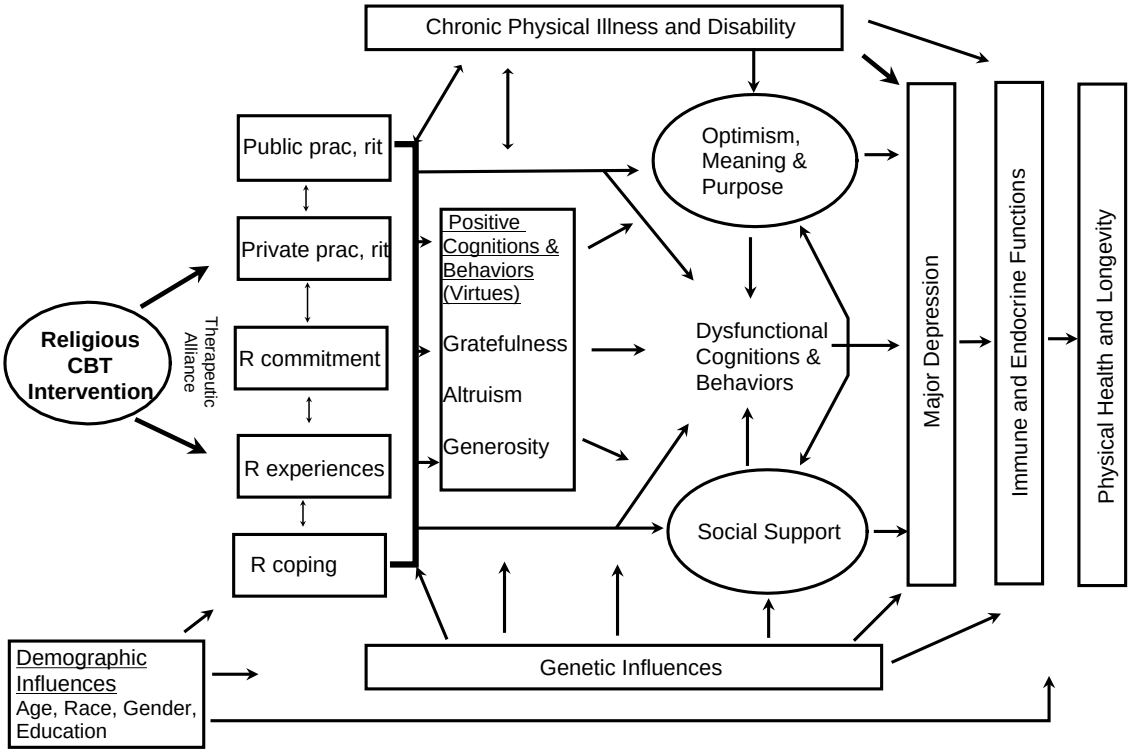
To our knowledge, no study has yet examined the impact of 5-HTTLPR, MAOA-uVNTR, or rs6295 polymorphisms on the treatment of major depression with CBT (either secular or religious). For that matter, no study has yet determined the prevalence of genetic polymorphisms in depressed religious persons. If religious persons are especially likely to have genetic polymorphisms that increase their sensitivity to life events (disabling chronic illness, for instance) and risk for major depression, then religious CBT may be particularly effective in this group, more so than conventional CBT that does not utilize these beliefs in therapy (beliefs central for religious patients' coping). We are not suggesting that religious people are more genetically flawed, but only that religious persons may have a genetic makeup that makes them more emotionally sensitive to their environments, which may have distinct evolutionary advantages particularly in terms of social relationships, yet at the same time make them more vulnerable to situational depression. Of course, there may be many factors other than genetic influences that cause people to become religious, from early environmental influences (family and school) to life experiences during adulthood (including social and cultural influences), so these must be considered when examining gene-environment interactions.

B.8. Summary of Background and Significance

If a religious intervention (i.e., religious CBT) reduces depression and thereby improves immune and endocrine functions, then this would verify a central mechanism by which religion could affect physical morbidity and mortality. A randomized clinical trial is the only way to either verify or disprove such a causal mechanism. Furthermore, identifying a genetic link between religion and depression, one that may influence response to treatment, could help to explain why religious individuals are more or less depressed and identify those more likely to respond to religious interventions. Finally, the results from this research program will be relevant not only to therapists who explicitly practice pastoral counseling, but also to many secular therapists who wish to use their patients' religious resources in therapy.

The possible etiologic pathways that describe how a religious CBT intervention might act through positive cognitions and behaviors (based on human virtues), positive emotions, and social factors to reduce depression and ultimately influence physiological functions affecting health and longevity, all influenced by predisposing genetic factors, is summarized in the Figure (next page).

Theoretical Model of Causal Pathways



C. PRELIMINARY STUDIES

Our research team is well equipped to successfully conduct the proposed feasibility studies. We have decades of experience doing research on religion and depression in those with chronic illness, experience running clinical trials, and expertise in both neuroimmunology and psychiatric genetics.

C.1. Investigators and Consultants

A large research team has been assembled, larger than might be expected for a feasibility study or a small randomized clinical trial. However, our goal is to establish a smoothly working team that will be capable of executing the immediate next step after establishing feasibility and determining effect sizes that would involve a much larger RCT that will require a team of this size and expertise.

Harold G. Koenig, MD, MHSc, Principal Investigator and Duke site PI, is Professor of Psychiatry and Behavioral Sciences and Associate Professor of Medicine at Duke University Medical Center (DUMC), and Director, Duke's Center for Spirituality, Theology and Health.

Michael B. King, MD, PhD, Project Co-Leader, is head of Research Department of Mental Health Sciences and Professor of Primary Care Psychiatry, University College London Medical School; Co-Director of the UK CRC registered Primary Care & Mental Health Clinical Trials Unit; and Co-Director of the UCL Research Design Service. He is a clinical trials specialist in psychotherapy studies involving depression in primary care medical patients. Dr. King also has special expertise in religion and health, arguably Europe's foremost researcher on this topic.

Harvey Jay Cohen, MD, Co-Investigator and Duke site consultant, is recent past chairman of the Department of Medicine at DUMC, and is head and director of the Center for Aging and Human Development, in which the Center for Spirituality, Theology and Health resides administratively.

Clive Robins, PhD, Co-Investigator, is Professor of Psychology and Medical Psychology at DUMC, and has extensive experience designing and running psychotherapy clinical trials involving CBT. He is in charge of initial training of all therapists and supervision of CCBT therapists during the trials in this application.

Michelle Pearce, PhD, Co-Investigator, is Assistant Professor of Psychology and Medical Psychology at DUMC, trained at Yale University, broad experience using CCBT, extensive experience using religion as part of CBT, seasoned researcher familiar with clinical trials, and has published on religion and mental health for nearly a decade. Dr. Pearce is in charge of the RCBT manual development and the training and supervision of RCBT therapists during the trial.

Rebecca Propst, PhD, consultant for developing RCBT intervention, is a psychologist in private practice, former faculty at Ohio University and Lewis and Clark College.

Jack Yu, MD, Co-Investigator, is the Associate Director of a Family Medicine Residency Program and an Associate Professor at three California medical schools, and is the site PI for Glendale Adventist Medical Center, Glendale, CA.

Bruce Nelson, M.A., Co-Investigator, is the Administrator for GAMC Department of Clinical Research Quality Assurance & Monitoring Division.

Larry Ereshefsky, PharmD, consultant, is Chief Scientific Officer for California Clinical Trials (part of PAREXEL, one of the world's largest commercial clinical trials organizations), and is an expert in designing and monitoring clinical trials. He will serve as a primary consultant to GAMC Department of Clinical Research Quality Assurance & Monitoring Division, and co-lead the Quality Assurance committee for the proposed studies.
Noha Daher, DrPH, consultant, principal statistician, holds a BS and MSPH in biostatistics, and a DrPH in epidemiology from the Loma Linda School of Public Health. She is Associate Professor, Department of Research and Statistics, School of Allied Health Professions at Loma Linda University.
Lee S. Berk, DrPH, MPH, **CLS,** consultant (neuroimmunology), is Director of Loma Linda University's Neuroimmunology Research Laboratory, Associate Professor of Allied Health Professions, and Associate Research Professor of Pathology and Human Anatomy, Loma Linda University School of Medicine, Loma Linda, CA.
Denise Bellinger, PhD, consultant (neuroimmunology), is Associate Professor at Loma Linda School of Medicine in the Center for Neuroimmunology, and works with Dr. Berk in his Neuroimmunology Research Laboratory.
Jorge Cervilla, MD, PhD, consultant (psychiatric genetics), is Professor, Department of Psychiatry, University of Granada, Spain, and director / principal investigator of the PSYBAM research group within the university's *Center of Biomedical Research*.
Blanca Gutiérrez, PhD, consultant (psychiatric genetics)**,** is Associate Professor, Department of Psychiatry, University of Granada, Spain, and works with Dr. Cervilla in the *Center of Biomedical Research*.

C.2. Preliminary Studies

C.2.a. ***Depression and Religion in the Medically Ill.*** Our research group (Koenig, King) has been studying the epidemiology of depression in the medically ill for over two decades.[163] This research includes some of the first reports on the prevalence of depression and depression treatments in hospitalized medically ill patients. Most recently, we identified 1,000 hospitalized patients with CHF or COPD and depressive disorders, following up 85% of this sample tracking the course of depression and disability after hospital discharge.[164,165] We have also examined the effects of religious involvement and religious coping on prevalence and course of depression in medical patients with chronic illness.[166,167,168] *These studies indicate that depressive disorders are widely prevalent among medical patients with chronic illness, and that religious coping behaviors predict lower rates of depression and faster recovery from depression.*

C.2.b. ***Conventional and Religious Cognitive and Behavioral Treatment Studies***. Our group (Robins, Propst, Pearce, King) also has a strong background in designing and successfully managing clinical trials involving conventional CBT treatments, as well as specifically religious CBT.

In a randomized clinical trial of Dialectical Behavior Therapy (DBT), Robins and colleagues randomized 20 women veterans with borderline personality disorder to DBT or treatment as usual for six months.[169] Subjects receiving DBT experienced significant

decreases in suicidal ideation, hopelessness, depression, and anger, as well as near-significant reductions in para-suicidal acts, dissociation, and number of hospitalizations. In another DBT treatment study of persons with severe mental illness in vocational rehabilitation, Robins and colleagues found that weekly treatment over six months significantly improved depression, hopelessness, and anger levels, which were maintained over a 6-month follow-up period.[170] In a third clinical trial examining the effects of DBT in depressed older adults, Robins and colleagues randomized 34 depressed patients to either 28 weeks of antidepressant medication plus clinical management or to medication plus DBT and telephone coaching sessions; only those receiving DBT and telephone coaching sessions experienced a significant reduction in mean self-rated depression scores, and at 6-month follow-up, 75% of DBT patients were in remission compared to only 31% of medication only patients.[171] Finally, in a treatment study that examined the effects of a 12-week CBT intervention on depressive symptoms in 65 patients with Type 1 and Type 2 diabetes mellitus, the CBT intervention significantly decreased depressive symptoms, which was maintained over 12 months.[172] In all of these four trials, Robins designed or helped design the trials, trained the therapists, provided clinical supervision of therapists, and/or oversaw data analyses.

A number of studies by our group have examined the effects of CBT interventions in depressed primary care patients. Michael King's clinical trials group at the University College of London has managed these studies. The first involved a RCT involving twelve 50-min sessions over 12 weeks of non-directive psychotherapy vs. routine care by their physician in 136 primary care patients with depression. Non-directive psychotherapy was shown to be no more effective than routine general practice care, although patients preferred the psychotherapy to care from their GP (general practitioner).[173] Next, King and colleagues randomized 464 depressed primary care patients to usual GP care, non-directive counseling, or CBT provided by therapists. In the non-directed counseling and CBT groups, subjects received 12 sessions over 4 months, and were assessed at treatment completion and 12 months.[174] Patients randomized to non-directive counseling or CBT improved more on the BDI than those receiving usual care from GP (12.9 and 14.3 vs. 18.3); by 12 months, there was no difference on BDI between any of the three arms.

In a third RCT, King and colleagues compared the effectiveness of six one-hour sessions of either counseling or CBT on outcomes in 160 primary care patients with chronic fatigue syndrome; no difference on fatigue, depression, or other measures was found between treatments at 3 and 6 month follow-ups.[175] In a fourth clinical trial, King and colleagues randomized 84 general practitioners (GPs) to either a group receiving brief CBT training (four half-days) or a control group (no training), and examined outcomes in 272 depressed patients being treated by these GPs.[176] Results post-intervention and at 3 and 6-month follow-ups indicated that there was no major difference between physician knowledge of depression or depression treatments between intervention and control groups, and there was no difference on patients' BDI scores either. In the fifth RCT, King and colleagues randomized 204 older depressed primary care patients to either treatment as usual (TAU), a talking control (TAU+TC), or CBT (TAU+TC) delivered in twelve 50-minute sessions and followed up at 4 months and 10 months using the BDI-

II.[177] In the intent-to-treat analysis, subjects receiving CBT improved significantly more than those receiving TAU or TAU+TC (3.1 and 3.7 point differences on the BDI, respectively).

With regard to *religious CBT* and related spiritual interventions, Propst compared the effects of CBT plus religious imagery vs. CBT and nonreligious imagery in 44 depressed religious subjects who received twice weekly 1-hour sessions for 4 weeks.[178] Outcomes were assessed immediately following the treatment and at 6-week follow-up. Subjects receiving the religious imagery had significantly greater response on the BDI (14% with BDI>9) compared to those receiving nonreligious CBT (60%). Next, Propst and colleagues conducted a larger RCT of religious CBT vs. conventional CBT in 59 religious patients with depressive disorder by RDC criteria.[179] Subjects were randomized to RCBT (n=19), CCBT (n=20), or two control groups (n=21) (pastoral counseling or a wait-list control group (WLC)). A total of 18-20 one-hour sessions were delivered over 12 weeks, and outcomes assessed at completion of treatment, three months, and at two-year follow-up. Results indicated that only subjects receiving the RCBT reported significantly lower post-treatment BDI scores than did the WLC group ($p<0.001$), whereas the CCBT showed only a non-significant trend in that direction; likewise, only RCBT showed a clinically meaningful change on BDI score compared to WLC group (68% vs. 27%).

Finally, **Pearce and colleagues** designed and conducted a spirituality-oriented group intervention for HIV-positive adults. In this 8-session intervention, based on the cognitive theory of stress and coping and the framework of spiritual coping, the focus was on stressors unique to HIV disease. Changes in spiritual coping and mental health were evaluated using a within group pretest-posttest design. Results revealed that, at post-intervention, participants reported more use of positive spiritual coping, lower use of negative spiritual coping, and lower depression.[180]

C.2.c. ***Online CBT Treatment Studies***. King and colleagues randomized 297 depressed patients with BDI scores of 14 or higher to either TAU or TAU + online CBT, with outcomes assessed at 4 and 8 months (n=149 for CBT, n=148 for TAU). Ten online sessions of 50-minute of CBT with a therapist in real time were administered over 16 weeks.[181] Therapists worked for the organization PsychologyOnline, were CBT trained, and had experience providing psychotherapy in this setting. A total of 113 participants in the intervention group (76%) and 97 in the control group (66%) completed 4-month follow-up assessments on the BDI. Of patients receiving the online CBT, 38% recovered (BDI < 10) compared to 24% in the control group (OR 2.39, 95% CI 1.2—4.67, $p=0.01$). At the 8-month follow-up, recovery rates were 42% in the intervention group vs. 26% in the control group ($p=0.02$).

C.2.d. ***Studies of Psychological Effects on Immune/Endocrine Functions***

Drs. Berk and Bellinger have strong backgrounds in psychoneuroimmunology. Dr. Berk's research examines positive emotions and their effects on endocrine and immune

functions.[182,183,184,185,186] He is a world renowned for his studies of the effects of mirthful/laughter on immune and endocrine functions, working for years with Norman Cousins. He also studies immune modulation that occurs with exercise. Additionally, Dr. Berk has conducted research on music, spirituality and anticipatory perception and their effects on neuroendocrine and immune modulation. Dr. Berk is principal investigator of an ongoing study looking at the effects of religious/spiritual "rest" on the sympathetic nervous system, limbic-HPA axis, and immune functions.

Dr. Bellinger and her colleagues (including David and Suzanne Felten) helped to establish in the 1990s that lymph nodes had input from sympathetic nerves, providing a pathway by which emotions could impact immunity.[187,188] The team demonstrated that cells of the immune system in primary and secondary lymphoid organs receive a direct supply of nerves, particularly from the sympathetic nervous system but also from small viscero-sensory fibers. These connections provide an anatomical basis for neural-immune interactions. Dr. Bellinger's current research involves psychosocial-neural-immune interactions that affect health and disease, and in particular, the physiological mechanisms through which acute and chronic stressors modulate immune functions.[189,190] Dr. Bellinger is also co-investigator on an NIH grant to investigate the relationships between religious experiences and biochemical and physiological indicators of stress and immune system function in older adults.[191]

C.2.e. *Studies on Psychiatric Genetics*

Studies led by Cervilla and Gutierrez, in cooperative with Michael King's clinical trials unit, have examined the role of genetic polymorphisms on the risk of depression in primary care patients. In the PREDICT-Gene Study, Cervilla and colleagues found that the SS genotype at the 5-HTTLPR serotonin transporter polymorphism increased the risk of depression, a relationship that increased in severity depending on the severity of depression in 737 consecutive primary care patients.[192] These investigators also examined how a combination of individual, environmental, and genetic risk factors (5-HTTLPR polymorphism at SLC6A4) could be used to predict depression risk in medical patients, finding that both the SS genotype and exposure to increasing number of traumatic life events were significantly associated with depression.[193,194,195] Also as part of the PREDICT-Gene Study, Gutierrez and colleagues explored the association between depression and high activity uMAOA alleles in a cohort of 1,228 primary care patients. Depression was categorized into ICD-10 Depressive Episode, ICD-10 Severe Depressive Episode, and DSM-IV Major Depression. In both sexes, independent of age, high-activity uMAOA alleles nearly doubled the likelihood of all three depressive types.[196]

C.3. Institutional Resources

C.3.a. Center for Spirituality, Theology and Health (CSTH). The Center has been existence since 1998 and is part of the Duke's Center for Aging and Human Development, one of the first multi-disciplinary research centers in the world focusing on biomedical, psychological, and social factors affecting health in later life (directed by Harvey Jay Cohen). CSTH is an interdisciplinary center directed by Dr. Koenig and an

Executive Team consisting of Harvey Jay Cohen, M.D. (medicine, chair), Dan G. Blazer, MD, PhD (psychiatry), Linda K. George, PhD (sociology), and Allen Verhey, PhD (theology). This research group has published dozens of original data-based studies on religion/spirituality, depression, immune biomarkers, hypertension, mortality, and health services use in older adults and in medical patients with chronic illness. The department of medicine's Site Based Review (which is helping to monitor the current study) is in the Center for Aging and directed by Dr. Ken Lyles, a long-time Center for Aging faculty member and mentor of Dr. Koenig. Also immediately available to Dr. Koenig and CSTH is the Aging Center's biostatistics laboratory with a team of biostatisticians to assist as needed.

C.3.c. Glendale Adventist Medical Center (GAMC). This is a large urban community hospital operated by Adventist Health with 510 beds. This hospital serves a rich diversity of communities in Los Angeles County. GAMC admits over 17,000 patients yearly, sees more than 34,000 emergency room visits, and provides over 70,000 outpatient visits yearly. GAMC operates seven residency programs. GAMC provides a full range of inpatient, outpatient, emergency and diagnostic services and are dedicated to improving the health status and quality of life of its community residents. They have a Department of Clinical Research that has two divisions, a Recruitment Division and a Quality Assurance & Monitoring Division, both of which focus on clinical trials in medical populations.

C.3.d. University College of London Priment Clinical Trials Unit. Embedded in University College London, this clinical trials unit (www.priment.mrc.ac.uk) specializes in trials of psychiatric treatments and has particular expertise on conducting RCTs in primary care and community settings. Examples of current national trials include effectiveness of treatment of chronic major depression, supplemental medication in patients with schizophrenia unresponsive to clozapine, and effectiveness of CBT for patients suffering with depression in the last months of life. The Unit is directed by Michael B. King, MD, PhD, and Irwin Nazareth MD and contains a team of trialists, doctors, nurses, epidemiologists, statisticians and health economists.

C.3.e. Quality Assurance & Monitoring Division (QAMD), the clinical trials *Coordinating Center* for this study, is a division within Glendale Adventist Medical Center's Department of Clinical Research that works with Los Angeles County physicians and other community healthcare providers engaged in clinical trials. QAMD is a division within GAMC's Department of Clinical Research that is completely separate from GAMC's Recruitment Division and has different staff. QAMD's mission is to increase patient access to innovative therapies conducted through clinical trials in community settings. The purpose of QAMD is to bring the latest medical science technologies and best practices to patient care, ensuring a comprehensive, innovative, and community-based healthcare research program. QAMD's goals are to increase collaboration and communication among clinicians interested in conducting healthcare research, and work with them to execute innovative pharmaceutical, biotech and other

healthcare-related research protocols. QAMD interacts with researchers to set up clinical trials, providing oversight and administrative management of RCT protocols and other study-related activity. The QAMD is affiliated with Loma Linda University (LLU) and the Adventist Health System.

C.3.g. Johns Hopkins Center for Inherited Disease Research (CIDR)
CIDR is a centralized facility that provides genotyping and statistical genetics services for investigators seeking to identify genes that contribute to human disease (see website: http://www.cidr.jhmi.edu/). The facility is supported through a $115 million federal contract to The Johns Hopkins University (JHU) with Dr. David Valle of the JHU Institute of Genetic Medicine as Principal Investigator. Dr. Lawrence Brody of the National Human Genome Research Institute (NHGRI) serves as the government Scientific Officer. CIDR was established in 1996 and is jointly supported by fourteen Institutes at the National Institutes of Health (including the NIMH). Blood samples collected in this study will be sent to CIDR for DNA extraction and genotyping.

C.3.h. Neuroimmunology Research Laboratory
The Neuroimmunology Research Laboratory is part of the Department of Pathology and Human Anatomy at Loma Linda University. The facility performs basic science and clinical research that investigates neural-immune interactions in normal aging, autoimmunity and cancer. The research space is located on the third floor in Alumni Hall for the Basic Sciences, and consists of three laboratories occupying approximately 2,000 square feet and is well equipped to perform histological staining, cell culture, and immunological, neurochemical (including ELISAs and HPLC proposed in this application) and pharmacological assays. The facility houses three -80 °C freezers for the storage of samples collected in this study. All ultralow freezers are connected to a central alarm system monitored by engineering and maintenance 24/7, and freezer and room will be locked at all times. This room is supported by back-up power for the freezers and air conditioning. Norepinephrine and epinephrine concentrations in samples from this study will be analyzed using an ESA CouleChem III HPLC system with a Compaq computer and printer. ELISAs for inflammatory mediators will be carried out using kits according to manufacturer's instructions and analyzed using μQuant ELISA plate reader with a PC computer. This laboratory also houses a Luminex 100 Total System with PC computer, equipment to multiplex ELISAs. The facility is staffed by personnel with over 20 years of expertise in performing the assays proposed in the study. The facility is supported by intramural and NIH funded grants and by the Departmental Pathology and Human Anatomy.

C.3.i. University of Granada (Spain) Center for Biomedical Research (CIBM). The PSYBAM research group within CIBM is a member of the Spanish National Network for Biomedical Research in Mental Health (CIBERSAM). PSYBAM is among the most productive research groups at the University of Granada, currently running six major public-funded projects. This research is focused on three main research lines: 1) psychiatric phenotype redefinition, 2) gene-by-environment interactions and psychopharmacogenetics and 3) social psychiatry and psychiatric epidemiology. The group is currently made up of three senior researchers plus ten full-time junior

researchers, including six PhD students. The PSYBAM group is based at two different sites within the University of Granada, namely, the Departmental Section of Psychiatry in the Faculty of Medicine (offices) and the Institute of Neuroscience at the Biomedical Research Centre (labs). At the CIBM main building, PSYBAM occupies two lab areas: 1) a data-analysis and bio-informatics center, and, 2) a psychiatric genetics laboratory. The data-analysis and bio-informatics center has advanced computing facilities, both hardware and software, including advanced licensed statistical packages, 8 networked desktop computers, 6 laptops and a server. In addition, there is office space for up to 8 people. The psychiatric genetics lab is also fully equipped including, among general standard facilities, an Open Array system, several thermo-cyclers, a last generation real-time PCR machine and a modern image analysis set. Drs. Gutierrez and Cervilla work out of PSYBAM, which Dr. Cervilla directs.

D. RESEARCH DESIGN AND METHODS

D.1. Overview

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 the primary endpoint and also possibly secondary endpoints. This study will take place in two phases.

D.1.a. Phase I

In Phase I (Rounsaville 1a), we will further develop and refine a manual to guide the delivery of RCBT and conduct an open trial to assess subject recruitment, assess compliance to and acceptability of the treatment, and allow therapists to gain experience with the treatment and method of delivery. We will also decide on whether the majority (or all) of the treatment will be delivered online, by telephone, or via Skype.

Manual Development

Beginning with a RCBT manual that has already been used to compare the efficacy of RCBT and CCBT in the treatment of depression (and shown superior results),[197] we will revise it to target major depression in persons with chronic medical illness. Michelle Pearce, Assistant Professor of Psychology, will lead this effort, in consultation with Dr. Rebecca Propst, the developer of the original manual. Dr. Pearce has published on religion/spirituality and coping in healthy and well populations for nearly 10 years, has conducted clinical trials examining spiritual cognitive-behavioral interventions, and has participated in psychotherapy clinical trials using non-religious interventions.

Open Trial

We will conduct an open trial, identifying and enrolling 30 subjects 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 the RCBT manual and study protocol, (4) develop a workable system of therapist supervision, (5) assess subject acceptability and compliance with online/telephone therapy, (6) decide whether telephone therapy or Skype should supplement or replace the online therapy (12 online, 12 Skype

and six by telephone to start),, depending on acceptability to patients and ease of recruitment of subjects with necessary computer skills and equipment, (7) and enable therapists to gain experience with online, telephone, and or Skype delivery of CBT, as well as the new RCBT intervention. If technical difficulties arise while using Skype or online, the default will be to use the telephone. Technical problems will be documented.

We will identify and enroll 15 subjects meeting eligibility criteria, administer the interventions (divided between RCBT and CCBT), and run subjects through the first three months of the study protocol. We will then revise, and run 15 more subjects through the first three months before finalizing the protocol. By revise, we mean not only revising the manual text but procedures and entire protocol as necessary. For both parts of Phase I, we will not be doing the 6-month assessment (reserved for Phase II). Patients in Phase 1 will only complete visits through Week 12.

D.1.b. Phase II

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) for a definitive R01 application.

Randomized Clinical Trial

In this head-to-head trial, 70 religious persons ages 18-85 with a DSM-IV diagnosis of major depression using the MINI Neuropsychiatric Inventory, mild to moderate depression severity defined as a score of 10-40 on the BDI, and at least one chronic medical illness will be randomized to either CCBT or RCBT (30 each arm, anticipating a 15% dropout rate; if > 15%, will replace to ensure 30 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 a continuous BDI score. Subjects will be assessed on the BDI at baseline, 4 weeks, 8 weeks, 12 weeks (end of treatment), and 24 weeks.

D.2. Participants and Sampling Frame

D.2.a. Overview

Selection of participants is based on (1) the high rate of depression among the medically ill, (2) the situational stressors likely driving depression in this population, (3) the desire to treat depression non-pharmacologically (in those taking a host of other medications that increase potential for drug interactions and side-effects), and (4) chronically ill disabled patients' difficulty getting into therapists' offices due to problems with mobility.

D.2.b. Subject Identification, Selection and Enrollment

The sites for recruitment will be: (a) outpatient primary care clinics of Duke Health Systems (North Carolina) and of Glendale Adventist Medical Center; and (b) general medical-surgical patients hospitalized at Duke University Hospital and Durham Regional Hospital (combined 1300 beds), and at Glendale Adventist Medical Center (550 beds).

The Raleigh-Durham-Cary metropolitan area has 1.5 million residents, and Los Angeles County (where Glendale is the 3rd largest city) has over 10 million residents.

Why are two sites necessary for this feasibility study? *The reason is 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. Given our inclusion and exclusion criteria, it is possible that we may need to screen as many as 50,000 medical patients to obtain the numbers needed in the future study (especially if genetic and biological analyses are planned). Furthermore, having two sites will increase the generalizability of our results, especially sites that are at opposite ends of the country.*

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; 2) we will post flyers (with inclusion and exclusion criteria) in clinics throughout the Health System and in hospital as allowed, on Duke University campus and other local university campuses, in local mental health clinics such as ACCESS, and distribute to community groups, including churches, nursing homes, and other community organizations who may have contact with depressed persons who would benefit from this study; 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, and (6) if necessary, screening at the bedside of consecutive hospital admissions to the medical-surgical services of the hospitals above.

Duke chaplains will assist in distributing flyers about the study. If a chaplain identifies an inpatient who appears depressed and is in the age range required for study participation, he/she will give that patient a study flyer. If the patient has questions, the chaplain will simply refer the patient to the information on the flyer and tell them to call the telephone number on the flyer for additional information if the patient is interested in participating. We will obtain permission from the patients' attending physician for the chaplain to give patients flyers and will obtain permission from the nurse managers on the units. For obtaining physicians' permission, either (1) the medical director of the unit will send out a general email to the attendings under his/her direction asking for permission for the chaplains to hand out flyers and requesting anyone who does not wish to give permission to notify us, or (2) we will contact physicians directly and get their individual permissions to allow chaplains to give out flyers to patients they think are depressed. For obtaining the nurse managers' permissions, we will directly contact the nurse manager for each unit and get their permission individually. Patients will be screened by telephone [see telephone script] or in-person.

The flyer above includes guidelines for patients to help them to identify whether they have “significant depressive symptoms” by including a list of depressive symptoms. Persons with chronic illness who have four or more of these symptoms have been shown to be at significantly greater risk for major depression.[198] Physicians and nurses are often too busy to identify patients with depression, as we have experienced by the low rate of referrals from Duke clinics. Therefore, rather than rely on physicians and nurses to

identify depression, we think that patients themselves can do this, given some simple guidelines.

For outpatients in Duke clinics, we would proceed as follows: the treatment team (receptionist, nurse or physician) gives patients our flyer that explains the study and provides guidelines on symptoms that place them at high risk for a significant depression. After reading the flyer and completing the questions, if they wish to participate in the study, patients provide contact information on the flyer, place it in an envelope provided with the flyer, seal the envelope, and hand it to the receptionist who then puts the envelope in a box, which we will then collect and later contact the patient. We will obtain permission from treating physician, the Clinic Manager, and Clinic Administrator for their staff to distribute these flyers.

Similarly, for inpatients in the hospital, the treatment team (ward clerk, nurse, chaplain, or physician) on the unit will give the flyer and envelope to admitted patients. We would provide a box on the unit that the staff can place the envelope with the flyer if the patient fills out the information and wishes to be contacted about the study. We will obtain permission from treating physicians and the Head Nurses for their staff to distribute the flyers.

For staff cooperation in this regard, we will pay the outpatient clinic or hospital unit a flat amount each year that can be used for continuing education or other purposes.

The information provided on the flyer by patients concerning depressive symptoms they are experiencing will not be used for research or clinical purposes or recorded in any database, but simply as a guide for patients to determine whether they have enough depressive symptoms that might make them eligible for the study. If they wish to participate in the study, they will turn in the sealed envelope with their contact information to the receptionist or nurse, and our research staff will call them on the telephone, ask them some further screening questions (see telephone script, unaltered) and if they qualify, an appointment would be made for in-person screening, when they would be given further details about the study and asked to sign the consent to participate before the in-person screening takes place.

D.2.c. Inclusion and Exclusion Criteria

Inclusion Criteria are: (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); (2) ages 18-85; (3) indicates that religion is at least somewhat important (see below); (4) a DSM-IV diagnosis of major depression using the MINI Neuropsychiatric Inventory;[199] and (5) moderate depression severity defined as a score of 10-40 on the Beck Depression Inventory (BDI).[200] 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 are: (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 verbally and in written English; and (8) lack of telephone AND lack of access to a computer or the Internet or inability to type fluently[1] (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).

Religious Criteria. Subjects will also be pre-screened with the question, "Is religion/spirituality at least somewhat important in your daily life?" (yes or no). Those who indicate that religion is not important will not be enrolled in this trial, thus limiting subjects to those for whom religion (or spirituality) is at least somewhat important (65-75% of Americans). Including those indicating that religion is only "somewhat" important will allow some variability in religiousness in order to test effects of religiosity on treatment response, although multi-item measures of religiousness and spirituality will be administered at baseline to further discriminate subjects based on level of religiosity/spirituality (see below). This variability will also be important in addressing the study's genetic, immune and endocrine hypotheses.

Although most U.S. adults with a religious affiliation are Christian (94% based on 2007 Pew Survey, n=35,556)[201], persons of other religious faiths will be included and the therapy will be adapted to their particular religious beliefs (Jewish, Muslim, Hindu, or Buddhist). We believe it is important to include those from faith traditions other than Christianity because these individuals may have particular difficulty obtaining adequate psychiatric care due to their minority religious status (Muslim, etc.). We recognize that given the small numbers of subjects from non-Christian religious faiths likely to be enrolled in this planning study (estimated 3-4% of the sample based on the Pew Survey above), we will not be able to determine reliable effect sizes for RCBT in any of these faith traditions other than Christianity. However, CBT manuals based in Jewish, Muslim, Hindu, and Buddhist faith traditions will be developed, and experts from those traditions will guide therapists delivering the therapy to patients from those traditions, allowing us to refine these faith-specific treatments for a future larger trial where we will stratify recruitment based on the most prevalent religious traditions in the population.

D.3. Feasibility Issues and Challenges

In this section, we briefly address key practical and methodological challenges that we grappled with in choosing how to identify, classify, and enroll subjects into this study. We first present the issue, define options we considered, and then discuss why we made the choices we made.

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[1]This will limit study to persons of a higher socioeconomic/educational class – those who can afford computers and are sufficiently technical to use them – however, this is the group that this form of therapy would apply to. Doing intervention by telephone would largely eliminate this concern.

D.3.a. Feasibility
The challenge will be identifying a sufficient number of patients that fulfill the inclusion criteria and are willing to participate in a clinical trial. The greater challenge may be identifying depressed patients with chronic illness who have Internet access and are sufficiently fluent in typing, if we go with the online method of treatment delivery. If we go with the telephone therapy, then recruitment may be easier, although issues related to hearing and privacy could be a problem.

Based on demographic characteristics of patients in Durham, North Carolina, and Glendale, California (with a relatively high percentage of minorities in both locations), religious patients with major depression and chronic illness should be readily available for recruitment. Furthermore, both recruiting teams led by Dr. Dolor and Dr. DeLeon have plenty of experience recruiting patients for clinical trials, including patients for clinical trials involving depression. In addition, these teams have administrative support at the highest levels (at Duke, Harvey Jay Cohen, immediate past chairman of medicine, and at Glendale, Morre Dean, president and CEO of the healthcare system).

D.3.b. Subject Identification and Classification
Subject identification. Subjects will be identified using the inclusion and exclusion criteria above. The minimal level of cognitive functioning will be 14 or higher on the brief Mini-Mental State Exam (MMSE), which indicates no more than mild cognitive impairment.[202] Average MMSE for 413 hospitalized medical patients with major depression in a recent Duke study was 16.9 (SD 1.2), well above that cutoff.[203]

Classification. Many studies fail to identify clinically significant effects because patients in the study are not classified accurately. Given that this is a planning study, carefully defining our "phenotypes" for the study becomes crucial.

<u>Major Depression</u>. Patients will fulfill criteria for major depression using appropriate modules of the MINI (Mini-International Neuropsychiatric Interview), a structured psychiatric interview that follows DSM-IV criteria.[204] These criteria are standard and have changed little over the past 20 years. Depressed mood (most of the day and nearly every day) or loss of interest (inability to experience pleasure) must be present for at least two weeks and associated with four of the following eight symptoms: feelings of worthlessness or guilt, fatigue or loss of energy, difficulty thinking or concentrating, loss of appetite (significant weight loss or weight gain), difficulty sleeping, psychomotor retardation or agitation, or recurrent thoughts of death or wanting to die (suicidal ideation). These symptoms must be severe enough to interfere with functioning. In previous prospective research with chronically ill medical patients, we have shown that counting symptoms toward the diagnosis of major depression using the "inclusive" approach is more reliable and accurate (i.e., not trying to decide whether the symptoms are from medical or psychiatric causes, but simply counting symptoms regardless of presumed etiology).[205]

In addition, patients will need to score between 10 and 40 on the Beck Depression Inventory (BDI-II), which is a self-rated measure of severity of depressive symptoms. Scores of 0-10 are considered minimal, 11-15 mild, 16-35 moderate, and above 40 severe (score range 0-63). Thus, patients with major depression of mild-moderate severity will be enrolled, as those who are severely depressed may not be able to participate in the therapy. The BDI-II is also our primary endpoint, so this measure has a score range that is sufficiently broad to provide good variability in responses, and should be able to detect clinically significant improvement (a 3 point reduction in score; see below).

Deeply Religious Persons. Although subjects do not need to be deeply religious for study entry, we will be comparing responses to treatment in deeply vs. less deeply religious subjects. This will also be relevant to our genetic hypotheses (i.e., deeply vs. less deeply religious more likely to have genetic polymorphisms that predispose to depression). To be considered "deeply religious," subjects will need to fulfill three of four criteria below:
(1) Indicate "very important" in response to the question on the baseline interview, "How important is religion in your daily life?"
(2) Score 45 or higher on the 10-item Hoge intrinsic religiosity measure (range 10-50). Among 838 hospitalized patients age 50 or over at Duke Hospital, the average score was 39.9 (SD 6.8)[206] for all patients and in a separate study of 411 patients with major depression, the average score was 39.7 (SD 8.3).[207] This means that subjects will have to score roughly one standard deviation above the mean.
(3) Score 70 or higher on the 16-item Daily Spiritual Experiences Scale (range 16-80). In our sample of 838 hospitalized patients noted above, average score was 61 (SD 12.1). Again, subjects would need to score roughly one standard deviation above the mean.
(4) Attended religious services weekly or more in the past when physically able (since many disabled subjects not able to attend now), and pray privately at least once/day.

Note that in a prospective study of depressive disorder in 864 medical patients age 50 or older hospitalized at Duke (all levels of religiosity or lack thereof), we found that 14% (n=118) met all of the following criteria: attended religious services weekly or more, prayed daily or more, read the Bible several times per week or more, and scored 45 or higher on intrinsic religiosity.[208] Given that we are including only subjects who already indicate that religion is at least someone important to them, we expect a high percentage of subjects to meet the broader criteria above (three of four criteria).

Chronic Illness. Subjects must have at least one chronic illness (broadly defined). By this we mean patients diagnosed with a medical condition that has been present for at least 6 months. By chronic medical illness, this means one or more of the 31 medical illnesses listed on the Charlson Comorbidity Index based on the International Classification of Disease, 10th edition (ICD-10) (including symptoms, signs, and ill-defined conditions). In our study of 413 consecutive medical inpatients at Duke Hospital with major depression, the average number of medical illnesses on the Charlson scale was 7.4 (SD 3.1) (unpublished data); bear in mind, though, that those results apply to hospitalized patients. As noted above in Exclusion Criteria, patients with HIV/AIDS, autoimmune diseases, or a prognosis of less than 6 months will not be included in this study due to the proposed immune and endocrine analyses.

D.3.c. Sources of Confounding

Since the purpose of randomization is to balance out sources of confounding, and the purpose of this planning grant is feasibility not perfect randomization, sources of confounding may influence study results in a small clinical trial and could affect the accuracy of effect size determination, the goal of Phase II. For these reasons we now describe sources of confounding that may influence study results.

The variability associated with potential confounding factors may be compounded by the large number of patient variables (potential covariates) that are inherent in a study that recruits patients with an assortment of medical illnesses and chronic conditions at different levels of severity, with varying histories of depression for which they may be receiving treatments. In a clinical trial that involves only 30 subjects in each group, the potential for such issues to affect results are magnified. These are realistic concerns that need to be addressed. Besides paying careful attention to characterization of subjects (as described above in section D.3.b.), we will at least partially mitigate this concern by measuring and controlling for the primary confounding variables —past history of depression, physical disease severity, psychiatric medication, and certain demographics (race, gender, etc.). We recognize that the small size will also limit the number of variables that can be taken into account in our analyses; however, we plan to examine only one or two covariates at a time to minimize this problem.

We considered limiting subjects to a specific medical condition; however, this would significantly affect recruitment and prior research suggests that the specific medical condition is less important (with regard to depression) than the functional disability that results from the medical illness or combinations of medical illnesses.[209]

Prior history of depression. Question A6 on the MINI asks about how many episodes of major depression (similar to current episode) the subject has experienced in his/her lifetime (with at least 2 months without depression between episodes).

Treatment with antidepressants. We will ask subjects if they are currently taking an antidepressant medication (showing them a list of commonly used drugs today) and if so, how long they have been taking it. If subjects are not taking an antidepressant drug, we will ask if they ever took one and how many months or years ago that was. We will also ask subjects during follow-up evaluations if they have been placed on any antidepressant drugs during the course of the psychotherapy intervention, and if so, this will be controlled in the final analyses.

Treatment with other medications. Other medications may influence either the responsiveness of the depression to treatment or may interfere with immune/endocrine measures being assessed in this study. Thus, we will obtain a list of all medications – prescription and non-prescription that the patient is taking. Patients taking immuno-suppressant drugs (corticosteroids, methotrexate, etc.) will be excluded from the study. Medications that may influence mood state (i.e., antihypertensives, beta blockers, anti-anxiety, sedative-hypnotics, anti-psychotic or mood-stabilizing drugs, etc.) will be recorded and taken into account in the final analyses.

Disease state. A list of acute and chronic illnesses will be obtained using the Charleson Co-morbidity Index, and severity of illness determined using the interviewer-administered Cumulative Illness Rating Scale. Subjects with autoimmune disorders, primary endocrine disorders likely to affect stress hormone levels, HIV/AIDS, dementia, or prognosis less than 6 months will be excluded.

Demographics. Demographics likely to affect depression outcomes will be collected including gender, age, race, education (proxy for socioeconomic status), living circumstances, and marital status.

D.3.d. Interpretation of Results

We recognize that the purpose of this planning grant is not to find significant results, but rather to determine feasibility and effect sizes for a future more definitive clinical trial. However, considering beforehand how we plan to interpret results from this small trial is important. Clearly, the opportunity for Type I and II error is non-trivial despite careful classification of subjects and control for a limited number of covariates. Since the proposed sample size is almost certainly insufficient for statistically significant effects, we will avoid over-interpretation of the results by (1) strictly adhering to hypothesis testing procedures; (2) reporting all contrasts and resulting p values whether positive or negative; and (3) considering the findings to be hypothesis generating only.

D.3.e. Implications for Power

In a strict sense, power calculations are irrelevant since we are not powering the study to determine a significant effect. However, to get some sense of the kind of power that such a small study might have, consider the following. In order to detect a clinically significant difference (3 points on BDI or treatment effect of 0.3) in a head-to-head trial between RCBT and CCBT at a significance level of 0.05 and a power of 0.90, this could require as many as 300 participants in each trial arm, based on results from our previous Lancet study of online CBT. We consider these issues in more detail in section D.11.e -- Power Analyses and Sample Size Considerations.

D.3.f. Miscellaneous Challenges

Other challenges also confront us in a feasibility study of this nature, which will provide information to help us deal with those issues in the larger, more definitive study to follow. One challenge has to do with whether changes in immune and endocrine function can be detected in the range of depression severity that subjects will have in the present study. Will those with major depression and BDI scores of 10-40 have large enough adverse immune/endocrine changes such that a CBT intervention can have any chance of reversing them? Previous research reviewed above suggests that even in non-depressed stressed samples (i.e., those with HIV/AIDS), that significant immune/endocrine changes can be detected in response to psychosocial interventions.

A second challenge is whether our RCBT intervention is strong enough in this small sample with moderate depression severity to show superiority over a high quality proven CCBT intervention. Most head-to-head comparisons of different kinds of psychotherapy do not find significant differences between treatments. However, we are convinced that the rationale for including religious resources in therapy is strong enough (especially in religious patients) to achieve such a detectable difference.

A third challenge that confronts us has to do with our proposed genetic analyses. The size of our sample (100 subjects overall for the baseline genetic analyses, and 70 for the RCT portion) is small when compared to studies that have reported associations between genetic polymorphisms, depression, and stressful life events (n=847 in the original Caspi study; n=737-1228 in the PREDICT-gene study). Those latter samples, however, were not depressed patients, and other studies reporting positive findings among depressed subjects in response to treatment have involved smaller samples (n=137).[210] Likewise, studies reporting associations between spiritual variables and genetic polymorphisms have also been smaller (ranging from n=40 to 200).[211,212,213] Finally, a recent comprehensive review of this area emphasized that gene-environment hypotheses could be tested with both large and small samples.[214] Thus, we are hopeful that our sample will at least be large enough to determine trends verifiable in a future larger study.

D.4. Enrollment and Randomization

D.4.a. Enrollment

Those who meet study criteria and agree to participate in the trial will undergo further baseline assessment by a research assistant. After assessment is complete, the research assistant will then enter the screening and baseline information into OpenClinica [the software program being used for study coordination, data entry, and monitoring, and is equivalent to other programs like ClinTrials and InForm]. The patient's name, contact information, and study number will then be added to a confidential enrollment log of study participants and kept in a locked cabinet in a secure location at each respective site -- separate from paper forms with patients' data that will include only the patient's study number, not name or contact information.

Study Staff will then contact the Coordinating Center (QAMD) and provide the Coordinating Center with the patient's initials, study number, and randomization number The Coordinating Center will determine which therapist is assigned to that specific randomization number. 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.

D4.b. Randomization to Treatment Arm

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 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.

D.5. Interventions

Both interventions will take a CBT approach, involving online therapy over the Internet in real time supplemented with telephone contacts, or if necessary, entirely by telephone. The primary objective of CBT is to change thinking, i.e., change "the mind." Depressed persons with chronic medical illness have often allowed their health problems and disability (i.e., circumstances) to shape the way they think and their view of the world. Depression is often maintained by a negative worldview that sees the person's situation as hopeless and without meaning or purpose. Both conventional and religious CBT seeks to alter these dysfunctional, maladaptive beliefs, replacing them with positive, realistic beliefs and behaviors that generate positive emotions.

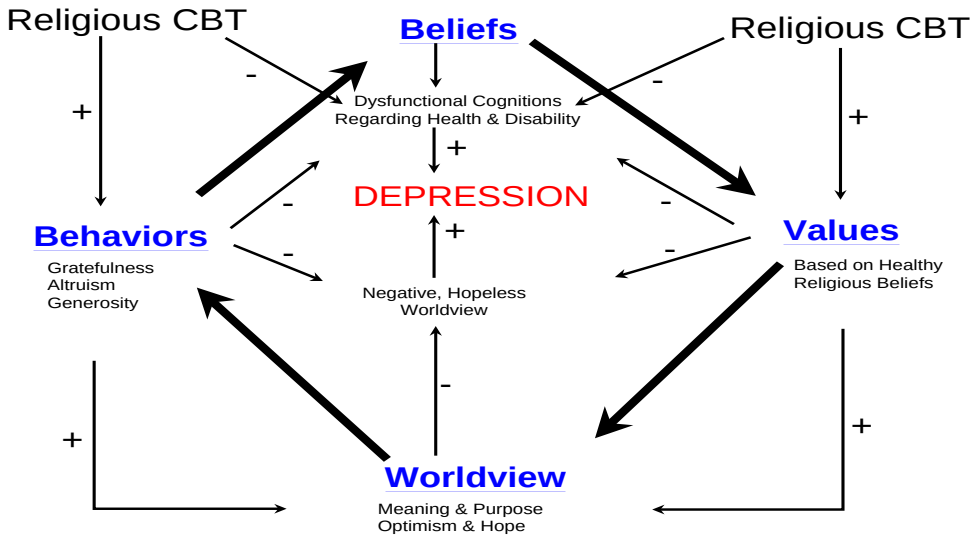
D.5.a. Conventional CBT

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 their cognitions and determine problematic behaviors. Interventions include activity scheduling, along with 'practice assignments', in which clients test out ideas and behaviors discussed during sessions. In this arm, therapists will be asked to avoid reference to the participant's faith or religious belief. 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.[1] We understand that not all conventional CBT ignores the religious beliefs of patients if they come up during therapy. However, in order to contrast the two approaches (conventional vs. religious CBT), the therapists delivering CCBT in this trial will concentrate on the non-religious aspects of CBT.

[1] We understand that this may be challenging, especially if patients are expecting religious CBT. However, recruitment of patients into the trial will be largely by referral or identified by screening, rather than responding to advertisements. The advertisements will be relatively vague – emphasizing the online/telephone CBT for depression rather than the particular nature of the CBT. Finally, the consent form will specify that if assigned to conventional group, then religious issues will not be specifically addressed.

D.5.b. Religious CBT

Religious CBT will follow exactly the same process described for CCBT above. *Except*, in this form of treatment the therapist will be explicitly open to, and bring into the therapy, the participants' thoughts about their religion/faith. RCBT uses religious rationales (based on the subject's faith tradition) and religious arguments to counter irrational thoughts. Religious patients already have the tools and the motivation to change their negative thinking, although they may not realize that. RCBT teaches patients to use religious teachings, doctrines, and behaviors to help change maladaptive beliefs, values, and behaviors so as to transform their worldview into one that is meaningful, hopeful, and optimistic, which is incompatible with depression. RCBT seeks to change dysfunctional beliefs and behaviors (related to self-preoccupation) that may be rooted in values that have created a negative worldview based on physical illness and disability. RCBT seeks to bolster powerful religious beliefs that promote behaviors such as forgiveness, gratitude, generosity, and altruism (focusing on others and on God) that generate meaning and purpose, optimism and hope, which neutralize depression (Figure below adapted from 9/09 JMT, Jr., "Circle of Inter-related Components of Culture").



The RCBT manual will initially be developed within a Christian framework, and then will be adapted to the subject's faith tradition if that is not Christian (see below). Since clients vary a lot in their expectations of religious therapy[215] – some wanting quite overt expressions of religion during therapy – we will stress that the therapy is *not* a prayer or healing based intervention. Rather, it will be strictly limited to CBT that takes account of the participant's religious faith in its focus on thinking and emotion, and emphasizes spiritual practices and behaviors that may help reduce depressive symptoms. 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 the participant's religious language, symbols, and particular faith tradition; this information will guide integration of the participant's beliefs into the therapy.

D.5.c. Treatment Manuals

Although we will briefly describe versions of the conventional and religious CBT manuals here, and include draft versions in the Supporting Materials, both will need field testing and further development in Phase I prior to finalizing the manuals for the Phase II trial. This especially applies to the RCBT manual, which is the primary intervention to be tested against the standard version of CBT.

CCBT manual. There is some question about whether a session-by-session CCBT manual is even needed, since this treatment has become standard. In fact, a recent well-designed RCT of cognitive therapy for depression[216] did not follow a treatment manual but simply indicated in the method's section that they used experienced cognitive therapists and that the treatment was consistent with the work of Aaron Beck[217] and Judy Beck.[218] However, for completeness sake, since we are using a session-by-session manual for the RCBT treatment, and will be adding sessions on gratitude and altruism to the CCBT protocol, and supplementing with mindfulness meditation, we will also use a manual for the CCBT treatment. Our CCBT manual is closely modeled after the original manual developed by Aaron Beck. Our conventional CBT specialist, Clive Robins, will reduce this 18-session manual down to 10 sessions for our study, and include new sessions focusing on dealing with loss (for this population), gratitude, and altruism (and meditation), parallel to the RCBT manual.

To summarize, the CCBT intervention will help participants to (1) develop the ability to identify problem situations and associated cognitions and behaviors that promote depressed moods; (2) increase behaviors that promote feelings of mastery or pleasure; (3) evaluate their thoughts and beliefs about current problematic situations or issues, including their medical conditions, by examining evidence regarding them and engaging in behavioral experiments to test them; (4) develop alternative, more adaptive beliefs and assumptions; (5) increase behaviors involving expression of gratefulness and altruism; and (6) engagement in a secular meditative practice (mindfulness). In this population, particular emphasis will be given to themes of loss of function and identity related to their medical conditions, as well as worries about the future.

A session-by-session description of CCBT now follows. <u>Session 1</u> will focus on discussion of the patient's experience of depression and his or her current life situation, including family relationships, and on introducing the cognitive model of depression, noting the relations among environmental situations, thoughts, emotions, physical reactions and behaviors. In <u>Session 2</u>, therapist will review homework assignments, focus on behavioral activation, introduce and explain mastery/pleasure worksheets to increase pleasant events and mastery experiences, and introduce concept of Mindfulness Meditation (secular). <u>Session 3</u> focuses on learning to identify moods and thoughts that accompany changes in mood (continue with introduction to meditation). <u>Sessions 4 and 5</u> focus on CBT methods for evaluating thoughts of loss related to chronic illness and disability,

developing more balanced or realistic appraisals when appropriate and developing greater acceptance as well as problem-solving ways to alleviate losses; subjects begin to practice MM. Session 6 focuses on identifying underlying assumptions, rules and core beliefs that may give rise to negative thoughts and emotions, and on identifying and strengthening alternative beliefs. Session 7 focuses on CBT methods for dealing with feelings of lack, and alternative reactions including being thankful and expressing gratitude; begin gratitude exercises. Session 8 focuses on dealing with anxiety and worry, incorporating behavioral exposure, methods to counteract self-centeredness, emphasis on altruism and expressions of generosity, and other ways of reducing unjustified anxiety. Session 9 focuses specifically on stress-related growth as a way of dealing with experiences of guilt, shame, and anger, and utilizes CBT techniques such as the responsibility pie chart to address these negative emotions. Session 10 is a review and termination session, in which plans for maintaining treatment gains from CBT are developed; for continuing to practice CBT techniques, mindfulness meditation, gratitude exercises, and altruistic behaviors; and for ways of maintaining hope into the future.

All sessions will be characterized by a collaborative therapeutic style, agenda-setting, frequent eliciting and responding to feedback from the patient, empathic communication, Socratic questioning and guided discovery, homework assignments and review the following session, and attention to difficulties in the therapeutic relationship. See Supporting Materials for a version of Beck's CCBT Manual that will be modified by Dr. Robins for the trial.

RCBT manual. RCBT – developed originally by Rebecca Propst and modified by Michelle Pearce – is a therapeutic approach that will parallel the CCBT sessions in every respect, except that religious resources will be relied upon to address cognitive-behavioral issues. The RCBT manual will conventional CBT worksheets into the Christian model so that it follows conventional approaches but with distinctive Christian features. The manual aims to use faith-based CBT models comparable to secular-based CBT models that have the ability to reach the majority of persons' faith experience who are suffering from depression in the midst of (and often in reaction to) chronic disabling medical illnesses.

A session-by-session description of RCBT now follows. Session 1 will focus on discussion of the patient's experience of depression and his or her current life situation, including family relationships, and on introducing the cognitive model of depression, noting the relations among environmental situations, thoughts, emotions, physical reactions and behaviors. As part of this initial assessment, therapist will assess religious beliefs and background, introduce RCBT rationale, and encourage identification of a memory verse and focus on positive scriptures. In Session 2, therapist will review homework assignments, finalize the religious assessment and discuss role of faith and prayer, as well as focus on behavioral activation, introduce and explain mastery/pleasure worksheets to increase pleasant events, and introduce concept of Christian contemplative prayer. In Session 3, the therapist will focus on helping patient identify moods and thoughts accompanying changes in mood, all within a framework of Christian beliefs and

Biblical principles; will also work with patient to come up with a memory verse to serve as the focus of contemplative prayer. Sessions 4 and 5 focus on CBT methods for evaluating thoughts of loss related to chronic illness and disability, developing more balanced or realistic appraisals when appropriate, developing greater acceptance and other problem-solving techniques to alleviate sense of loss, all within a Christian framework (sacred loss, Biblical examples of loss, true self as spiritual self); patients begin to practice contemplative prayer with focus on memory verse. During Session 6 the therapist will help patient identify underlying assumptions, rules and core beliefs that give rise to negative thoughts about God or members of faith community (spiritual struggles) and the accompanying negative emotions, while helping to identify and strengthen alternative beliefs. In Session 7, therapist focuses on CBT methods for dealing with feelings of lack and taking things for granted, and alternative reactions of being thankful and expressing gratitude to God through the practice of gratitude exercises. Session 8 will focus on dealing with anxiety and worry, incorporating behavioral exposure, methods to counteract self-centeredness, and ways of expressing religious gratitude (from last session) by practicing altruism and generosity towards others for religious reasons (serving and loving God and thereby casting out fear). Session 9 will focus on stress-related growth as a way of dealing with experiences of guilt, shame, and anger, utilizing a variety of standard CBT techniques but from a Christian perspective that emphasizes spiritual growth by a series of exercises that help patient focus on positive outcomes. In the final termination session, Session 10, plans will be made for maintaining RCBT treatment gains; for continuing to practice RCBT techniques, contemplative prayer, gratitude exercises, and altruistic practices; and for ways of maintaining hope into the future (based on Christian beliefs).

As with CCBT, all sessions will be characterized by a collaborative therapeutic style, agenda-setting, frequent eliciting and responding to feedback from the patient, empathic communication, Socratic questioning and guided discovery, homework assignments and review the following session, and attention to difficulties in the therapeutic relationship. See Supporting Materials for Propst's original RCBT Manual and an initial outline of the RCBT Manual to be used in the trial.

For a summary comparison of CCBT and RCBT per session, see next page.

Direct Comparison CCBT vs. RCBT

Conventional CBT

Session 1. Discussion of the patient's experience of depression and current life situation, including family relationships, introduce CBT.

Session 2. Focuses on behavioral activation, increasing pleasant events and mastery experiences. Intro secular mindfulness med.

Session 3. Focuses on learning to identify moods, and to identify thoughts accompanying changes in mood. Continue to introduce mindfulness.

Session 4. Focus on both cognitive and behavioral methods for evaluating thoughts; develop more realistic appraisals; begin mindfulness meditation practice.

Session 5. Focus on using CBT methods for dealing with themes of loss associated with chronic illness & disability.

Session 6. Focuses on underlying assumptions, rules and core beliefs that give rise to negative thoughts & emotions, and on identifying alternative beliefs.

Session 7. Focus on CBT methods for evaluating thoughts/emotions related to lack; switch to feeling thankful for good in life; expression of gratitude exercises.

Session 8. Focus on CBT methods for behavioral exposure for worry/anxiety, other methods to counteract self-centeredness; encourage altruistic, generous behaviors.

Session 9. Emphasize stress-related growth; focuses on guilt, shame, anger; utilizes CBT tech such as responsibility pie chart, others.

Session 10. Review, termination, focuses on maintaining treatment gains, hope in future.

Religious CBT

Session 1. Same as CCBT; assess religious beliefs, background; introduce RCBT rationale; introduce memory verse and focus on positive scriptures.

Session 2. Same as CCBT; complete religious assessment, discuss role of faith and prayer. Intro Christian contemp prayer.

Session 3. Same as CCBT; place within a framework of Christian belief system; finalize socialization into RCBT; work with pt to identify memory verse.

Session 4. Same as CCBT; challenging unhealthy thoughts; place within a Christian religious context; begin contemplation Christian practice

Session 5. Same as CCBT; place within framework of Christian belief system; sacred loss, Biblical examples; spiritual self.

Session 6. Same as CCBT; focus on dealing with spiritual struggles, negative religious beliefs involving anger, guilt, resentment toward God and others.

Session 7. Same as CCBT; focus on taking things for granted; Biblical examples of grumbling; religious reasons for gratitude; expression of gratitude to God exercises.

Session 8. Same as CCBT; focus on expressing religious gratitude by practicing altruism and generosity to counteract worry, anxiety; stress religious reasons for altruism.

Session 9. Same as CCBT; focus on spiritual growth from Christ persp; focus on positive outcomes thru series of exercises.

Session 10. Same as CCBT; emphasizes spiritual reasons for & ways to maint hope.

D.5.d. Interfaith Council of Advisors
We will be developing versions of Pearce's 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. These versions of the manual will be prepared under the direction of our Interfaith Council of Advisors, which is made up of experienced psychotherapists from each of these traditions. In addition, members of the council will help supervise therapists during the intervention with these patients, will serve as advisors to study investigators throughout the project, and will participate in the interpretation of results. The following are the Advisors who have agreed to be on the Council (for full CV's and letters of support see Supporting Materials).

Chairperson
Ken Pargament, Ph.D., is professor of clinical psychology at Bowling Green State University, and is an expert in spiritually integrated psychotherapy. He is author of *The Psychology of Religion and Coping: Theory, Research, Practice* and the more recently published book, *Spiritually Integrated Psychotherapy: Understanding and Addressing the Sacred*. Dr. Pargament has received many awards for this work, including the William James Award for excellence in research in the psychology of religion from Division 36 of American Psychological Association, and most recently, the 2009 Oskar Pfitzer Award from the American Psychiatric Association. As the person in charge of quality control for the religious CBT, Dr. Pargament's role will be to ensure that all five religious versions of the manual integrate religious beliefs and practices into the therapy to a similar extent, degree, and depth. His extensive experience with integrating spiritual beliefs from many different faith traditions into psychotherapy makes him ideal for this position.

Jewish
Jonathan Schwartz, PsyD, is an experienced CBT therapist and Jewish rabbi. His PsyD is from the Ferkauf Graduate School of Psychology at Yeshiva University. He is a senior staff psychologist at the Center for Cognitive Behavioral Psychotherapy in New York, NY, since 2004, and is visiting assistant professor at Stern College for Women, New York, NY, also since 2004.

Assisting Dr. Schwartz will be **David Hillel Rosmarin**, **Ph.D.** He is a clinical fellow in the department of psychiatry at Harvard Medical School where he is completing a psychology internship at McLean Hospital. David has an M.A. in counseling psychology from the University of Toronto, and completed his Ph.D. in clinical psychology at Bowling Green University in 2010. He has experience doing online CBT with Jewish patients, and has recently completed a clinical trial testing this intervention ["A randomized controlled evaluation of a spiritually-integrated cognitive-behavioral (online) intervention for sub-clinical anxiety among religious Jews"] published recently in the Journal of Anxiety Disorders.[219] He is also familiar with manual development and has experience creating user-friendly on-line interventions. Dr. Rosmarin will also serve as our PsychologyOnline administrator (see below).

Muslim
Sasan Vasegh, M.D., is a psychiatrist from Iran, who is an expert in Shia, but is also very familiar with Sunni Muslim beliefs and practices. He has had approximately 1 year of specific training in CBT at Tehran University of Medical Sciences, along with supervision. Since then, he has guided weekly discussions, training and supervision groups to educate and train psychiatry residents and psychologists in CBT for more than 5 years. He is currently at Ilam University of Medical Sciences as an assistant

professor of psychiatry and his clinical practice involves doing 10-20 CBT sessions with clients per week. With longstanding interests in religion and psychiatry, Dr. Vasegh for the last year has been developing a religious CBT intervention for Muslim patients.

Hindu

Nalini V. Juthani, M.D., is professor emeritus of psychiatry at the Albert Einstein College of Medicine (AECOM) in New York City. She was the residency program director and assistant dean for undergraduate affairs at the Bronx Lebanon Hospital Center for 25 years. She is currently an accreditation representative of the Accreditation Council for Graduate Medical Education (ACGME), and was appointed by ACGME as a member of the Residency Review Committee (RRC) of Psychiatry. During her career of 30 years in psychiatry, she has served the APA through various Committees including the religion and spirituality sections. She has made numerous presentations, written a number of articles and two book chapters on Hinduism in major textbooks dealing with integrating spirituality into clinical practice. Dr. Juthani has been actively involved in conducting psychotherapy with an emphasis on CBT with Hindu patients for over 30 years.

Buddhist

Jean Kristeller, Ph.D. is Professor of Psychology and the co-Director of the Center for the Study of Health, Religion, and Spirituality at Indiana State University, where she teaches in the doctoral program in clinical psychology. Previous academic appointments in behavioral medicine have been at the University of Massachusetts Medical School and Harvard University. She received her doctorate in clinical and health psychology from Yale University in 1983, and her M.S. from the University of Wisconsin in 1978 in clinical human psychophysiology, both within a cognitive-behavioral framework. She has also spent time studying and conducting research in Japan, China, Thailand, and Indonesia. She has a number of publications on the psychology of Buddhism. Her other work has been on the psychology of religion and spirituality, including an NIH-funded trial investigating the role that different aspects of religion and spirituality play in protecting against alcohol dependency in college students. Dr. Kristeller is an experienced CBT therapist who has in depth knowledge about Buddhism and its integration into therapy.

D.5.e. Delivery of the Interventions

In both arms the intervention will consist of ten 50-min sessions of CCBT or RCBT delivered either online or by telephone, to be completed within 12 weeks. Scheduling will be left to the discretion of the therapist and participant. Each participant will be assigned a single therapist for the duration of the study. All therapists delivering the intervention will be trained in CBT and will be trained in providing psychotherapy online and by telephone. Participants receiving CCBT will be assigned to a therapist who does not deal with religious issues; those receiving RCBT will be assigned to therapists who are trained in that therapy. Participants will be allocated on a rotating basis to the next available therapist, depending on group, and will make their own appointments online. The sessions will be secured by individual passwords. Participants and therapists will type free text into the computer, with messages sent instantaneously, or will communicate by telephone. Therapists in California will deliver the therapy to subjects recruited in California and therapists in North Carolina will deliver the therapy to subjects recruited in North Carolina.

In order to minimize study dropouts (see rationale in section B5), we will be supplementing the online therapy with at least three telephone CBT sessions. The number of CBT telephone sessions will be determined in Phase I and may eventually be 0 (all sessions online) or 10 (all sessions by telephone),

although we will start with three of the 10 sessions by telephone. We will also explore the use of Skype to enhance the telephone sessions and allow more direct contact between subjects and therapists.

D.5.f. Psychology Online

The website technology for the online psychotherapy sessions will be provided by a commercial, for-profit organization in the United Kingdom titled PsychologyOnline (www.psychologyonline.co.uk). This is the organization that provided both the technology and the therapists for the online CBT intervention for depression in medical patients published by Michael King's group in the Lancet. PsychologyOnline markets itself as the UK's leading provider of live online CBT technology. PsychologyOnline operates according to the Code of Conduct, Ethical Principals and Guidelines of the British Psychological Society and adheres to the standards of clinical governance of the National Health Service. It is listed in the Department of Health's "Organizing and Delivering Psychological Therapies" document. It provides confidential live online therapy through a secure website. We have checked with our IRB specialist (Lawrence Muhlbaier, Ph.D.) on issues related to patient confidentiality. Since PsychologyOnline is merely hosting the online site but not treating the patients, we can add their group to the list of disclosures in the informed consent, and set up an outside services agreement with PsychologyOnline to host the online CBT on their servers.

D.5.g. Treatment Timetable

CCBT and RCBT will begin and run concurrently, with each subject receiving 10 treatment sessions during a 12-week period. The first week of treatment is labeled week 1; sessions are scheduled by week of treatment. Session 1 takes place during week 1 and at the end of that week denotes one week of treatment, whether it be CCBT or RCBT. Stated differently, irrespective of the actual number of treatment sessions received, all patients will be considered to have completed an amount of treatment in weeks equal to the number of weeks since the initial treatment session (Session 1). For example, at the start of week four, a patient receiving CCBT will have completed three weeks of treatment. Similarly, at the beginning of week 12 the patient would be considered as having completed 11 weeks of treatment, and be ready for the 12-week assessment at the end of the week.

D.6. Training and Supervision of Therapists

D.6.a. Therapists

Therapists (n=6-8) will be masters' level trained psychotherapists who are familiar with and already practice CBT. For subjects recruited in California, the therapists will reside in California; for subjects recruited in North Carolina, therapists will reside in North Carolina.

D.6.b. Supervisors

All therapists administering the CBT online will receive baseline training by Clive Robins, PhD, Professor of Psychology at Duke University Medical Center, a member of the Academy of Cognitive Therapy, and a diplomat in Cognitive Behavioral Therapy from the American Board of Professional Psychology; Dr. Robins has broad experience conducting psychotherapy clinical trials. Michelle Pearce, PhD, will oversee the training of therapists in RCBT. Dr. Pearce a young Duke faculty member, trained in psychology at Yale University, who is Assistant Professor of Psychology in the Department of Psychiatry and Behavioral Sciences at Duke University Medical Center. Rebecca Propst, PhD, who led the original religious CBT study,[220] will serve as a consultant to Dr. Pearce as she develops the manual, and trains and supervises

therapists. In addition to being a certified CBT therapist, Dr. Propst is also certified as an interpersonal psychoanalyst, trained at the White Institute in New York City, and has over 20 years experience supervising and training therapists both in a PhD program (Ohio University) and in an MA academic program (Lewis and Clark College).

D.6.c. Preliminary Preparations

Dr. Robins and Dr. Pearce will each see one practice patient using the internet/phone protocol to get a feeling for what this is like and to iron out difficulties that may arise with online or telephone therapy. Prior to the single day of onsite training, efforts will be made to prepare therapists for the training, including methods of therapy delivery, development of materials, logistics, etc. Finally, on the afternoon prior to the On-site Training (see below), Drs. Robins, Pearce, and Koenig will meet with co-investigators from the University College of London Clinical Trials Unit (Priment) and GAMC's Quality Assurance & Monitoring Division, and a representative from PsychologyOnline and David Rosmarin (administrator) (via conference call) to discuss the protocol and go over issues related to the online and telephone psychotherapy.

D.6.d. On-site Training

All therapists will receive initial baseline training together onsite at Duke in conventional CBT led by Dr. Robins. During this time therapists will receive a brief refresher course on CBT for depression, be provided with specific examples, modeling, will be taught the techniques of online CBT and telephone CBT, and will be allowed to practice each of these modalities. The group will then break up into two groups (those doing the CCBT and those doing the RCBT), each receiving additional training of similar duration in their respective modalities. The therapists assigned to the RCBT treatment arm will receive training in RCBT by Dr. Pearce; those assigned to the CCBT arm will receive additional training by Dr. Robins (during that time, attention will also be paid to working out a sensitive strategy to gently avoid discussing religious issues during the therapy). In this session, members of each group will get to know one another and their supervisor, since they will be involved in supervision as a group throughout the trial (so that therapists can learn from each other).

D.6.e. Off-site Training

After the onsite training, therapists will do one training case from start to finish, in which they proceed through the protocols with an actual patient; during this time, they will receive weekly or bi-weekly group supervision by telephone conference call with their supervisor (Pearce or Robins). This training will check for adherence to protocols, discuss alternative ways of adhering to protocols, answer questions, and provide help with difficult issues. An average of 40 or higher on the Cognitive Therapy Scale[221] will be required for qualification as a study therapist, based on ratings by their supervisor (based on practice sessions documented by transcripts of online sessions and audiotapes of telephone sessions).

D.6.f. Supervision During the Trials

During the trial, Dr. Robins will supervise the three or four therapists delivering conventional CBT and Dr. Pearce will supervise the three or four therapists providing religious CBT. Therapists will have weekly or bi-weekly group supervision done via phone conference call with their supervisor until all therapists have completed at least one subject. After this, group supervisions will occur monthly until supervisors determine that therapists are comfortable and

competent delivering the online and telephone CBT. This will be kept flexible, though, with the goal of ensuring that therapists follow the protocols, deal with difficulties, and stay with the protocols. Ad hoc groups and/or individual supervision times will be held as necessary. The frequency of and time involved in supervision times will be recorded and if significantly different between groups, will be addressed in the analysis.

Group supervision of therapists during the trial will consist of 1.5-hour sessions with their respective supervisors. While group supervision sessions during the trial will be done separately for religious and conventional CBT therapists, Drs. Robins and Pearce will regularly consult with each other to ensure that supervision and handling of problems are similar. For therapists delivering RCBT to patients from non-Christian religious traditions, members of the Interfaith Advisors Council will assist Dr. Pearce in supervising therapists using versions of the RCBT manual for the patient's specific faith tradition (Jewish, Muslim, Hindu, and Buddhist).

D.7. Quality Assurance

D.7.a. Overview

To ensure that subject recruitment complies with the protocol and all therapists conduct the therapy in the same manner, quality assurance (QA) procedures that cover administration of both recruitment/assessment and CBT treatments are critical to the success of a complex trial such as this one with multiple recruitment sites and therapist-subject modes of communication. In particular, QA procedures are necessary to guarantee (1) consistent standardized administration of the CBT treatments, and (2) reliability defined as consistent standardized assessment of the primary and secondary endpoint measures. Without QA procedures, the potential for variability increases, with no *a priori* guarantee that if differences are found, they are not the result of divergent administration of the treatment protocol at the individual level. Hence, by enhancing reliability of assessment and administration of treatment, QA procedures are essential to securing valid data and, ultimately, to interpreting the findings from the trial.

Ordinarily, QA would occur by a group independent and separate from the clinical trial coordinating center (QAMD), the site recruitment and enrollment groups (Duke and Glendale), and the steering committee. However, in this feasibility study, cost constraints prohibit hiring an independent and separate group specifically for this purpose. Instead, a QA Committee will be established. The QA Committee will consist of the following: Harold G. Koenig, M.D., co-Chair of the QA Committee and PI; Larry Ereshefsky, PharmD, co-Chair of the QA Committee with Dr. Koenig; Bruce Nelson, QAMD Administrator; Drs. Clive Robins and Michelle Pearce, CBT supervisors; Noha Daher, DrPH, project statistician; and Lee Berk, DrPH, immunology consultant. The QA Committee meetings will occur at least every two months (spaced appropriate to the implementation of study tasks), in conjunction with Steering Committee meetings (see Section D.12.b) via teleconference. Teleconferences will take place before enrollment of study subjects for Phase I and II, during implementation of Phase I and II, and at the end of Phase II, as well as at other times as necessary. The QA Committee as described above is deemed appropriate for the scope and size of the proposed study.

Specifically, the QA Committee will perform quality control and assurance checks for the proposed study, including 1) monitor patient enrollment, i.e. eligibility checking, monitoring protocol accrual, etc.; 2) perform quality control of forms and database documentation to maintain data integrity; 3) audit

delivered treatment and a review of subjects' responses to treatment; 4) provide verification of interviewers' and CBT therapists' compliance to protocol; and 5) develop recommendations for protocol amendments. The QA Committee will maintain a written cumulative operations log. The operations log will document decisions that affect the treatment protocol.

D.7.b. Site Screening, Enrollment, and Outcome Assessments

In charge of the day-to-day QA operations will be the Trial Coordinating Center (QAMD). The Coordinating Center places QA procedures at the heart of site implementation of the protocol, thereby maximizing site attention and allegiance to QA while at the same time minimizing costs and administrative inefficiencies associated with centralized QA monitoring. The Coordinating Center will monitor the conduct of the study, both via off-site telephone and Internet connections and via onsite visits to recruitment and trial supervision sites (Glendale and Duke). During the study, information recorded in the data forms will be verified against source documents. Before enrolling any subjects in the study, the Coordinating Center personnel will review the protocol, treatment manuals, assessment administration booklets, data forms, instructions for completion of the data forms, the procedure for obtaining informed consent, and the procedure for reporting adverse events (AE) or serious adverse events (SAE).

The Coordinating Center will also ensure that site PIs, interviewers, data technicians, CBT supervisors, and therapists are trained according to the protocol and study procedures. The training includes (1) study materials, (2) a one-day onsite training session at Duke, (3) certification that site PI's, study coordinators, interviewers, and data technicians are familiar with and trained in all protocol procedures, and (4) certification that therapists are sufficiently trained and competent in the CBT intervention that they deliver. Materials for review sent out in advance of the group training session include treatment manuals, assessment administration booklets, and data forms. The agenda for the centralized onsite training session includes (1) an overview of the study protocol, study organization, and staffing requirements; (2) detailed training on study procedures, including recruitment and screening, randomization, regulatory requirements, adverse events, data collection procedures and quality assurance; and (3) training on the delivery of the CBT and administration of the study instruments.

For screening, recruitment, and study enrollment, the Coordinating Center uses a "training of trainers" (TOT) model to train site supervisors so that they, in turn, train and supervise the interviewers and study data technicians at their sites. "Trained trainers" leave the centralized training with an in-service manual for each of their respective sites. For intervention delivery, supervisors and therapists (present at the onsite meeting) will leave with a manual of the study protocol, study procedures, and their respective CBT manuals.

D.7.c. Therapist certification and skill level
CBT supervisors will send a minimum of three online session transcripts/audiotapes of telephone sessions with volunteer or feasibility study patients to QAMD for review for certification. Certification will be based on successful completion of a CBT knowledge test, demonstrated ability to adhere to the treatment protocols as described in the CBT manuals, and a score of 40 or higher on the Cognitive Therapy Rating Scale (based on rating by supervisor). The CBT supervisors will be certified by the Coordinating Center prior to training therapists during the onsite training session.

The CBT supervisors (Robins and Pearece) will train therapists on the content and procedures for their specific form of CBT and have contact with therapists on a regular basis to review adherence to treatment protocols and to answer questions about session content and flexibility. CBT sessions are recorded via copies of transcripts of online sessions and audiotapes of telephone and Skype sessions throughout the trial. After each session, CBT therapists complete a checklist indicating the topics and skills that were introduced, reviewed or used in the session.
Also after each session, therapists will download transcripts of the online sessions into Microsoft Word. Therapists will de-identify the transcripts (remove patient names) in the Word document prior to sending, via secured e-mail, the transcripts to QAMD and the CBT supervisors.

For telephone and Skype sessions, each therapist will utilize InterCall toll-free 800 conference call line, one line per therapist. The 800 number includes a recording capability. During Skype sessions, therapists and patients will also call the 800 number to record the audio portion of the Skype session. The Coordinating Center will access the recorded telephone sessions through InterCall's website, which can then be transcribed.

The Coordinating Center will pre-select 10% of CBT transcripts and audiotapes for QA review using an algorithm designed to ensure variation in the focus, content, and types of sessions reviewed (e.g., online vs. telephone) and to minimize the potential for selection bias. Independent CBT specialists will then be assigned by the Coordinating Center to review these online and taped telephone sessions using structured forms to rate adherence, competence and flexibility. See fidelity assessments below.

To identify problems early in the startup phase of the trial, this 10% sample will be front-loaded, that is, more transcripts/tapes will be reviewed from earliest sessions. CBT therapists who receive unsatisfactory ratings for adherence or competence by site supervisors or transcript reviewers for three sessions will not be assigned additional subjects and replaced.

D.7.d. Therapy fidelity
As noted above, a 10% random sample of the therapy transcripts (a record of the actual text messages and transcripts of audio-taped telephone sessions) for each subject will be reviewed for quality and adherence to protocol by CBT experts independent from the study and blind to the study hypotheses. Lack of adherence to the CBT protocol will be reviewed with the therapist by their supervisors (Robins or Pearce) to avoid future deviations. Transcripts will be rated for overall competence (Cognitive Therapy Scale, see above) and protocol compliance (using an Adherence Rating Scale developed for this study, based on completion of predetermined procedures for the therapy session).[222] Therapists will also keep an ongoing record of subjects' compliance with homework assignments.

D.7.e. Regular Teleconferences

Uncertainties regarding how to administer the protocols are certain to arise. Members of the Steering Committee (see Section D.12.b) will engage in regular teleconferences. Using the teleconference mechanism, a set of precedents will be established regarding how best to manage situations that call for screening and enrollment of subjects, and flexible administration of the CBT protocols. In turn, this set of precedents will contribute to the development of a cross-site common culture, which will insure that screening procedures and assessments are administered in the same fashion at all sites, and CBT supervisors are training and supervising therapists in a similar fashion.

D.8. Study Endpoints

D.8.a. Primary Endpoint

Depressive symptoms. Beck Depression Inventory (BDI)-II score at baseline, 4 weeks, 8 weeks, 12 weeks (end of trial), and 24 weeks.[223] The BDI is a 21-item self-report depression inventory, one of the most widely used instruments for assessing severity of depressive symptoms, especially in studies of medical patients. It is particularly useful for studies examining depression course in response to CBT (both developed by Aaron Beck originally). Symptoms of depression assessed by this scale include hopelessness, loss of interest, irritability, guilt or feelings of being punished, and physical symptoms such as fatigue and weight loss. Three versions of the BDI exist. The original BDI was first published in 1961 and later revised in 1978 as the BDI-1A, and then again in 1996 as the BDI-II.[224] A value of 0-3 is assigned to each of the 21 questions resulting in a score range from 0 to 63. Standard cutoff scores are as follows: 0–9 indicates no significant depression; 10-15 indicates mild depression, 16-40 indicates moderately severe depression, and 40-63 indicates severe depression.

D.8.b. Secondary Endpoints, Mediators, Moderators, and Controls

With the exception of genetic analyses, medical co-morbidity, religious activity, suicidal thoughts, and therapeutic alliance, all measures will be assessed at baseline, 12, and 24 weeks. Genetic analyses, medical co-morbidity, and religious activity will be assessed at baseline only; suicidal thoughts will be assessed at baseline, 4, 8, 12, and 24 weeks; and therapeutic alliance will be assessed at 4, 8, and 12 weeks.

In some cases, secondary endpoints will also serve as mediators (gratitude, generosity, optimism, purpose in life, daily spiritual experiences, social functioning, physical functioning, therapeutic alliance) to explain the intervention's effects on the primary endpoint and at other times as moderators of that effect (religiosity). Again, we acknowledge that this study (Phase II) has very little power with 60 subjects to identify mediators of the effect (assuming there is an effect), although trends should be identifiable for future confirmation. Nevertheless, we think these are the primary mediators for effects on depressive symptoms that are observed.

Secondary Endpoints/Mediators

Gratitude. The Gratitude Questionnaire is a 6-item measure of general thankfulness and gratitude (GQ-6).[225] Each item is assessed on a 7-point scale from strongly disagree to strongly agree, and so has a score range from 6 to 42. Internal reliability is acceptable and ranges from 0.76 to 0.84. The scale is being used in medically ill patients in several studies, but results have not yet been reported. The GQ-6 has been used in PTSD and found to be associated with greater well-being in war veterans.[226] To our knowledge, the GQ-6 has not been previously used in depressed medical patients.

Generosity. The Interpersonal Generosity (IG) Scale is a 10-item measure that assesses generosity in terms of attention, compassion, openhandedness, self-extension, courage, and verbal expression.[227] Each item is rated on a 1-4 scale, and so has a score range from 10 to 40. The IG scale has a high internal reliability (0.87). To our knowledge, the IG-10 has not been used previously in depressed medical patients.

Optimism. The Life Orientation Test-Revised (LOT-R) is a 10-item measure of dispositional optimism[228] that has been used extensively in psychological research and predicts improved medical outcomes in primary care patients, independent of depression and personality traits.[229] The 10 items are scored on a scale from strongly disagree (0) to strongly agree (4), and has a score range from 0 to 40.

Purpose in Life. The Purpose in Life (PIL) Test is a 20-item self-rated scale assessing meaning and purpose of life, based on the work of Victor Frankl.[230] Items are rated on a scale from 1 (completely bored) to 7 (exuberant, enthusiastic), resulting in a score range from 20 to 140. Since its development in 1964, the PIL has been the standard measure of this construct and used in many, many studies, including studies of medical ill populations. Internal reliability is high (0.91).[231]

Social Functioning. Social functioning will be measured using the social interaction and subjective support subscales of the Duke Social Support Index (DSSI).[232] The 11-item brief version of the DSSI asks about time spent interacting with friends, neighbors, and family, both in person and on the telephone, and also assesses the subject's satisfaction with social interactions and support received. The brief DSSI has been validated in adults with chronic medical illness,[233] and has a score range of 11 to 33. In a sample of 413 consecutively admitted medical inpatients over age 50 at Duke Hospital with major depression the average score was 25.8 (SD 4.3).[234]

Physical Functioning. Physical functioning will be measured using the 12-item Duke Activity Index, which assesses both physical and instrumental activities of daily living (ADLs) on a 1 to 3 scale (unable to do, able to do but hard, able to do and easy).[235] Scores on this scale correlate strongly with peak oxygen uptake in medical patients undergoing exercise testing (correlations 0.58-0.80). The score range is 12 to 36, with higher scores indicating better physical functioning. As noted in section D.3.b., medical patients at Duke Hospital with major depression score an average of 15.6 (SD 3.3) on this scale (unpublished data).

Spiritual Experiences. Daily spiritual experiences will be measured using the 16-item Daily Spiritual Experiences Scale.[236] This is a widely used scale to measure spiritual experiences and has been used in community samples and medically ill samples of all ages. Each item is scored from 1 to 5 ("never" to "many times a day"), and total score ranges from 16 to 80. Test-retest, inter-rater, and internal consistency reliability (Cronbach's alpha>0.93) are all acceptable. As noted in D.3.b., among 838 medical patients at Duke Hospital aged 50 or over, average score was 61.0 (SD 12.1).[237]

Therapeutic Alliance. The 19-item revised Penn Helping Alliance Rating Scale[238] is one of the most widely used measures of therapeutic alliance in the field[239] and has the highest correlation with outcomes for CBT of all six therapeutic alliance scales in the literature.[240] Each item is rated on a 6-point scale from 1 to 6 ("I feel strongly it is not true" to "I feel strongly it is true"), with a range of 19 to 114.

Other Secondary Endpoints

Immune/Endocrine Assessments. Blood and 12-hour urine samples will be collected at baseline, 12, and 24 weeks to assess inflammatory markers and stress hormones, respectively. Stress hormones measured will include norepinephrine and epinephrine, to assess sympathetic nervous system activity, and cortisol to evaluate hypothalamic-pituitary-adrenal activity. 12-hour overnight urinary collections will provide a better time-integrated view of the activation of stress pathways than isolated fluctuating serum levels, and collection of samples overnight should increase compliance with sample collection. Immune mediators to be assessed include TNF-α, IFN-γ, IL-1β, IL-1ra, IL-2, IL-4, IL-6, IL-17, and CRP. Collectively, these variables should provide a good index of immune reactivity, and were chosen for study based on reports of their association with major depression and/or their link to religious involvement. Measures of lymphocyte functioning were also considered (NK cell activity and lymphocyte proliferation), although these tests were prohibitively expensive for this feasibility study ($350-400 per test).

Genetic Assessments. A blood sample will be collected at baseline only for genetic analyses. The following polymorphisms will be analyzed in all subjects (assuming consent): **(1)** 5-HTTLPR and rs25531 at the serotonin transporter gene (5HTT), **(2)** rs6295 at the 5-HT1A receptor gene (HTR1A), and **(3)** uMAOA-VNTR polymorphism at the MAOA gene. These are well-known genetic markers that can be assessed by standardized molecular procedures based on PCR reactions and conventional electrophoresis techniques.

Other Measured Variables (moderators, controls, monitoring variables)

Intrinsic Religiosity (moderator). Will be measured using the 10-item Hoge intrinsic religiosity scale.[241] Response options for each item are 1 to 5 ("definitely not true" to "definitely true") with a score range of 10 to 50. The scale has both high internal reliability (Cronbach's alpha 0.87, same in two separate populations) and test-retest reliability (91% agreement after a six-week interval).[242] A high correlation was found between scale scores and ministers' judgments (r=+0.59). When the 10-item scale was administered to 458 medical patients at Duke Hospital, it demonstrated acceptable internal reliability (Cronbach's alpha 0.83); among 87 depressed patients, average score was 39.4 (SD 8.2) and baseline score predicted faster remission of depression over 11-month follow-up.[243]

Religious Attendance and Private Religious Activity (moderator). Two questions from the 5-item Duke University Religiosity Index[244] will be used to measure these variables. For religious attendance (adapted to chronically ill disabled patients), the question is "When you were physically able, how often did you attend religious services or other religious meetings?" Response options are 1 to 6, from "never" to "more than once a week". For private religious activity, the question is:" How often do you spend time in private religious activities, such as prayer, meditation or scripture study?" Response options are 1 to 6, from "rarely or never" to "more than once a day." Among 455 medical patients at Duke Hospital, average religious attendance (present attendance) was 21% for more than weekly and 33% for weekly; for private religious activities, average frequency was 12% for more than once a day and 46% for daily.[245]

Medical Co-Morbidity and Illness Severity (control). The Charlson Comorbidity Index (CCI) will be administered at the screening evaluation only to identify chronic medical illnesses and the determine degree of medical co-morbidity.[246] The CCI asks about 31 categories of illness based on the International Classification of Diseases, 10th edition. The CCI assigns "weights" to each active medical diagnosis in order to determine a total co-morbidity score, which has been shown to strongly predict 1-year mortality. The Cumulative Illness Rating Scale (CIRS) is a 12-item measure that assesses severity of impairment for 12 major organ systems.[247] Impairment of each organ system (cardiac, vascular, respiratory, EENT, upper GI,

lower GI, hepatic, renal, other GU, musculoskeletal, neurologic, and endocrine-metabolic) is rated on a 0 to 4 scale (0 none, 4 extremely severe), with a scale score range from 0 to 48.

Suicidal Thoughts (monitoring). The MINI has a module that assesses suicidal thoughts as part of the baseline evaluation. It also has a separate scale, called the MINI Suicide Tracking Scale (STS) that can be used to measure suicidal ideation during follow-up.[248] This 8-item measure is brief enough to be administered regularly to monitor patients for significant suicidal ideation that would trigger our Suicide Protection Plan (see section E.3.d.).

D.8.c. Premature Withdrawal, End-of-Study Debriefing and Referral Options

All prematurely terminating subjects who receive open treatment outside the study will be asked/expected to return for the full assessment batteries. Some patients may exhibit transient worsening at an assessment point, but in the judgment of the therapist (and study psychologist, as necessary) warrant continuation in the study. Should severe worsening occur, or development of active suicidal thoughts or behaviors, then subjects will be withdrawn from the study. There are no procedures for maintenance of treatment following premature withdrawal from the study or at the end of the 10 sessions of the online and/or telephone CBT intervention. Hence, ethical principles require that at study withdrawal or end of the treatment period, all participants be given recommendations for any indicated further treatment and appropriate referrals. To standardize this process across therapists, we will use a standardized debriefing script. Briefly, this script will a) provide the subject a chance to state any concerns or questions they have; b) provide a summary of progress using clinical indicators; c) outline the possible available treatments; and d) make recommendations about appropriate continuing treatment.

In a standardized manner, each subject will be given an end-of-treatment (or study termination) recommendation score of 1, 2 or 3 as follows:
Level 1: Participants who are well, i.e., do not need further treatment for depression, receive a recommendation to discontinue all treatment unless (1) in the opinion of the therapist continued treatment is indicated, for example, because of a history of relapse or (2) there is a strong subject preference for continuing treatment
Level 2: Participants who are mildly ill or who require treatment for other emotional conditions will receive a recommendation (as appropriate clinically) to continue psychological treatment for MDD and to add other treatments if necessary.
Level 3: Participants who are moderately ill or worse will receive whatever recommendation the therapist (in consultation with study psychologist and psychiatrist Dr. Koenig) deem clinically and ethically appropriate. All end-of-treatment recommendations will be coded for data entry.

All subjects needing or requesting further treatment will be given a list of possible providers for the recommended treatment and will be told that a clinical report could be sent with the subject's authorization to any new treatment provider(s).

D.8.d. Subject Safety and Adverse Events Reporting

An adverse event (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person in a research study. The event does not need to be causally related to the research study. Site coordinators will only record adverse events and serious adverse events that pertain to suicide attempts or complete suicide. Site coordinators will record all serious adverse events (SAE) on source documents and data forms, as well as complete appropriate serious adverse event reporting forms and forward to the Coordinating Center (QAMD) (and each site's representative IRBs) within the required time frame for reporting, but in no case beyond these time frames. SAEs will be reported to the Coordinating Center within 24 hours of occurrence via fax or e-mail with a written report submitted within seven (7) calendar days. The PIs will follow up on all SAEs until the events have subsided or until the condition has stabilized. The Coordinating Center will maintain detailed records of all SAEs reported by the site coordinators in accordance with good clinical practice and applicable regulations.

D.9. Assessment Instruments and Procedures
Screening, baseline assessment and follow-up assessments are described below.

D.9.a. Screening Assessment
Primary care physicians in the outpatient practices at Duke Health Systems in central North Carolina and the physician networks of Glendale Adventist Medical Center in Los Angeles County will be alerted to the study by in-person meetings. Flyers will be posted in their offices and rooms. Promising patients will then be referred to the project coordinator at each site. As necessary, project personnel will screen consecutively admitted hospitalized patients at the bedside for eligibility, and hospital staff will be notified about the study, flyers posted, and referrals requested. Pre-screening will occur either by telephone, in the clinic, or at the bedside in the case of hospital inpatients using the telephone script. The screening evaluation will include an initial explanation of the study. If the patient is determined eligible based on the prescreening telephone script , then a time to meet in-person will be arranged with the study staff for the patient to review the informed consent and discuss the study related procedures in depth. Once the patient signs the informed consent the in-person screening evaluation will occur. . Screening evaluation will consist of the following:

- Brief Mini-Mental State Exam (12 items)
- MINI Neuropsychiatric Interview (15 min)
- Beck Depression Inventory-II (21 items)
- Importance of religion (1 item, at least somewhat important)
- List of chronic illnesses (31 disorders based on Charlson Co-Morbidity Index)
- Duke Activity Status Index (12 items)
- List of prescription and over-the-counter medications
- History of antidepressant use (3 items)
- History of psychotherapy (3 items)

D.9.b. Baseline Assessment Following Enrollment
The Baseline Assessment will occur immediately following the screening evaluation to determine if the patient meets the eligibility criteria. Patients that meet the eligibility criteria will proceed with the collection of blood for the genetic and immune analyses and complete the baseline evaluations if time allows (patients will have the opportunity to complete any uncompleted baseline evaluations when they return with their urine specimens). The patient will be instructed how to collect the baseline 12 hour urine specimen for endocrine analyses. The patient will be instructed to return to DUKE or GAMC to deliver the urine specimen and complete any baseline evaluations required. Once the patient completes all the baseline assessments and all the baseline blood and urine specimens have been collected per protocol, the patient will be randomized into the study.. The baseline evaluation will consist of the following measures:

- Demographics
- Purpose in Life Test (20 items)
- Life Orientation Test (10 items)
- Gratitude Questionnaire (6 items)
- Generosity Questionnaire (10 items)
- Brief Duke Social Support Index (11 items)
- Cumulative Illness Rating Scale (12 items)
- Daily Spiritual Experiences (16 items)

- Self-rated religiosity (1 item)
- Intrinsic Religiosity (10 items)
- Public and Private Religious Activity (2 items)
- Brief RCOPE (14 items)
- List of chronic illnesses
- List of medications
- BDI-II will be repeated at baseline if more than 5 days have lapsed from screening visit

D.9.c. Follow-up Assessments During and After Trial

During Trial. Once patients have completed 4 and 8 weeks of therapy, therapists will contact the Coordinating Center upon completion of the therapy sessions. The Coordinating Center will then notify the study personnel (blind to treatment group). Study personnel will then contact subjects by telephone to complete the following:

- Beck Depression Inventory-II (21 items)
- Penn Helping Alliance Rating Scale (19 items)
- MINI Suicide Tracking Scale (8 items)

After Trial. Once patients have completed 12 and 24 weeks of therapy, therapists will contact the Coordinating Center upon completion of the therapy sessions. The Coordinating Center will then notify the study personnel (blind to treatment group). Study personnel (blind to treatment group) will contact subjects to schedule in-person follow-up evaluations, ensure that they have adequate urine collection supplies, and then re-contact them the night before the scheduled evaluation to remind them to complete the overnight 12-hour urine collection. Blood for immune analyses will be collected during the in-person meetings. The follow-up evaluation will consist of the following:

- Beck Depression Inventory (21 items)
- Penn Helping Alliance Rating Scale (19 items)
- Purpose in Life Test (20 items)
- Life Orientation Test (10 items)
- Gratitude Questionnaire (6 items)
- Generosity Questionnaire (10 items)
- Brief Duke Social Support Index (11 items)
- Duke Activity Status Index (12 items)
- Daily Spiritual Experiences (16 items)
- Brief RCOPE (14 items)
- Mini Suicide Tracking Scale
- Final questions

These data will be entered at each site into OpenClinica. The Coordinating Center will track BDI completion to ensure that these are completed in a timely manner. Enrollment site personnel will make three attempts by phone to contact the subject to set up these evaluations. After three unsuccessful attempts by phone, site personnel will contact the subject's "other contact" person identified during the baseline evaluation (relative or friend who will always know where the subject is). After two unsuccessful attempts to reach the other contact person or two failed attempts to contact the subject based on information from the contact person, the subject will be send a certified letter. If the subject

does not respond within one week of the certified letter mailing, the subject will be considered lost to follow-up and withdrawn from the study.

D.9.d. Assessment Procedures for Immune/Endocrine Measures

Collection of Samples

Blood samples will be collected by venipuncture for laboratory testing, with proper specimen identification, handling and shipping, while ensuring participant and staff safety. Blood will be collected to evaluate cytokines and inflammatory markers. Urine will be obtained for cortisol and catecholamines. Strict adherence to standard operating procedures (SOP) will ensure quality laboratory results. Obtaining sufficient volume of blood in the proper collection tubes containing correct subject bar-coded IDs is essential. Mislabeled specimens can jeopardize the outcome of the laboratory results, causing incorrect participant management or the discarding and thus loss of specimens with ambiguities that cannot be resolved. The Loma Linda laboratory receiving the specimens will notify the study staff if inadequate specimens are received, so that corrective action may be taken if possible. Such specimens include those in poorly labeled tubes, insufficient specimen volume, or inadequate specimens.

A trained nurse or phlebotomist will draw blood into three 10-ml red and gray striped (tiger)-topped serum separator tubes (SST) using standard protocol. In addition, one additional tiger-top tube will be drawn on every 6th or 7th patient for quality control purposes (as be Loma Linda lab protocol). One tube will be needed for every 3-4 ml of serum needed; two aliquots of 0.5 ml needed for each analyte for a total of 8 ml of serum. After verifying the identity of the participant, the vacutainer tubes will be labeled by study name and participant identification number. The date and time of blood draw will be recorded using a 24-hour clock, and placed on the specimen label. Samples will be allowed to clot in an upright position for 30 minutes (no longer than 1 hour), and then centrifuged for 20 minutes at 2000-3000 rpm in a refrigerated centrifuge set at 4 ºC to separate serum from the rest of the blood components and aliquoted into sterile – labeled microfuge tubes so that individual cytokines can be assayed without concern of freeze thaw effect (store at -80 deg C). The aliquoted specimens will be kept at -80°C until they are packaged for shipping. All blood samples will be shipped to the Neuroimmunology Research Laboratory via overnight delivery using Federal Express as the courier. Specimens will be batch sent at the end of each phase. Samples will be accepted at the Laboratory on Tuesday-Friday only.

Stress pathway activity will be assessed by measuring the concentrations of cortisol, norepinephrine and epinephrine in 12-hour, overnight urine samples collected from subjects at baseline, 12 and 24 weeks. With regard to urine collection, participants will be mailed the collection kit with instructions on how and when to collect each urine sample, and how to store the sample until it is returned to the clinic. Prior to sample collection, participants will receive a reminder call, instructions for urine collections will be reviewed with participants, and participant will be able to clarify any questions pertaining to sample collection. Over-the-phone instructions will be scripted to ensure accuracy and consistency of procedures. Subjects will be instructed to void into the toilet and then record the time of the void as the start of the 12-hour collection. All subsequent voids for the next 12 hours will be collected and transferred to the urine collection container. Samples will be returned to the clinic at the participant's scheduled appointment. Participants will be asked whether they were able to collect all urine or if some fraction was inadvertently discarded. If the sample is reported to be incomplete, if it was not refrigerated throughout the procedure, or if the volume is less than 1 liter (or minimal amount necessary), the subject will be asked to repeat the collection, and return it the next day. Total urine volume and total time for

sample collection will be determined and recorded. Up to six aliquots containing 4 ml of samples per vial will be prepared in cryovials – 2 samples to assess cortisol concentration, 2 samples (pH 2-3 by adding hydrochloric acid) to assess catecholamines (norepinephrine and epinephrine), and 2 samples to serve as quality controls in randomly selected participants.

Certain medications and foods, alcohol intake, smoking, and level physical activity may affect accurate measurement of stress hormones and immune parameters. Participants will be advised on these factors and asked to follow our guidelines for sample collection. Participant compliance with our guidelines will be ascertained at collection in order to assess the quality of the samples. The use of medications will be disclosed at the time of collection and data analysis will determine whether they have an effect on analyte concentrations in our study. Similarly any concurrent known acute infectious disease will be disclosed so that these subjects can be excluded from the analyses at that time point.

Packaging and Shipping. Blood samples will be shipped in leakproof vacutainer tubes using a standard operating procedure that ensures safety of staff and sample integrity until samples can be appropriately stored by the clinical testing laboratories, according to federal regulations (Department of Transportation, IATA) and the guidelines set forth by Federal Express for shipping biological category B substances within the United States. Vacutainer tubes will be packaged with biohazard labeling (absorbent material and waterproof plastic bag to protect primary receptacle and absorb any fluids should the primary receptacle leak). Either the primary or secondary package must be capable of withstanding, without leakage, an internal pressure producing a pressure differential of not less than 95 kPa. Absorbent material (desiccant) will be placed between the primary receptacle and the secondary packaging. Sturdy outside packaging constructed of corrugated fiberboard (cardboard), wood, metal or plastic will be used. Exterior package must be capable of passing a drop test of at least 1.2 meters, and must contain an "air eligible" requirement. Prior to packaging gel packs will be refrigerated for at least 48 hours.

Study staff will freeze aliquoted urine samples and will store aliquoted speciments at -80 degrees Celsius until they are packaged for shipping. The packaged specimens will be packed on dry ice for express overnight transport and delivery by Federal Express to the Neuroimmunology Research Facility at Loma Linda University. Study staff will follow manufacturer's instructions for packing materials used, and comply with all DOT/IATA shipping regulations, as described above. Upon arrival samples will be logged in, inspected for sample integrity, and then stored at -80 ^{o}C until assays for stress hormones are performed. Logs will be used to track samples from each participant in various stages of sample collection, storage, processing, and data collection. Samples will be maintained for the study period, or until exhausted.

The courier will be called when the specimens are ready for batch shipment, and study personnel will follow-up to ensure that the courier picks up the specimens, that recipients of the shipment are notified, and will track the shipping of samples in-route to the testing laboratory. The airway bill will include the name and telephone number of the responsible person. This person will be knowledgeable and accessible 24/7. The mailing form will be placed in the shipping pouch (address window), and the barcode numbers will be affixed to the blood tubes. Multiple patient samples may be shipped together in the same box with proper sample labeling. A copy of the Specimen Collection and Procession Form will be placed inside a waterproof bag along with the samples. Study personnel will ensure that each blood tube is labeled with the participant's ID; collection date, time and initials of the phlebotomist;

name of sending lab. All samples will be sent to Dr. Denise Bellinger, Ph.D., Department of Pathology and Human Anatomy, Loma Linda University School of Medicine.

Analysis of Immune Markers and Stress Hormones

All immune / inflammatory markers (TNF-α, IFN-γ, IL-1β, IL-1ra, IL-2, IL-4, IL-6, IL-10, IL-17, and CRP), cortisol and creatinine will be determined by ELISA kits with the highest sensitivity commercially available. R&D Systems High Sensitivity (HS) ELISA's for TNF-alpha, IL-1B, IL-4, IL-6, but it is not available from this company for IFN-gamma, IL-2 or CRP in HS Kits. eBioscience carries HS kits for human, IL-2, IL-10 and IFN-gamma, and C-Reactive Protein Ultra Sensitive ELISA Kit is available from Calbiotech. All ELISA kits used in this study employ the quantitative sandwich enzyme immunoassay technique. Briefly, a monoclonal antibody specific for the analyte has been pre-coated onto a microplate by the manufacturer. Standards and samples are pipetted into the wells and any analyte present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for analyte is added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of analyte bound in the initial step. The color development is stopped and the intensity of the color is measured using an ELISA plate reader set at the appropriate wavelength. Samples assessed by ELISA kits are run in duplicate along with duplicate standards that are used to generate a standard curve, according to manufacturer's instructions. The amount of analyte in the unknown samples are calculated from the standard curve, and expressed as a mean ± SEM of the two samples in pg or ng/ml as appropriate. If coefficient of variance between the duplicates is greater than 10%, then another aliquot of the sample will be thawed, and the ELISA repeated in this sample. Samples will be assayed in batches to limit any potential of inter-assay variability.

Urinary catecholamines will be determined by HPLC because of the accuracy and sensitivity of this method. Samples will be run in duplicate along with standards and quality control samples. Urine samples (200 µl) containing 1.0 ml of phosphate buffer (pH 7.0), 1.0 ml of 1.5 M (pH 8.6) Tris buffer and 50 µl DHBA (10 ng/ml) will be vortexed, 50 mg of acid washed alumina added, and the tubes were placed on a C10 platform shaker (New Brunswick Scientific, Edison, NJ) for 5 min at 175 rpm. Then, the alumina will be allowed to settle, and the samples aspirated until dry. The alumina will be washed with double-distilled H_2O three times, the resulting alumina slurry transferred to microfilterfuge tubes, and centrifuged for 2 min at 9,000 rpm. To harvest the catecholamines from the alumina, the alumina will be transferred to a new microfilterfuge tube, 200 µl of $HClO_4$ (0.1 M) added, and samples vortexed. The tubes will be centrifuged for 2 min at 9,000 rpm, and the supernatants collected. NE concentrations will be determined using HPLC with electrochemical detection with a CouloChem III HPLC System (ESA, Chelmsford, MA) and an ESA Model 542 autosampler. The mobile phase will be delivered at a flow rate of 1.0 ml/min through a Resolve C18 reverse phase 5-µm, 8x100-mm Radial-Pak analytical column (Canton, Massachusetts) using an ESA Model 582 solvent delivery module. The potentials of the guard cell and two detecting cells of the ESA CouleChem III coulometric detector cell system will be set at 400 mV, 350 mV, and -350 mV, respectively. The signal from the detector will be recorded and the peak heights and area under the curves analyzed using EZChrom Elite Software (Scientific Software Inc. Pleasanton, CA). Urinary catecholamine concentrations will be determined based on standards of known concentrations of norepinephrine and epinephrine, and expressed as µg/g creatinine to normalize for 12-hour urine volume.

Data Processing. The extracted blood and urine samples will be assigned a consecutive sample number, and identifying information provided on the sample will be replaced by a computer-generated bar-coded label. The link between the bar code and subject identifying information will be retained in a HPLC database at the Coordinating Center, as well as backed up in a secure server. No identifying information will be stored in analyte database at Loma Linda University. ELISA data can be exported directly from the computer readout from the Plate Reader Software into an Excel file, which can then be exported into SPSS. HPLC data will be inputted into an Excel spreadsheet. All ELISA and HPLC data will be securely sent electronically as an Excel or SPSS file from Loma Linda University to the Coordinating Center. These data will be examined and depurated prior to transfer to the main SPSS database

D.9.e. Assessment Procedures for Genotyping

Specimen Collection

After enrolling the subject in the study (i.e., written consent has been obtained and baseline interview completed), the Interviewer will immediately take subject to have his or her blood drawn (as described above for immune analyses). 3-4 milliliters blood will be collected in an EDTA (purple top) tube, followed by mixing well to avoid small clots from forming. Blood tube will be labeled with participant identifier number (not participant name). Blood may be stored at room temperature for up to 24 hours prior to shipment. Alternatively, blood can be stored at 4°C for up to 3 days or at –80°C for at least 2 years prior to shipment. We will not freeze blood in glass collection tubes. Blood may be frozen in 15 ml or 50 ml centrifuge tubes. We will store the blood samples at –80°C until shipping. Blood samples will be batched shipped to Johns Hopkins at the end of each phase of the study.

Packaging and Shipping

Using a kit with a pre-addressed mailer capable of transporting pre-labeled (already bar-coded) tubes for whole blood, research personnel will prepare the blood tube for shipping. Research personnel will complete the DNA Isolation Request form and enclose with specimens, and will follow manufacturer's instructions for packing materials used, complying with all DOT/IATA shipping regulations. Samples will be collected and stored at -80ºC, we will ensure that they remain frozen and are shipped on dry ice using standard shipment next day delivery via Federal Express (Monday, Tuesday or Wednesday) to the Fragment Analysis Facility, Johns Hopkins University, Baltimore, MD. Once the specimens have been sent, research personnel will email the tracking number to Laura Kasch (lkasch@jhmi.edu), and will request feedback when the sample arrives to ensure that it has been received intact.

Isolation of DNA

Once received at Johns Hopkins, the samples will be stored and run as a batch. The DNA will be isolated from blood using an established interface with the PUREGENE DNA purification system (Gentra systems, Minnesota, USA). The PUREGENE DNA Isolation Kit is a gentle DNA Isolation procedure that isolates DNA using detergents and salts. The PUREGENE DNA Isolation Kit does not contain any toxic chemicals and isolates DNA in high yield from a variety of sample sources. Briefly, the PUREGENE Kit isolates DNA by first using a hyptonic Red Blood Cell LysisSolution to selectively lyse red blood cells. Then, the Cell Lysis Solution lyses the white blood cells. RNA can then be removed if necessary using the RNase A Solution provided in the Kit. Then, proteins are precipitated and removed using the Protein Precipitation Solution. DNA is then precipitated out with alcohol, washed, dried and re-hydrated.

The extracted DNA sample will be given a consecutive sample number, and identifying information provided on the sample will be replaced by a computer-generated bar-coded label. The link between the bar code and subject identifying information will be retained in a DNA database at the Coordinating Center, as well as backed up in a secure server. Identifying information in this DNA database will be made available to principal investigator, and other designated laboratory personnel on a "need to know" basis. Records that identify subjects will be kept confidential as required by law. Samples will be maintained for the study period, or until exhausted. Samples will be stored at Johns Hopkins CIDR in a dedicated room, which will be locked at all times. The room is supported by back up power for both freezers and air conditioning and an alarm system will be monitored for freezer or air conditioning failures by engineering and maintenance. At the written request of the subject, samples and records can and will be destroyed.

Procedures for Genotyping

We understand that relevant genes and SNPs /polymorphisms are being identified every day. However, we plan in this pilot study to examine candidate genes involved in the pathways of serotonergic and monoamine neurotransmission. Purified genomic DNA will be screened for polymorphism genotypes of susceptibility loci by PCR reactions.

<u>HTTLPR Long and Short Alleles</u>. The human serotonin transporter (5HTTLPR) short and long alleles are PCR amplified using forward primer 5' TCTCCCGCCTGGCGTTGC-3' and reverse primer 5'-GCCGGTTGGGCTGAGCGTCT-3'. PCR is performed in a 10µl reaction consisting of 0.4 µM primers, 0.15 µM 7-deaza dGTP, 1X MasterAmp™ 2X PCR PreMix K, (Epicenter Biotechnologies, Madison, WI), 1 unit Taq DNA polymerase (Applied Biosystems, Foster City, CA), and 40 ng DNA. Amplification is carried out in a Veriti thermocycler (Applied Biosystems) for 4 min at 95°C, followed by 35 cycles of 94°C for 30 s, 62.8°C for 30 s, and 72°C for 30 s, followed by a final extension step of 72°C for 10 min. PCR products are resolved on 2% NuSieve (FMC BioProducts, Vallensbaek, Denmark), 1% agarose (Invitrogen, Carlsbad, CA) gels, and visualized by ethidium bromide staining. The short and long alleles are characterized by 515 bp and 560 bp products, respectively.

<u>HTTLPR A/G SNP (rs25531)</u>. Allelic discrimination analysis is used to genotype SNP rs25531 using primers and probes described by Hu, et al. PCR is carried out in 5µl volume with 20ng DNA, 0.48µM primers, 0.48µM VIC labeled G allele probe, 0.2µM FAM labeled A allele probe, 1X Master Mix (Applied Biosystems, Foster City, CA), and 4% DMSO (Sigma). Amplification and analysis is performed on an Applied Biosystems 7900HT Sequence Detection System. PCR conditions are 2 min at 50ºC, 10 min at 50ºC, followed by 45 cycles at 96ºC for 30sec and 66ºC for 60sec. Genotypess are determined using end-point analysis with SDS v2.1 software (Applied Biosystems).[249]

<u>MAOA uVNTR</u>. Primer sequences are MAO APT1 (5'- ACAGCCTGACCGTGGAGAAG-3') and MAO APB1 (5'- GAACGGACGCTCCATTCGGA-3') described by Sabol *et al*., The MAO APT1 was 5'-labeled with 6FAM fluorophore. PCR was carried out in 10ul containing 0.1uM primers, 0.1mM dNTPs (Amersham), 10mM Tris (pH8.3); 50mM KCL, 1.5mM MgCl, 0.6 units of Taq DNA polymerase (Perkin Elmer) and 40ng DNA. Amplification was carried out in a Thermo Hybaid MBS 0.2S (Needham Heights, MA) using the following cycling conditions: initial 4-min denaturing step at 94°C, followed by 35 cycles of 94°C for 30 sec., 58°C for 30 sec. and 72°C for 30 sec., followed by a final extension of 72°C for 10 min. PCR products were assayed on a 3730 DNA Analyzer (Applied Biosystems). Data is collected and analyzed with GeneMapper software (Applied Biosystems) that

calculates fragment length in reference to an internal lane standard (Genescan-500 labeled with LIZ) and quantitates the amount of fluorescence in each fragment.[250]

5-HT1A SNP rs6295. Genotyping of the rs6295 is carried out using a pre-designed TaqMan® SNP Genotyping Assay (Applied Biosystems, Foster City, CA) following manufacturers supplied protocols. PCR and endpoint detection of fluorescence is carried out in an ABI Prism7900HT Sequence Detection System (Applied Biosystems, Foster City, CA) using default settings. Fluorescence data is analyzed with ABI Prism 7900 allelic discrimination software.

The Coordinating Center will receive genotyping data from Johns Hopkins in an Excel or SPSS file. These data will be examined and depurated before transfer to the main database, what will take place once data from both databases are ready to be merged. An electronic copy of the entire database will be sent to our genetics consultants in Spain for statistical analyses.

D.9.f. Assessment Schedule During Intervention and Follow-up

Assessment schedule for subjects will be at baseline (full assessment with questionnaire data and laboratory specimens), 4 weeks from baseline (BDI, Penn, suicidal tracking only), 8 weeks (BDI, Penn, suicidal tracking only), 12 weeks (full assessment), and 24 weeks (full assessment, minus Penn) [see Section D.13 Timeline for more details]. Complete screening, baseline, and follow-up questionnaires are provided in Section F at the end of this protocol. Coordinating Center staff must also complete several trial management and administrative forms by site to assess adherence to the protocol and to address other fidelity and quality assurance issues. With the exceptions noted below, all subjects are expected to complete all assessment points. The only subjects who are not expected to return for major assessments are those who withdraw consent, die or are lost to follow-up. Continued treatment in the intervention phases of this study is contingent on participating in the assessment portion of the study, e.g. if the subject withdraws consent for assessment, treatment ends. This is distinct from poor cooperation, where only some assessments are completed but the subject indicates willingness to continue with assessments. Subjects who terminate prematurely will complete only full assessment points (usually at 12 and 24 weeks from baseline) after their premature termination.

D.9.g. Electronic Data Capture

The Coordinating Center will utilize OpenClinica to oversee and manage data collected in this proposed research study. OpenClinica has a web-based electronic case report form, and therefore, site personnel will have access to this at their respective sites. Site personnel will enter the data from the paper assessments and paper data forms twice into OpenClinica's form. The OpenClinica software provides immediate validation by "flagging" any inconsistencies in the data for immediate resolution. OpenClinica includes a user-friendly interface with efficient navigation and effective workflow, integrated medical coding, built-in edit checks to reduce input errors, real-time access to study data for effective subject management, query management functionality to easily address discrepancies, study design and library management, as well as role-appropriate monitoring and data review workflows.

D.10. Data Management

D.10.a. Overview

The Coordinating Center (QAMD) is responsible for all data management activities, including between-institution, and study-wide tracking functions. The Coordinating Center has extensive experience providing data management and collection in clinical trials. The Coordinating Center will generate numerous data collection and tracking forms per subject over the course of the recruitment, 12-week intervention, and F/U periods. The Coordinating Center will provide centralized data management services for data collected. Measures across the domains of depressive symptoms, purpose in life, optimism, gratefulness, generosity, social and physical functioning, daily spiritual experiences, therapeutic alliance ratings, and medication use will be completed at various assessment points throughout the study. Considering that there will be at least 100 subjects (30 during Phase I and 70 during Phase II) at six time points, it is clear that a well-organized, well-regulated system of data collection, entry, management, transmittal and editing is essential.

A critical component is the development of a data management plan that documents key processes and procedures. The plan will be incorporated into a project specific data management binder that includes the protocol, scope of work, annotated data forms, database structure, query rules, data flow scheme, Trial Specific Work Instructions for all Data Management processes, copies of supporting forms and data clarification forms, test plans and audit plans. The data management binder, developed and maintained by the Coordinating Center, will be regularly updated to reflect the current status of the study, audited prior to production work on the trial being performed, and audited at planned Data Management Quality Control audits.

D.10.b. Training and Standardization

Study coordinators and interviewers will be trained on the use of the OpenClinica software using web-based as well as on-site training at Duke University. This on-site training will ensure standardization of data entry and protocol procedures. Study personnel will have their own username and passwords to obtain access to a website specific to this study. The website will be set up by the makers of OpenClinica. During the on-site training, the Coordinating Center will provide step-by-step instruction regarding data entry and reporting.

Instructions include, and may not be limited to, the following: a) Site investigators have the overall responsibility for ensuring the accuracy and completeness of data entry. Coordinating Center staff will instruct site personnel to ensure that the observations and findings are recorded correctly and completely (double-entry) in the data forms or case-report forms (CRFs) and signed by the interviewer and the person inputting the data into OpenClinica database, which may be the same person. Also, all printouts and back-up records must be signed and dated for adequate safeguard to ensure validation. b) All corrections to CRFs and to raw data must be inserted with the reason for the correction, the date, and the initials of the investigator or authorized person. c) For electronic data processing, only authorized persons will be permitted to enter or modify data in the computer and there will be a record of changes and deletions. If data are altered during processing, the alteration must be documented. Coordinating Center staff will keep a list of these authorized persons. d) Laboratory values with normal reference ranges, preferably together with the specificity and sensitivity of the methods used, will always be recorded on the CRF or attached to it. Values outside a clinically accepted reference range or values that differ significantly from previous values will be evaluated. e) Data other than that required by the

protocol may appear on the CRF, provided they are clearly marked as additional or optional findings, with an explanation of their significance. f) Units of measurement must always be stated, and conversion of units must always be indicated.

D.10.c. Database Development

The database development environment used at the Coordinating Center is OpenClinica. All development within OpenClinica and all additional programming performed in development of the database are validated according to a predetermined plan. Key components of this activity include data entry screen programming and database testing and validation. OpenClinica allows the Coordinating Center to set up study default parameters for database, protocols, users, access rights, and user groups without requiring Oracle database expertise.

The Coordinating Center will use an electronic data capture (EDC) routine with a database designed specifically for the needs of this study. Because all data capture routines are web-based, this database has a "no query" structure descried below, eliminating opportunities for missing or ambiguous data. Data entry will be completed according to current Good Clinical Practice (GCP) guidelines. Scheduled "data dumps" will allow real-time monitoring of data quality. Each database will be logged into a tracking system to manage data flow, cleaning and archiving.

D.10.d. Subject Database

A database will be created on a computer network specifically for this study. The database will be designed for browser-based data entry. For every record type, the data dictionary will identify key fields (e.g., the participant's PIN, and the type and date of evaluation); skip patterns, etc. and, for each field, the field type (e.g., numeric, character, checklist, or date) and ranges for impossible and improbable values. A corresponding database will be constructed in SPSS at the Coordinating Center, with oversight of the entire data structure by the principal statistician (Noha Daher).

D.10.e. Data Coding/Entry/Verification/Tracking

OpenClinica is equipped with flexible standardization capabilities. Study definitions and medical dictionaries (i.e. MedDra, WHO DRUG, COSTART, ICD9-CM) are standardized through a multi-tier global library that supports many different levels of standards. Reusability is available at all levels from a single data item to a complete study database. Enforcement options can be set at varying levels, from copied object lockdown to complete freedom to change the attributes and composition of copied objects. Flexible standardization enables maintenance of essential data consistency across different studies, facilitating data pooling and analysis, while still supporting the varying requirements of individual research studies. Code assignments for terms that fail auto-encoding are completed after clinical review. Study sites retain all assessments and data forms. Site personnel enter all data from these forms into the OpenClinica study database. The ID of the data entry person and the date of entry (an automatic, derived variable) are included on each record in the database as well as on the actual form to aid tracking. During site visits by Coordinating Center staff, the forms are checked for completeness and compared to the assessment checklist. These forms are processed according to trial specific requirements. OpenClinica allows Coordinating Center staff to perform quality-control checks and identify discrepancies at entry. OpenClinica flags any discrepancies for resolution. Other key component activities include receipt and tracking of physical data forms, secure storage of physical data, first and second entry of data, coding of entered data (e.g., questionnaire data, concomitant medications, etc.), and transfer of data at conclusion of trial.

D.10.f. Data Validation
The primary validation of data occurs in the OpenClinica database. Data-quality procedures include checks for completeness, real-world values, logical inconsistencies, compliance, safety irregularities, and fraud. Electronic data validation checks are developed using data entry discrepancy flags, programmed rules within OpenClinica and, in certain cases, external rules using PL/SQL or SPSS code. The query rules that are used to define range and limit checks for individual variables and to check for consistency among a combination of variables are specified based on past experience with similar types of data. Key components of this activity include preparation of query rule specifications; data validation check programming; specification of test plan, entry, and review of test data; review discrepancy reports from validation test; preparation of data clarification forms for sites; and review and reconciliation of data clarification forms.

D.10.g. Database Quality Control
Quality control consists of programmatic range and consistency checks, as performed by OpenClinica. These checks are specified in a document called the query rules. The programmatic checks will be scheduled as well as conducted on demand. OpenClinica is also able to identify suspected duplicate and blank or missing records and records not double entered within and across database tables. These programs will be scheduled as well as executed on demand. Furthermore, OpenClinica can generate complete study metadata reports (including item definition, edit check logic, and data entry screens) to assist in system validation and audit metadata changes.

D.10.h. Query Identification
Given the structure of the electronic data capture, which is designed to embed edit checks for missing data, out-of-range values, and complex logical dependencies with skip patterns, queries take place in real time, conforming to the "no query, no missing data" rule. We anticipate that subsequent queries, if required at all, will only be generated by the Coordinating Center for information regarding adverse events related to the intervention (i.e., progression of depression, suicidal events, etc.). Nonetheless, the Coordinating Center will perform an extensive series of computer validation checks, run in SPSS. These will be written and run at regular intervals to automatically check for data integrity and to perform the data checks that are instituted as part of the embedded query rules. In all cases, acceptable "windows" for forwarding new data and resolving data edits will be derived.

D.10.i. Query Resolution
Queries will be resolved by Coordinating Center working with the study sites (Duke and Glendale).

D.10.j. Website (database)
Within the main OpenClinica website, a separate site will be created specific to this study. The website will be used to report information back to the study sites (e.g., study and site activity reports, number of patients screened and/or enrolled at each site). The study website will be located on a SSL (secure socket layer, 128 bit encryption web server) and will be username and password protected. An additional site level will exist within the website that will contain specific site appropriate files and reports viewable only by the appropriate site and the Coordinating Center.

D.10.k. Electronic Data Transfers

Electronic data will be transferred from Duke, Glendale, Loma Linda, and Johns Hopkins to the Coordinating Center, and electronic data will be transferred from the Coordinating Center to Glendale, Duke, and Loma Linda University. Procedures for transferring these files, via secure FTP will be used. The format of data records and the structure of the electronic file will be established by consultants and project investigators. Validation procedures will be developed to verify the electronic records.

D.10.l. SPSS files

After the data have been transferred to SPSS for statistical summarization and data description, further consistency checking and crosschecking of the data will be performed, with discrepant observations being flagged and appropriately resolved through the data query system.

D.10.m. Coding Dictionaries

As referred to above, we will uses standard terminology for identifying and labeling medications, for standardized reporting of medical conditions, and other data collected from questionnaires and lab specimens.

D.10.n. Data Access During Trial

Statistical analysis of baseline measures will commence once the entire sample has been recruited in each Phase. With the exception of embedded psychometric and quality assurance analyses, statistical analysis of treatment outcomes will not be conducted until the final subjects have completed each Phase; this applies particularly to Phase II (since the purpose of Phase I is to work out problems in the system). For Phase II, no access will be granted to baseline or after-baseline data other than measures specifically intended for ongoing treatment monitoring according to the treatment protocol, except: (1) baseline and the most recent full assessment visit will be made available to the site team for the purpose of generating end-of-treatment recommendations; and (2) therapists will have access to the BDI scores in tabular or graphical form beginning with the baseline data.

D.10.o. Data Safety Monitoring Board (DSMB)

A DSMB is not required for this planning study. However, we will have an ombudsman assigned to the study (Doug Nies, Ph.D.) who, together with Dr. Koenig, will be available to make decisions regarding suicidal risk and will direct our suicide protection plan.

D.11. STATISTICAL ANALYSES [for Phase II]

D.11.a. General Analysis Conventions

Loma Linda University (LLU) statisticians will perform statistical analyses as required and prepare periodic reports for presentation to study investigators. Reports will include findings of progress and statistical analyses of both primary and secondary hypotheses. The lead statistician (Dr. Daher) will participate in the preparation of scientific papers for publication and presentation based on the study data.

D.11.b. Descriptive Analyses

Data will be analyzed using the statistical package SPSS for Windows, Version 18.0.[251] The demographic and clinical characteristics of the subjects receiving CCBT and those receiving RCBT in both groups (e.g., age, gender, ethnicity, education, baseline scores, medical disorders) will be summarized using frequencies and descriptive statistics, e.g., mean $\pm$ SD or median and range. For categorical data, subjects in both groups will be compared using Chi-square or Mantel-Haenzel analysis where appropriate. Odds ratios and, 95% confidence interval, will be calculated to provide a pooled measure for evaluating the strength of association between treatment condition and the variables of interest. For quantitative variables, groups will be compared using independent t-test or Mann-Whitney U test.

D.11.c. Overview of Outcomes of the Study

The primary statistical analyses will include all randomized subjects in the group to which they are initially assigned (intent-to-treat), as well as only subjects who have completed the full intervention (per protocol). Comparisons will be made between subjects receiving CCBT and those receiving RCBT.

The primary outcomes are: a) score on the BDI at baseline, 4, 8, 12, and 24 weeks from baseline. Change in BDI score will be compared between the two groups over time using mixed factorial Analysis of Variance (ANOVA). Analysis will be conducted using intent-to treat principle in which all assessment points obtained and analyzed irrespective of "dose of treatment." In step two, we will conduct analysis based on cases that are available at each time point.

Secondary Outcomes

The secondary outcomes are gratefulness, generosity, purpose in life, optimism, social functioning, physical functioning, daily spiritual experience, and therapeutic alliance scores. Other measures include cortisol, epinephrine, norepinephrine, anti-inflammatory and pro-inflammatory cytokines, and C-reactive protein.

Secondary Statistical Analyses

The primary outcomes will be analyzed for subjects who complete the study in their assigned groups using regression, and analysis of covariance, and logistic models.

Continuous BDI score and categorical BDI response rate (BDI < 10) will be examined by the using of survival methods. Kaplan-Meier will be used in analyzing "time to response" during the 12 weeks of the intervention and 12-week follow-up (24 weeks from baseline). Kaplan-Meier plots and log rank tests will be used for assessing differences in "survival" curves for the two groups in the absence of covariates. Overall differences in curves may be assessed as well as differences at specified time points during follow-up. Cox regression will also be conducted to evaluate the effect of the confounders on outcome.

D.11.d. Hypothesis-Specific Analyses

D.11.d.1. Primary Endpoint: Depressive Symptoms

Specific Aim/Hypothesis #1: RCBT is more effective than CCBT in treating major depression in religious patients with chronic illness, and religiosity is a moderator of the effect.

Our primary hypothesis is that at the 12-week follow-up, subjects receiving RCBT will experience an average reduction in their BDI score that is at least 3 points greater than that achieved by those receiving CCBT and this difference will be maintained at the 24-week follow-up. We realize that a treatment effect of 0.3 is small. However, this is a trial of RCBT compared head-to-head with a treatment that is known to be effective (CCBT). We chose 3 points because this is considered the threshold for a clinically meaningful difference.

Analysis

Continuous Outcome: Individual slopes of BDI change for each patient will be examined as the outcome variable using multi-level, growth curve models. We will plot the growth curves in SPSS using the IGRAPH Command. The CASESTOVARS will be used to disaggregate the data for growth curve analysis. The linear mixed-effect model (MIXED) procedure in SPSS enables us to fit linear mixed-effects models. MIXED procedure is based on maximum likelihood (ML) and encompasses all models in the variance components (VARCOMP) procedure. Restricted maximum likelihood (REML) methods allows us to make inferences on the covariance parameters in the model.[252,253]

Categorical Outcome: We will also analyze the BDI score as a categorical variable at 12-week and 24-week follow-up (score of 0-9 vs. 10-63), where it could be modeled as a 2 (CCBT vs. RCBT) x 2 (BDI 0-9 vs. BDI 10-63) table; in addition, conditional logistic regression will also be conducted to determine predictors of recovery after controlling for confounders.

Initially, for the dichotomized outcome, Pearson's chi-square statistic will be used to examine whether proportion of subjects recovered is the same in both groups. There will be a number of covariates to consider in the analysis. Among covariates of interest are recruitment site (Duke vs. Glendale), age, gender, religiosity, and ethnicity. Thus, the chi-square and Mantel-Haenszel statistic will be used to test for overall treatment differences on a dichotomous response. Logistic regression models will be used, in general, to quantify the effects of covariates on outcome while controlling for other variables in the model. The analysis methods are easily implemented using SPSS for Windows Cross- tab (Pearson's chi-square and Mantel-Haenszel statistic), and BINARY LOGISTIC for modeling.

Time-to-Event Analysis. Time-to-recovery during the treatment period and follow-up over 24 weeks is another way that we will compare response to treatment. Kaplan-Meier[254] methods and Cox regression[255] will be used to analyze the interval of time from randomization to recovery (defined as a BDI of <10). Kaplan-Meier curves provide estimates of the recovery-time distribution of the cumulative proportion of patients that recover by time t. A log-rank statistic will be provided to assess differences in the curves; and a stratified log-rank statistic will be provided to assess treatment differences while accommodating heterogeneity across clinical sites. Control for additional covariates and the evaluation of the effects of covariates on outcomes will be handled using Cox regression.

Moderators: For any type of outcome— continuous, categorical, or time-to-event—it will be important to assess the homogeneity of effects across various subgroups. The assessment for interaction of a covariate with treatment or another covariate will be through the corresponding parametric model for the outcome. Consideration of interactions will be necessary for evaluation of goodness-of-fit of the model as well as to strengthen the conclusions of the study with respect to generalizability, although the small sample size is likely to prohibit determination of stable estimates.

D.11.d.2. Secondary Endpoints I: Psychosocial and Physical Functioning

The secondary outcomes include various measurements of psychological, behavioral, spiritual, social and physical functioning. The hypotheses for the psychosocial and physical functioning endpoints are:

Specific Aim/Hypotheses #2a-h. RCBT will be more effective than CCBT in: a) establishing a strong therapeutic alliance, b) improving optimism; c) improving purpose in life, d) improving gratitude; e) improving generosity; f) improving social functioning; g) enhancing spiritual experiences; and h) improving physical functioning. These effects will explain why RCBT is more successful than CCBT in reducing depressive symptoms.

The Mann-Whitney U test for 2 independent will be used to assess the effect of treatment differences on these outcomes in addition to ordinary regression methods. If the baseline values of the outcome variables differ by groups, they will be included as covariates in the regression model. Thus, the linear model will include treatment, covariates, and the baseline prognostic variable. The assumptions in these regression analyses including normality of the data and homogeneity of variance will also be examined. Where treatment effects are found, this variable/s will be added singly and in combination with the treatment variable to regression models predicting change in depressive symptoms.

These methods can be implemented using SPSS via non-parametric statistics and the Mann-Whitney U test. In addition, linear regression with many diagnostic capabilities will be conducted. Finally, we will use multi-level models wherever appropriate as implemented in MIXED procedures.

D.11.d.3. Secondary Endpoints II: Immune/Endocrine Analyses

The hypotheses for the immune/endocrine analyses are:
Specific Aim/Hypotheses #3a-c. RCBT is more effective than CCBT in a) *reducing* urinary cortisol, norepinephrine, and epinephrine; b) *reducing* pro-inflammatory cytokines (interferon-γ, IL-1β, IL-2, IL-6, IL-17, TNFα) and C-reactive protein; and c) *increasing* anti-inflammatory cytokines (IL-4, IL-10).

The immune/endocrine outcomes will be compared between the two treatment groups using independent t- test in addition to linear regression models. If the baseline values of the outcome variables differ by treatment arm, they will be included as covariates in the regression model.

D.11.d.4. Secondary Endpoints III: Genetic Analyses

Specific Aim/Hypothesis #4. 5-HTTLPR S allele carriers, 5-HT1A G allele carriers, and high activity allele carriers at the uMAOA locus will be more common among subjects who are deeply religious vs. less religious.

Specific Aim/Hypothesis #5a-b. (a) Subjects with one or more of the above genotypes will have a more robust response to RCBT than to CCBT, compared to those with none of these; (b) the difference in effect between RCBT and CCBT will be especially large in deeply religious subjects with one or more of the above genotypes

Association Analyses. Both allele and genotype frequencies will be compared by constructing 2 x n tables. Odds ratios will be calculated with Haldane's modification, which adds 0.5 to all cells to accommodate possible zero counts. Initially, SNP validation will be performed. The minor allele frequency and missing rate of genotypes will be checked. Marker informativeness will be measured by two indices, polymorphism information content (PIC) and allelic diversity. Preliminary exploratory analyses will be conducted to explore data distribution and to establish univariate associations between genetic risk factors and the outcome variable. Associations will then be adjusted by potential confounders (gender, ethnicity) to establish independent associations using binary logistic regression where odds ratios and 95% CI for the association will also be calculated. Analyses will be stratified as indicated to address the specific hypotheses.

Multi-loci Analyses [combinations of the three candidate genotypes]. Relationship of outcome status and genetic markers will be modeled via a conditional logistic regression model using procedure BINARY LOGISTIC in SPSS. The interaction effects of markers will also be tested. Risk factors and covariates will be used to adjust the possible confounding effects in the regression model.

D.11.e. Power Analysis and Sample Size Considerations

Important: See D.11.e.3 below for comment on power for this feasibility study.

D.11.e.1. Detection of Differences in Response Rates (continuous BDI score)

For the primary analysis, using continuous BDI score, we are presenting a power analysis to detect an advantage for RCBT over CCBT of 3 points (SD 9.5, treatment effect 0.3) or more on the BDI. We believe anything less than this would not be worth the research investment needed to demonstrate it. Although there is no agreement on what constitutes a clinically significant difference in effectiveness between two treatments, treatment effects of 0.2 to 0.3 are conventionally viewed as small and of limited clinical value.[256,257] Moreover, our discussions with primary care physicians and psychologists indicate that less than 3 points on the BDI (e.g., 1 or 2 points) is not perceived as clinically important. For a treatment effect of 0.3, a type I error of 5% and 30 in each group, the power achieved is 31%.

D.11.e.2. Detection of Differences in Response Rates (categorical BDI score)

For the categorical analysis, where treatment response is defined as a score of 0-9 on BDI, the following procedure to determine power will be followed. In our recent trial of Internet delivered CBT, 38% of participants in the CBT arm had recovered from major depression by the 4-month follow-up versus 24% of those receiving usual care arm.[258] If we assume here that the difference between RCBT and CCBT will be similar to that of the above study for CCBT vs. usual care, and increases over time (20% CCBT vs. 40% RCBT), which are both quite generous assumptions, then we would proceed as follows.

Consider the power for detecting differences in two response groups based on the Pearson chi-square statistic, X^2. Under the null hypothesis, the sampling distribution of the statistic is an approximate central chi-square with 1 degree of freedom. Using the chi-square statistic, power estimates for

detecting differences in response at 12-weeks between the two treatment groups are computed using the following assumptions:

1. H_0: $P_{CCBT} = P_{RCBT}$,
   Ha: Proportions are different [i.e., P_{RCBT} is .14 greater than P_{CCBT}].
2. N = sample size in each treatment group = 35 (with 15% loss to follow-up, resulting in n=30 each arm) and $\alpha = .05$ (two-sided test).

Under these assumptions the power can be shown to be between 12% and 34%. If we assume a 30% difference in proportion and a sample size of 45 per group, the power is 81%.

D.11.e.3. Other Sample Size Considerations

The study does not have adequate power, as expected. The sample size is small and the findings are for planning purposes only (feasibility, effect-size estimates). *This especially applies to the hypothesis that seeks to identify mediators of the effect on the primary endpoint.*

D.11.e.4. Dropouts

Since we are expecting a 15% dropout rate in this trial, we will need to recruit at least 70 subjects to end up with 30 subjects in each arm of the trial. If dropout rate is greater than 15%, then we will replace subjects until we have 30 subjects in each arm.

D.11.f. Preparation for Scientific Meetings and Manuscripts

Coordinating Center staff will provide assistance and coordination in the preparation of data for scientific conference presentations (e.g., the American Psychiatric Association, American Psychological Association), abstracts, and manuscripts for peer-reviewed journals. These will include efforts led by the Duke (e.g., Drs. Koenig, Robins, Pearce, and Cohen) and UCL (MB King) investigators as well as by efforts led by GAMC's Recruitment Division and GAMC's Quality Assurance and Monitoring Division staff (e.g., Drs. Doug Nies, Dennis deLeon, Bruce Nelson). Coordination of the analytic and other efforts by the Coordinating Center is necessary to prioritize and ensure adequate support as well as avoid duplication of effort. A schedule will be set up and guidelines written by a Publications Committee for this purpose.

Dr. Noha Daher will provide statistical support and will assume responsibility for the data preparation and analytical procedures. Statistical staff will also be available to run the analysis needed for the various presentations and manuscripts. The proposed Coordinating Center staff will present results of the study at scientific meetings alongside their colleagues. They will be authors and co-authors of abstracts and manuscripts describing results from the study. The status and progress of the presentations and publications will be tracked electronically and presented to the study investigators, and hard copy materials will be maintained in the study library.

D.11.g. Final Statistical Reports of Protocol Outcomes

Throughout the data collection phase, we shall prepare interim statistical reports of protocol outcomes. We will revise our presentations as needed to address concerns raised by our colleagues and consultants. At least one month before the end of the study, we will submit drafts of the final statistical report to the funding organization. It will include outcome analyses from the final database in a format that incorporates suggestions received throughout the study.

D.12. Organization, Personnel, and Training

This study will be carried out via subcontracts between Duke's Center for Spirituality, Theology and Health and (1) Glendale Adventist Medical Center (GAMC) and (2) GAMC Department of Clinical Research's QAMD (working collaboratively with the University College of London Clinical Trials Unit).

D.12.a. Research Centers, Coordinating Center (QAMD), and Collaborators

This team of investigators is experienced at conducting efficacy and effectiveness trials in psychotherapy, participating in and coordinating multi-site clinical trials in adults with medical illness, and in data management and analysis. Research scientists comprising the team have their primary academic appointments in the Departments of Psychiatry and Medicine at DUMC, Psychiatry at University College of London, Neuroimmunology Research Laboratory at Loma Linda University, and the Neurosciences Institute at the University of Granada. DUMC is the primary contractor with the Center for Spirituality, Theology and Health (directed by Dr. Koenig), administratively housed within the Aging Center at DUMC, assuming overall responsibility and leadership for the scientific integrity of the study, including coordinating the development of a final study design, site recruitment, intervention, follow-up, analysis and reporting of results.

The Coordinating Center and its collaborators provide expertise in clinical trials randomization, serious adverse event reporting, and site management and monitoring. The Coordinating Center is also responsible for multi-site data management, data processing and statistical analyses. In relying on the collective experience of our team, the Coordinating Center draws on faculty, staff, and consultants who have a depth of experience in coordinating clinical trials, and developing, manualizing and assessing the fidelity of CBT interventions in depression, and in preparing materials for RCTs.

D.12.b. Steering Committee

Dr. Koenig, overall study PI, will lead the Steering Committee. Committee members include the study co-leader, Dr. King; co-investigators at each recruitment sites (Dr. Jack Yu, leader for the Glendale Adventist Medical Center site, and Dr. Koenig, leader for the Duke Health Systems site); co-investigator Dr. Cohen; CBT supervisors (Dr. Robins and Dr. Pearce), and the Coordinating Center administrator (Bruce Nelson). This committee will be responsible for the overall direction and execution of the study.

D.12.c. Recruitment Site Staff

Primary staff at each of the two sites includes:

Site Leader (Dr. Koenig at Duke; Jack Yu at Glendale)
Responsible for on-site adherence to study design; represents site on Steering Committee; participates in difficult clinical decisions about individual subjects; and presents study to physicians for purposes of recruitment.

Site Administrator (Dr. Koenig at Duke; Dr. Nelson at Glendale)
Responsible for all administration duties regarding site, and for communications regarding administration issues with the site leader and overall study PI.

Study Coordinator
Understands all aspects of recruitment at their site. Responsible for ensuring day-to-day operations at the site. Holds weekly meetings with all site study staff, and reviews with site leader any problems and issues related to recruitment goals. Oversees recruitment and screening process and assures that eligibility are met at each point; obtains random assignment; ensures that individual subject schedules are set up and that procedures for assessments (including biological assessments) run smoothly; establishes and oversees procedures for flow of paper data forms and transmission of data to Coordinating Center (QAMD); maintains close contact with Coordinating Center; maintains close contact with other project staff. Serves as supervisor to research assistants and data entry personnel.

Research Assistants
Conducts screening, baseline, and follow-up assessments; assists with consenting subjects into clinical trial; sets up appointments and follow-up; administering various computer-based tasks during assessment visits; ensures that biological specimens are obtained, packaged, and shipped to appropriate labs; mails information to subjects, including self-rating scales as per assessment schedule, and follows up to ensure completion; logs in receipt of data forms; reviewing paper forms for completeness; tracks down missing forms and items from subjects; accesses computer to run algorithms and reports to be reviewed by site leader and overall study PI.

D.12.d. Intervention Staff
Intervention Monitors (Shaw, and research associate TBD)
These are staff at Coordinating Center to ensure that all procedures related to the intervention protocol are followed correctly.

CBT Supervisors (Robins, Pearce)
Responsible for the identification, training, and supervision of CBT therapists throughout Phase I and Phase II. See Section D.6.b. for details.

CBT Therapists (TBD)
Responsible for coordinating and performing all components of CBT interventions, including setting up appointments with subjects; carrying out the intervention; ensuring subjects do homework and recording compliance with home work; and providing materials/documents necessary for quality assurance (paper copies of online sessions, audiotapes of telephone sessions). See Sections D.6.a. and D.7.b. for details.

Online Administrator (Rosmarin)
Ensures that all goes smoothly when therapists and subjects are communicating online; handles any technical problems related to the website interface (PsychologyOnline).

Psychology Online Personnel
Maintains website interface that therapists and subjects use to conduct therapy sessions; ensures confidentiality of all communications

D.12.e. Supervisor and Therapist Qualifications
CBT Supervisors. Supervisors are required to have extensive CBT experience and experience training others to conduct CBT (i.e., PhD level faculty at universities that train professionals in this area) (see

section D.6.b. for details). Similar requirements apply to Interfaith Council of Advisors who will be assisting in supervision of therapists treating patients within their particular faith tradition (see Section D.5.d for details).

CBT Therapists. Minimum qualifications are necessary for therapists and supervisors to insure a fair test of each of the treatments. CBT therapists (as noted in section D.6.a and D.7.b) must have a master's degree in counseling, have experience with CBT, and score 40 or higher on the Cognitive Therapy Rating scale. Other requirements include commitment to a CBT approach, and willingness to follow a "manualized" treatment and have transcripts of online sessions or audiotaped telephone/Skype sessions reviewed by CBT supervisor, other CBT specialists, and the Coordinating Center. If a supervisor wishes to propose a master's level therapist who does not meet all of these qualifications, but has equivalent background and experience, that proposal will be reviewed by a committee consisting of the two CBT supervisors and a representative from the Coordinating Center.

D.13. Timeline

Preliminary

Dec 2010: Notification of award
Dec 2010-Mar 2011: Obtain IRB approval, recruit staff, develop interventions

Phase I

Apr 2011 (1 mo): train staff, build database, etc
May-July 2011 (3 mo): enroll 15 subjects (7-8 at each site)
Aug-Oct 2011 (3 mo): complete intervention on 15 subjects
Nov 2011 (1 mo): revised protocol
Dec 2011-Feb 2012 (3 mo): enroll 15 subjects (7-8 at each site)
Mar-May 2012 (3 mo): complete intervention on 15 subjects
Jun 2012: protocol finalization

Phase II

Jul 2012 (1 mo): start up of Phase II
Aug 2012-Mar 2013 (8 mo): enrollment of 70 subjects - 35 at each site
Apr-Sep 2013 (6 mo): intervention & f/u completed for all subjects in Phase II
Oct 2013-Mar 2014 (6 mo): assessment of trial and preparation of definitive R01

D.14. Public Health and Scientific Significance of the Proposed Study

The importance of this study is that it may help identify several mechanisms by which religion may influence physical health. It does so by testing a religious intervention (RCBT) in a population of persons with a disabling physical illness and major depression. Religion is widely prevalent and is often utilized as a coping behavior in response to situational stressors. Major depression is a common, painful, physically impairing, and financially costly psychiatric illness with a prevalence of nearly 15% and described as the second most disabling condition worldwide. Depression has been shown to adversely affects physical health and medical outcomes at least partly by adversely affecting immune and endocrine functions. A psychological therapy that takes advantage of the religious resources of religious patients ought to improve depression more quickly, as well as improve the adverse physiological changes associated with depression. Thus, if it can be shown that a religious intervention

(religious CBT) reduces depression and thereby improves immune and endorine functions, then this would verify a mechanism by which religion could affect morbidity and mortality. A randomized clinical trial is the only way to either verify or disprove this causal mechanism.

Furthermore, the results from this study will be important because they will be relevant to therapists well beyond those who explicitly practice pastoral counseling, extending to many secular therapists as well. If 65% of Americans indicate that religion is an important part of daily life and may wish to include it in their therapy, then all therapists (whether they have explicit training in pastoral counseling or not) are likely to encounter patients among their clientele in which this approach would be appropriate. In their 2009 review of religion and spirituality in psychotherapy, Post and Wade make two points relevant to this issue.[259] First, although therapists in general are less overtly religious than patients, many therapists have spiritual beliefs that should assist them in appreciating the role that patients' religious beliefs can play as a resource or a liability in their mental health. Second, while it is helpful for therapists to be well versed in the basic tenets of their patients' religious beliefs, it is not necessary for them to be experts in religion: "Instead, approaching religious/spiritual clients with an openness and willingness to engage the religious/spiritual conversation will help clients to feel comfortable expressing their needs." Consequently, they conclude that religious interventions in psychotherapy can be effectively delivered by therapists with a wide range religious/spiritual beliefs, not only experts in religion. Indeed, in their original study, Propst and colleagues found that the delivery of religious CBT by secular therapists was at least as effective (if not more so) than religious CBT delivered by religious therapists.[260]

Finally, this study will help determine if and how religious beliefs interact with genetic factors that may increase susceptibility to depression (especially in adverse situations such as disabling chronic medical illness) and influence response to psychotherapy. Not only will this information be of scientific value in explaining why religion and depression are associated and have persisted throughout human evolution, but will also be relevant to the many religious patients who struggle with depression and condemn themselves for having this disorder.

E. HUMAN SUBJECTS RESEARCH

E.1. Overview

This human subjects research meets the definition of 'Clinical Research'. The risks associated with this study are the risks involved in worsening depression and possible development of serious suicidal ideation that may precede suicidal acts. There are also risks involved in genotyping individuals and keeping these results confidential. All records will be kept confidential to the extent permitted by law. Patient identifying information will not be transmitted to or included in the database at the Coordinating Center. Access to such information will be allowed only to certain authorized members of the research team, institutional staff, and regulatory agencies. Genotypic information will be de-identified per NIH procedures, and all linking fields for other data will similarly be de-identified before combining genotype and treatment response or religious information into an analytic data set. In reporting the results, privacy will be protected by using coding systems that do not reveal the identity of individuals, and by reporting group results.

The consent form now indicates that the genetic testing will only involve very specific gene components and that there is no possible chance that genetic information will be found that would indicate an increased risk for a life-threatening disease unknown to the subject at the time of testing.

E.2. Recruitment and Consent Procedures

The recruitment procedures for our study will include a thorough explanation of the study, time commitment, possible risks and benefits, and alternatives for treatment. Participants will be informed about the purposes of the research study. Specifically, they will be informed about the diagnosis of MDD and its treatment. Through a combination of written materials and the consent form, they will be told that this is a treatment study, including details of the treatment component to which they have been assigned. Randomization will occur after informed consent has been obtained. Subjects will be informed that there is an equal chance (random assignment) to be assigned to either of the two study arms. Details of the study will be explained making it clear that subjects may not receive the RCBT intervention or may receive it. If not willing, then will be referred to other providers. Will also make clear differences between early termination and dropping out and the consequences of each. They will be further informed that their identity will be kept confidential through the use of a confidential code number that will allow all information to be entered into the database in an anonymous fashion, such that information cannot be linked or traceable to any person outside of the immediate investigative team. Aside from treatment planning, all information will be used only for group statistical analyses. All study participants will be told the expected duration of the study and informed that subjects' consent can be withdrawn at any time, at no risk to having other treatment in their clinical setting withheld.

E.3. Risks to the Subjects

This investigation will be conducted with prior approval from the Duke University Health System (DUHS) and Glendale Adventist Medical Center (GAMC) Institutional Review Boards (IRB). 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. In addition, details of how potential subjects will be ascertained and recruited for study participation, and how their rights and welfare will be protected, will be provided to the IRB.

E.3.a. Risk of Suicide

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 (see section E.3.d.).

E.3.b. Risk to Confidentiality

The most sensitive information involves the blood samples for genetics analysis, although confidentiality regarding personal information collected by questionnaires will also have to be carefully guarded. The DUHS, GAMC, and QAMD will be responsible for safeguarding the security of all study specimens, records and databases. As noted in the research plan, blood specimens will be collected from all participants for genotyping. Subjects who have provided written informed consent, will have 45 cc of blood drawn at a phlebotomy laboratory onsite at DUHS or GAMC. 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. Samples will be sent via Federal Express to Loma Linda Neuroimmunology Research Lab and to

Johns Hopkins CIDR. These specimens will be collected specifically for this research study. 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 Coordinating Center (QAMD). Only the Duke and GAMC's Recruitment Division sites will hold the code (PIN with patient name) for the subjects they recruit and need to follow up (not the Coordinating Center, which is a different division within GAMC's Department of Clinical Research with different staff). Personal identifying information, such as name, address, driver's license, 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 Coordinating Center. The control of access to databases will be managed centrally by the Coordinating Center through user passwords linked to appropriate access privileges. This protects forms from unauthorized view and modifications and from inadvertent loss or damage. The Coordinating Center has an extensive data security infrastructure. Database servers are secured by a firewall as well as through controlled physical access. The Coordinating Center 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.

Other Confidentiality Concerns. The first issue not addressed above is the securing of data collected during the therapy sessions themselves. All therapy sessions done via the Internet will be coordinated by PsychologyOnline, the web-based server used by research groups for online psychotherapy studies. As noted earlier, PsychologyOnline operates according to the Code of Conduct, Ethical Principals and Guidelines of the British Psychological Society and adheres to the standards of clinical governance of the National Health Service. It provides confidential live online therapy through a secure website. We have checked with IRB specialist (Lawrence Muhlbaier, Ph.D.) on issues related to patient confidentiality. Since PsychologyOnline is merely hosting the online site but not treating the patients, we can add their group to the list of disclosures in the informed consent. A second concern is securing the confidentiality of (1) transcripts of all online sessions that will need to be stored in electronic format and (2) audiotape-recordings of all telephone (and Skype) sessions that will need to be transcribed and stored in electronic format. In order to guarantee therapy fidelity (see p 48, Full Protocol), we need to retain copies of all therapy session so that a 10% random sample of these online transcripts and transcribed telephone/Skype sessions can be reviewed by outside experts. The following procedure will be used to secure confidentiality: (1) Therapists will retain the electronic transcripts of all online sessions in a special file on a password protected computer that is accessible to only the therapist; these electronic transcripts will be sent to the Coordinating Center (with patient study number only and no other identifying information) using the secured FTP method used for transferring our electronic data files; after the Coordinating Center has confirmed receipt of the files, the therapists will permanently remove the files from their computers. (2) Therapists will send audiotapes of all telephone/Skype sessions to the Coordinating Center via FedEx (with patient study number only and no other identifying information on tape); the audiotapes will then be transcribed at the Coordinating Center, and these along with the electronic transcripts of the online sessions will be stored in OpenClinica with the other confidential data from the study. The Coordinating Center will then use the secured FTP method for transferring electronic data files to transfer a 10% random sample of these transcripts to CBT experts at Duke (not participating in the study) who will then store these on a password protected computer that only they have access to and rate the transcripts for protocol fidelity,

after which they will delete the transcripts from their computer. Again, only the patient's unique study number will be included on these transcripts, and the key for patient identify will be held only by study investigators at the Duke recruitment site and GAMC's recruitment division (not by the Coordinating Center).

E.3.c. Risk from Blood Sampling

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 3-4 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 40 cc's for every 6th to 7th patient 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.

E.3.d. Adequacy of Protection Against Risks

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 and blood samples for genetic analysis at screening. IRB approval will be obtained for the informed consent form from the DUHS and GAMC IRBs. The descriptions given in the informed consent will conform to the guidelines provided in the Code of Federal Regulations. The nature and purpose of the investigation will be explained to subjects and written informed consent will be obtained from those persons prior to enrolling in the study. Also explained to subjects is that they are free to refuse to provide questionnaire information, urine or blood, or to withdraw from this study at any time, without jeopardizing their clinical care. If new information or new data becomes available during the study that is of value to the individuals, it will be provided to them.

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 the 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 would contact the family and physician without first assessing the patient, again

with or without the patient's consent. With the above in mind, the informed consent will indicate that in the event of the subject expresses serious suicidal thoughts as indicated below, study interviewers and therapists are duty bound to do whatever is necessary to ensure the subject's safety with or *without their consent.* In the event that Dr. Nies cannot be immediately contacted at the Glendale site (818-230-2290), then Dr. Koenig, study PI *who will carry a cell phone 24 hours/day during the study*, will be notified and fulfill this responsibility for Glendale site (919-949-3854), and vice-versa for Duke site (Dr. Nies). If neither Dr. Koenig nor Dr. Nies can be reached, then Bruce Nelson will be contacted (818-633-0069), or the onsite PI at Glendale (Dr. Jack Yu) if absolutely necessary.

The above plan would be put into action in the event of (1), (2), (3), or (4) below:

(1) If the patient has completed Q9 on the BDI and marked **3**
(i.e. I would kill myself if I had the chance)

(2) Has expressed suicidal intent based on responses to the Suicide Module of the MINI (adapted for this study). Specifically, on the baseline MINI, any subject responding affirmatively (yes) to any of the following:
a) B1a (plan or intend to hurt self in any accident either actively or passively (e.g., by not avoiding a risk)
b) B5 (think about killing self "often" or suicide intent of "moderate" or greater intensity)
c) B6, B7, B8, B9, B10, B11, B11a-c, B13, or 17 or more total points

(3) Serious or active suicidal thoughts or actions as indicated by the following responses on the MINI Suicide Tracking Scale (administered at 4, 8, 12 weeks and 24 weeks)
a) Response to 1a that indicates moderately (2) or higher with respect to hurt self during an accident and "yes" to 1b (intend to die)
b) Response to 2 (i.e., think better off dead) that indicates markedly (3) or extremely (4)
c) Response to 3 or 4 (i.e., wants to hurt self or thoughts about suicide) that indicates moderately (2) or higher
d) Response to 5 or 6 (i.e., plan or active steps to commit suicide) that indicates a little (1) or higher
e) Response to 7 that indicates has attempted to injure self intentionally
f) Response to 7a or 8 is a little (1) or higher

(4) The subject at any time during assessment interviews or during therapy sessions indicates serious or active suicidal thoughts.

E.4. Potential Benefits of the Proposed Research to the Subjects and Others

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.

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