OVERVIEW: COLLABORATIVE COMPONENTS

1. Individual Participating Sites: The Cornell group (PI: J. Sirey) and the University of Michigan (UM) group (PI: H. Kales) each bring specific expertise to this collaboration with a shared emphasis on improving quality depression care for older adults. Drs. Sirey and Kales have collaborated previously on a symposium panel on antidepressant adherence at the Annual Meeting of American Association of Geriatric Psychiatry in 2008. Drs. Sirey, Kales, Bruce, Blow and Leon have all contributed to the project development, with an in-person meeting held at Cornell in December 2008. This collaborative R01 application also is the first submission to bring together two university depression centers participating in the National Network of Depression Centers.

2. Rationale for Collaboration: The two research groups have complementary expertise necessary to conduct the proposed project. The focus of Cornell’s group has been on the documentation of the impact of stigma on adherence and the development of innovative interventions to improve depression outcomes and adherence for older adults in primary care (Preliminary Studies). The UM group has studied the impact of participant racial differences on later-life depression diagnosis, treatment and adherence; the effect of health beliefs including spirituality, and comorbid anxiety on depression care adherence behaviors in older adults; and the prevalence of alcohol use and health service utilization in geriatric depression (Preliminary Studies). The shared experience of the Cornell and UM groups indicates that depressed elders face numerous barriers to adherence to antidepressant therapy in primary care (Preliminary Studies). These common findings initiated a dialogue and data analyses (please see Preliminary Studies) that led to this application. Therefore, the proposed study builds on shared scientific interests and data, a history of effective collaboration, and complementary expertise. The objectives, rationale, and key methods proposed are identical for both Centers. Therefore, the collaborative sites would be interactive both by undertaking complementary scientific roles and by working on a common protocol. This application meets the requirements of the PA-07-092 Collaborative R01 mechanism because it: 1) needs a sample larger than any one of the two sites could recruit alone; 2) broadens the credibility of its findings by parallel collections of data at different sites and by investigators with differing theoretical backgrounds; and 3) uses complementary expertise at each site to investigate a common topic.

3. Administration: The study will be directed by a Steering Committee chaired in alternating years by Dr. Sirey and Dr. Kales and will include Drs. Bruce (Cornell), Blow (UM), and Leon (Cornell). The Committee will oversee: 1) the safety and burden of subjects; 2) the implementation of common procedures and training across sites; 3) the integrity of data; 4) the availability of data to qualified investigators of the project and of other Centers; 5) the prompt publication and presentation of findings; and 6) the arbitration of conflicts among investigators. Each of the two participating Centers will function as a specialized resource to the Steering Committee and provide expertise and coordination to the collaborating study sites. Accordingly, Cornell will be the Study Coordination and the Data Coordination Centers. UM will be the Assessment Coordination and Dissemination Coordination Centers. A Publication Committee, chaired by Dr. Kales, will assign authorship and prioritize analyses. A similar structure has functioned successfully in the NIMH-Funded PROSPECT, COPE-D, STOP-PD, and Geri-BD multisite collaborative trials based at Cornell. Finally, a Data Safety and Monitoring Board will be formed to oversee the safety of subjects and the integrity of procedures and data. Below are cited items that will be part of the meeting agenda of the specialized coordinating centers of the study.

**Study Coordination (Cornell)**
- Cross-Site Intervention Training (Quarterly)
- Publication Plans (Monthly)
- Intervention Fidelity

**Data Coordination (Cornell)**
- Missing Data (Monthly)
- Quality Control: Data Management (Quarterly)
- Interrater Reliability (Bi-Annually)
- Review of Descriptive Statistics (Quarterly)
- Planning Data Analysis (Monthly)

**Assessment Coordination (UM)**
- Cases at Risk (Weekly)
- Subject Flow (Weekly)
- Attrition & Side Effects (Weekly)
- Subject Burden (Monthly)
- Psychiatric Diagnosis (Monthly)

**Dissemination Coordination (UM)**
- Publication progress (Quarterly)
- Adaptation to PCP practices (Bi-annually)
- Communication with PCP practices
3a. Study Coordination Center (SCC; Cornell): The SCC will coordinate overall study implementation. Dr. Sirey will provide training, ongoing monitoring of implementation of the Treatment Initiation and Participation (TIP) program and rate fidelity to the intervention. Dr. Sirey will be the Director of the SCC and the Chair of the Steering Committee during the first year. She has served as the Core Director of the Research Network Core of the Cornell ACISR (P30 MH68638), and Coordinating Investigator of CARE-D, a two-center study (Cornell, UCSF, Coordinated R01 MH64099).

Prior to each meeting, data-based material will be circulated. The SCC will assist the Steering Committee in directing the study by providing data and implementing procedures to carry out the Steering Committee’s decisions. The SCC will rely on a communication structure that will consist of weekly telephone conferences and three in-person meetings per year (at national meetings to reduce travel cost). The following guidelines for review of ongoing issues have been used successfully by NIMH-funded multisite collaborative trials and will be used in the standing agenda for the telephone conferences of the proposed Study. During the conferences, objectives will be set and tasks will be assigned to the Specialized Centers and/or investigators. Timetables for the assigned tasks will be specified. Minutes will be obtained and the progress in assigned tasks will be monitored and reported back during the telephone and in-person conferences. The Specialized Centers will also convene weekly conferences to coordinate and implement specific tasks assigned to them by the Steering Committee. Typically 2-3 teleconferences will be convened prior to discussion during the SCC Teleconference.

3b. Assessment Coordination Center (ACC; UM) The ACC will coordinate and supervise the following activities across the two sites: 1) assessment procedures, including selecting instruments, and monitoring instrument performance; 2) training, credentialing, and supervising interviewers and conducting inter-rater reliability studies; 3) procedures aimed at reducing subject burden and increasing satisfaction and adherence to research procedures; and 4) coordinating interactions between the Centers to address proactively problems related to systematic assessment.

3c. Data Coordination Center (DCC; Cornell): The DCC will guide the design of protocols and standard procedures to ensure uniform implementation of the study. The Cornell DCC brings to this study the experience of developing the procedures for data tracking, entry, management and analyses for a number of collaborative R01s at Cornell. The DCC will standardize the data entry procedures, and implement a quality control system. The DCC will provide consultation and assist investigators in data analysis using the most current validated and appropriate analytic techniques. The DCC will provide the interim data needed by the Steering Committee and the DSMB to review the progress of the study.

3d. Collaboration & Dissemination Coordination Center (CDCC, UM): The CDCC will work towards future dissemination of TIP by tracking the implementation, collaboration with primary care and progression of reports about TIP. The CDCC will monitor publication progress (quarterly beginning in 2nd year), describe adaptation to primary care practices (bi-annually), and work towards sustainability of the intervention.

4. Data Safety and Monitoring Board (DSMB): A DSMB Board will be formed. We propose to include a geriatric psychiatrist, a psycho-interventions investigator, a primary care physician and a consumer from one of the practices. We will identify a biostatistician available for review of data. We will seek consultation with NIMH program officers before the membership of the DSMB Board is decided. The DSMB Board will review the study design, the IRB protocols of UM and Cornell, adverse events, and interim reports of the ongoing study. The Study Coordination Center will be responsible for preparing data and data analyses requested by the DSMB Board. The Study Steering Committee will hold teleconferences with the DSMB Board annually and, when needed, in-person conferences.

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A. INTRODUCTION AND SPECIFIC AIMS

The purpose of this research is to conduct a randomized clinical trial of a brief intervention to improve adherence to depression medication treatment delivered to older adults in primary care settings. Because improving medication adherence is fundamental to maximizing the impact of treatments for mental illness, developing innovative adherence interventions with the potential to enhance the delivery of quality health care is a key research objective according to The National Institute of Mental Health Strategic Plan (2008). Nonadherence undermines the potential benefits of pharmacologic treatments for mental illness. In depression care, the full benefits of the easy to prescribe, safe and tolerable antidepressants are unrealized due to medication nonadherence. Addressing the psychological, illness and tangible barriers to adherence and creating personalized adherence strategies for depressed elders can improve the utilization of evidence-based depression treatment and reduce the public health burden created by nonadherence.

Adherence is a challenge across the lifespan, but among older adults with depression this challenge is compounded by medical and psychiatric comorbidity, medical regimen complexity, as well as skeptical attitudes towards mental illness and its care. For older adults, the effect of stigma on seeking care for mental health issues such as depression is particularly strong. The decision to initiate treatment for depression entails both countering the ageist notion that depression is a normal outgrowth of aging, along with confronting the stigma of mental health treatment that is particularly prevalent in this age cohort. The “treatment gap” created by non-adherence in later life is becoming an even more critical issue as the nation’s demographic profile shifts: “America is a different nation than it was 10 years ago…we are aging” (NIMH Strategic Plan, 2008). Depression care adherence among older adults is a significant problem as a large proportion of the growing older adult population experience major depression with deleterious impact, making undertreated depression in later life a significant public health problem. Beyond personal suffering, untreated depression in later life worsens the outcomes of many medical disorders and increases the risk for falls [4], cognitive decline, and non-suicide mortality. [4-7] Depression is the condition most commonly associated with suicide in older adults, and the highest suicide rates of any age group occur among persons aged 65 and older, with one suicide occurring every 90 minutes [8]. Later-life depression contributes to excess health care utilization, increased nursing home placement, greater burden to medical care providers, and higher annual health care costs [8-13]. We note that throughout this application, we use the terminology “later-life” because in our clinical and research work with a large number of older adults, we have found this to be a preferred term rather than “late-life”.

Older adults with depression are usually identified by their primary care physicians and treated with antidepressants as part of their overall medical care [14]. Yet poor treatment adherence creates a ‘treatment gap’. Older patients often choose not to initiate (e.g. fill antidepressant prescriptions) or prematurely discontinue treatment. Even among those who begin treatment, subsequent non-adherence is common, with estimates ranging from 40% to 75%, which often prevents older adults from achieving desired outcomes. [14, 15] Establishing early adherence is the foundation of adequate pharmacotherapy and reduced depressive symptoms.

The proposed study will test the effectiveness of the Treatment Initiation and Participation (TIP) program, an intervention to improve antidepressant adherence and depression outcomes in older adults. The key to the intervention is the involvement of the older adult in creating an adherence strategy tailored to his/her barriers and needs. The proposed study will be conducted at two primary care centers with diverse older adult populations located in two complementary geographical settings (Ann Arbor, Michigan and New York City) using community samples that can ‘strengthen the public impact of NIMH-supported research’ (NIMH Strategic Plan, 2008). Our preliminary studies indicate that this brief, personalized, psychosocial intervention was well accepted by primary care physicians and older adult patients. In our pilot study, participants in TIP had better adherence to antidepressant therapy and better depression outcomes than older adults receiving usual care (Preliminary Data C3c). The TIP intervention is based on the Theory of Reasoned Action to address the potentially modifiable attitudes, beliefs and stigma concerns, as well as tangible barriers to adherence (e.g. inability to manage medications). The TIP intervention is tailored to individual barriers to adherence, helps define treatment goals, and develops a patient-specific plan for successful adherence.

Therefore, the Specific Aims of the proposed study are to conduct a two-arm randomized controlled trial of the effectiveness of the Treatment Initiation and Participation (TIP) program compared to treatment as usual (TAU) in a sample of 260 older adults drawn from two primary care sites and followed for 24 weeks. Specifically, the aims are: 1) to test the impact of the TIP intervention on adherence to antidepressant treatment, and 2) to investigate the impact of the TIP intervention on depressive symptoms. To achieve these aims we propose the following hypotheses:
Primary hypothesis:

1. Adherence Hypothesis: Participants randomized to the TIP intervention will be significantly more likely to be adherent (take more than 80% of prescribed doses) to antidepressant treatment at 6-week follow-up (immediately after the intervention is completed) and 12-week follow-up (6 weeks after intervention is completed) as compared to older adults randomized to the TAU control condition. Note: we have not included hypotheses about adherence at 24 weeks because we believe that adherence reports at 24 weeks (e.g. 6 months after prescription) may be a function of clinical response, physician prescribing procedures, and sustained side-effects. While continued adherence is important, the TIP intervention targets specifically early treatment initiation and adherence.

Secondary hypothesis:

2. Depression Hypothesis: Participants randomized to the TIP intervention will have a significantly greater reduction of depressive symptoms (on the HDRS) from baseline to the 6-week, 12-week and 24-week follow-ups than older adults who are randomized to the TAU control condition.

Exploratory Analyses: We propose to conduct three exploratory analyses to identify the moderating impact of subject characteristics, the mediating effect of adherence on depression outcomes, and the correlates of specific patterns of non-adherence.

1. Moderator analyses: We will explore the moderating impact of participant race and depression severity as well as clinical factors commonly co-morbid with later-life depression (baseline somatic anxiety, mild cognitive impairment and alcohol use) on the effect of the adherence intervention among participants. These analyses will enable the research team to gain knowledge regarding for whom the TIP intervention appears to be most effective. This information could be applied in the design of subsequent trials in different clinical populations of elderly patients (e.g., a trial targeting elders with mild cognitive impairment and depression).

2. Mediator analysis: We will examine early antidepressant adherence (at 6 weeks) as a mediator of the effect of the intervention on depressive symptoms. We hypothesize that TIP’s advantage over TAU will be greater (decrease in depressive symptom severity from 6 to 24 weeks) for those participants who were adherent in the first six weeks. The effect of TIP versus TAU will be greater on subsequent depressive symptoms among those participants who are adherent at 6 weeks.

3. Patterns of nonadherence: In the Primary Adherence Hypothesis, patients who did not initiate treatment, or took less than 80% of prescribed doses will be considered nonadherent. In exploratory analyses, we will characterize the various trajectories of adherence and explore the psychological barrier correlates of these adherence trajectories (e.g., stigma, necessity versus concern, self-reliance).

Summary: The proposed research will test an innovative intervention, the Treatment Initiation and Participation (TIP) program, to develop personalized antidepressant adherence strategies among older adults with depression being treated in primary care settings. This new intervention has the flexibility to address the individual barriers to participating in treatment as well as the potential to be sustained in a large primary care practice. It has the promise to impact the delivery of depression care by supporting antidepressant adherence to existing treatments for depression, thereby closing the treatment gap and lessening disease burden.

The proposed research study is aligned with the research targets of the NIMH Strategic Plan. Specifically, Objective 3.2 proposes to “expand research on treatment adherence to include systematic assessments on why patients do not adhere to treatment regimens, as well as how patients self-manage or individually tailor their treatments” and to “develop psychosocial and environmental interventions to improve adherence”. The proposed study translates these objectives into a research study with: 1) a personalized intervention tailored to the needs of the individual; 2) participation from a “diversity of people and settings involved in health care” by conducting the study in two primary care sites serving ethnically, socioeconomically and geographically diverse older adult populations; as well as examining 3) clinical predictors of response by identifying moderating factors that may impact on the delivery of the intervention in special populations with high comorbidity and inform future implementation of the program.

The methods for the proposed study have been developed in collaboration with the primary care sites that will host the study. The study brings together two teams of investigators with similar but different foci related to the area of barriers to depression care. Each investigative team contributes a study site that is ethnically and racially diverse. The Investigative team combines disciplines (Clinical Psychology, Geriatric Psychiatry, Epidemiology, Biostatistics, Public Health) and draws on the expertise and track record of conducting research in primary care settings at both the University of Michigan and Weill Cornell Medical College.
B. BACKGROUND AND SIGNIFICANCE

B1. Who is the target of the intervention? Mrs. B is a 73-year-old African-American widow who lives alone in NYC and is proud of her independence. She supports herself with Social Security, but is financially strained and worries about being able to make ends meet. She has diabetes and had hip surgery one year ago. She has an adult son who lives in Baltimore. He offered to relocate her to be nearer to him, but she declined and wishes to stay in her home. When seen by her primary care physician (PCP), she discussed her financial worries and appeared hopeless. She reported having difficulty falling asleep, waking frequently, spending more time alone and less time reading due to difficulties concentrating. Mrs. B was not feeling well, but thought “nothing can be done” as she saw the hip surgery as the “beginning of the end”. Upon inquiry, she reported having no real appetite, often until dinner time. Her greatest concern was that she would be unable to get around and would lose her independence. Mrs. B’s PCP identified her symptoms as major depressive disorder and prescribed her an antidepressant.

B1a. What did TIP do? The TIP counselor met with Mrs. B, who was reluctant to take a medication. She did not see herself as depressed, attributing much of her unhappiness to her financial strain. She believed her “low moods”, decreased energy and sleep difficulties were a natural outcome of aging. Mrs. B was worried that the medication would be addictive and had concerns about how she would feel. She was concerned that her friends would think she was “crazy”.

The TIP counselor reviewed Mrs. B’s concerns, and offered information about the symptoms of depression and the possibility that Mrs. B’s distress might have additional origins. The counselor told Mrs. B that many people endorse the myth that depressive symptoms are “a natural part of aging”. She acknowledged Mrs. B’s concerns about stigma and her shame about needing assistance. In review of Mrs. B’s recent history with the counselor, Mrs. B was able to say that prior to her hip surgery she did not feel so “hopeless and old”. This recollection gave her a different perspective on her symptoms. The counselor helped Mrs. B to distinguish realistic concerns about finances from hopeless thoughts. While Mrs. B was initially skeptical about treatment, she acknowledged that she would like to laugh more and enjoy visits from her neighbor more than she had.

Mrs. B was able to build a collaborative relation with the TIP counselor and consider the information the counselor provided. This gave Mrs. B the initial impetus to try the antidepressant. Mrs. B was not sure if she was going to tell her friends about her depression or taking the medication, but she realized that disclosure was her choice. This made it easier to cope with her fears about stigma. Thus, the TIP intervention, the cornerstone of which was Mrs. B’s participation: 1) allowed her depression care to become personalized to her particular situation; 2) incorporated her own goals for treatment; and 3) enabled her to overcome successfully barriers to treatment adherence.

B2. Background and Significance

Prevalence of depression in older adults: Older adults now comprise the fastest-growing segment of the US population, with 37 million people age 65 and over in 2006, accounting for 12 percent of the total population [17]. The number of older people will increase even more dramatically after 2010 when the Baby Boomers start turning 65, doubling the US population of older adults by 2030 [18]. Depression in later life is prevalent; It is expected that depression will become the second leading cause of disability worldwide in the next decade [19]. Later-life depression is associated with increased disability [20], poor medical outcomes, risk of decline in cognition, and compromised quality of life [21-23]. Depression among older adults is also associated with excess utilization of health care, increased placement in nursing homes, greater burden to medical care providers, and higher annual health care costs [8-13]. Depression, specifically, worsens the outcomes of many medical disorders and increases the risk for falls [3] and non-suicide mortality [4, 5, 7, 24, 25]. Of gravest concern, depression is the condition most commonly associated with suicide in older adults[26]. The highest suicide rates of any age group occur among persons aged 65 and older, with one suicide occurring every 90 minutes [8].

Depression treatment in later-life: Antidepressant therapy is safe, tolerable, easy to prescribe and can effectively ameliorate the symptoms of depression in older adults. [27-29] Effective treatment has a positive outcome beyond just symptom remission; it is associated with improved physical functioning, reduced instrumental activities of daily living disabilities [30], improved self-efficacy [31], and reduced mortality. [32]

Primary care physicians provide the majority of treatment for later-life depressive illness. [13, 33]

Antidepressant therapy is the evidence-based depression treatment for older adults in primary care because few physicians are willing to refer their patients for psychotherapy [34]. In recent years, with the availability of selective serotonin-reuptake inhibitors, screening initiatives, and collaborative care interventions, advances have been made in ‘first-generation problems’ [35], resulting in improved rates of detection and treatment of...
Adherence to depression treatment in later life: Adherence to recommended treatments remains a significant deterrent to quality care for mental illness across the lifespan. Among older adults with depression, this challenge is compounded by medical and psychiatric comorbidity, medical regimen complexity and skeptical attitudes towards mental illness and its care. Non-adherence is common with estimates ranging from 40% to 75%. To improve depression care, a number of multi-site studies such as PROSPECT [40], IMPACT [41] and PRISMe [42] have investigated the impact of introducing a care manager into primary care settings. Meta-analyses across studies have shown that collaborative care is effective in improving depression outcomes [43]; however, even in successful intervention studies for depressed older adults nonadherence was a challenge [44].

While nonadherence is problematic throughout the treatment course, the early phase of treatment (first six weeks) is a particularly critical time period with an increased risk of treatment drop-out, medication discontinuation [45, 46], and vulnerability to suicide [47]. There is evidence that antidepressant adequacy and adherence are associated with recovery from depression. Datto et al., found that early antidepressant adherence (6 weeks) predicted depression outcomes [48, 49].

There are a number of factors thought to influence adherence to depression care in later life; these are discussed fully in section Theoretical Model for TIP. Based upon an extensive review of the literature on factors that affect antidepressant adherence among older adults, Zivin and Kales [15] have argued that innovative interventions should target the potentially modifiable barriers to depression adherence such as attitudes, stigma, misconceptions about side effects and beliefs.

Why older adults?: Older adults faced with multiple barriers to adherence pose among the greatest challenges to improving depression treatment in primary care settings. Improving adherence in this growing population is the critical “next frontier” in later-life depression treatment, and our best hope to improving outcomes for these patients with the treatments currently in use. Adherence interventions that are successful with the challenging population of elders may also be tailored to other populations with multiple barriers.

Opportunities for additional depression quality care improvement: Care manager interventions to improve depression treatment for elders in primary care such as PROSPECT [40], IMPACT [41] and PRISMe [42] introduced a non-physician staff person who could help the older adult receive adequate treatment for depression. The care manager model follows the patient closely, consults with a psychiatrist and provides information on depression and its treatment. The addition of a care manager can make a clinically meaningful impact on the quality of care and depression outcomes for depressed elders. However, to date, few primary care organizations have adopted such models. A partial explanation for lower than optimal uptake of these models may lie with the unreimbursable costs of care management. For example, in the IMPACT study, care managers were nurses or psychologists specially trained for the study as depression clinical specialists. Interventions using non-medical support staff members already existing in a large primary care practice (e.g., social worker or physician assistant) could potentially be more sustainable.

Additionally, the care manager interventions have not generated specific and manualized intervention protocols with techniques that are both personalized and have proven impact on the problem of non-adherence. We propose that to improve adherence to the depression treatment it is imperative to address the specific barriers presented by each patient, allowing the adherence plan to be effectively tailored to their needs. The intervention proposed in this application, the Treatment Initiation and Participation (TIP) program targets early adherence, defined as the first six weeks of treatment. The TIP program may be used in the early
phase of a Care Management intervention for those sites who have adopted this model. Alternatively, the intervention can stand alone as a brief intervention to improve adherence.

Theoretical Model for TIP: There are a number of models of individual-level health behavior change; each model highlights different dimensions that influence health behaviors. The Theory of Reasoned Action [50] posits that behavioral intention and eventual treatment use are determined by a person’s weighing of the potential risks and benefits of the behavior (e.g. depression treatment). [37, 51] Howland’s [52] adaptation of the Theory of Reasoned Action divides factors impacting health behaviors into “internal” and “external”. Internal factors are beliefs (e.g. spirituality), attitudes, and social norms (e.g. family opinions, stigma) that are potentially modifiable through education or other experiences. External factors are either not modifiable (e.g. race) or modifiable only with significant effort (e.g. depression level, social support) [37, 51]. External factors may affect health behavioral intent through a person’s attitudes and beliefs (e.g., race may be associated with the internal variable of spirituality). The balance of factors favorable and unfavorable to treatment will determine intention, which in turn will lead to action [53]. Halgin et al [54] used the Theory of Reasoned Action to provide a framework for understanding why many patients will not accept a diagnosis of depression.

For older adults with depression, the barriers toward seeking treatment are compounded by associated symptoms of low energy and resignation (often exacerbating concomitant medical conditions), frequent cognitive deficits and other related disabilities [55]. Depression is often difficult to self-diagnose in later life due to a number of factors. Older adults may be unaware of the constellation of symptoms physicians diagnose as depression, or they may confuse depressive symptoms with symptoms of medical illnesses or losses associated with aging. Cultural assumptions about mental health needs and care may present additional barriers to accepting treatment for depression [56]. Concerns about stigma, fear of involuntary hospitalization and reluctance to divulge personal information are common among elders, and may be even more of a concern to minority patients [57, 58]. The individual-level reluctance to accept treatment among minority seniors may reflect previously effective coping mechanisms and adaptations to surviving poverty, racism and discrimination that become obstacles to health care in later life [59, 60].

Based upon an extensive review of the literature [15], we adapted the Theory of Reasoned Action and categorized potential factors impacting patient adherence based upon their modifiability—e.g. how specialized interventions might alter various barriers to adherence. Modifiable factors include psychological barriers such as stigma, beliefs about self-efficacy and depression etiology, resignation about limitations, fears about treatment, and misattribution of symptoms. Other factors that may be less modifiable per se (but that may have an impact on adherence that is potentially modifiable by specialized interventions) include illness barriers such as depression severity, somatic anxiety, alcohol use, mild cognitive impairment, and tangible barriers such as level of disability, distance to care, and treatment cost. Non-modifiable factors include patient gender and race. It should be noted that while the latter demographic factors are obviously not modifiable, attitudes and other factors that are associated with gender and race may be intervention targets (e.g. stigma beliefs in African-American older patients). While we recognize that barriers to effective depression care exist also at provider and systemic levels [61], the proposed Treatment Initiation and Participation (TIP) intervention targets individually identified barriers not previously targeted in intervention research.

**Patient-level barriers to care for the depressed older adult:** We have grouped these individual potentially modifiable barriers into three groups: tangible; psychological; and illness-related barriers. These barriers influence the older adult’s weighing of the potential risks and benefits of the treatment and thus impact on the...
behavioral intention to initiate treatment and eventual treatment participation. We provide a description of the three groups of barriers and evidence, where applicable, of their relation to adherence.

Tangible Barriers: The tangible barriers may affect the concrete ‘ability’ to adhere to an antidepressant medication regimen. Specific barriers may emerge with advancing age, such as impaired mobility, limited transportation, and living on a fixed income. For older adults, it has been reported that greater distance to travel decreases service use [62][83]. Once care is initiated, however, service volume is found to be unaffected by distance [62]. A Canadian study found that cost-sharing policies may prevent older adults from filling new antidepressant prescriptions, but also speculated that stigma may have curtailed use [64]. With the introduction of Medicare Part D coverage for prescription costs, U.S. elderly have had cost barriers to taking medication reduced [65]. From 2005 to 2006, the average out-of-pocket antidepressant expense dropped 21%, with a 7% increase in medication use [66].

Depression-specific challenges: Depressive symptoms and resulting impairments compound the psychological and tangible barriers to care and pose depression-specific challenges to being adherent to antidepressant medication. Depressive symptoms create low energy and lack of motivation to engage in the day-to-day activities, and lead to withdrawal from usually pleasurable activities. This is compounded by depression-specific beliefs (e.g., hopelessness, worthlessness) that distort the older adult’s perception of self-efficacy and ability to change which can create resignation and reduce the need for care. A vicious cycle exists where disabilities are compounded by resignation that further curtails activity and increases impairment.

While tangible barriers themselves may not be mutable, often they are not insurmountable. We propose that these tangible barriers become surmountable when they are stripped of psychological barriers.

Psychological barriers: Psychological barriers are the beliefs about depression (e.g. ‘depression is a natural outgrowth of aging’, ‘depression means you are weak’) and its treatment (e.g. ‘medications are addictive’), the social costs of being in depression treatment such as stigma (e.g., personal fears of discrimination or devaluation) and social attitudes (e.g., fearing family rejection, social exclusion). Within this broad domain of psychological barriers, each older adult has an individualized profile of the challenges s/he faces to be adherent. Psychological barriers influence the perception of the need to be adherent to antidepressant medication. The justification for our selection of these target barriers is below and in our Preliminary Studies.

Stigma and Social attitudes: In spite of the public education about depression and its care, stigma remains pervasive and familiar to older adults. Corrigan has defined stigma as having two facets: public and self-stigma [67, 68]. Link [69, 70] emphasized the views of devaluation and discrimination that characterize public views.

Community-dwelling elders who need care but have not yet contacted providers report concerns about social costs [67][71, 72]. To avoid stigma, community-dwelling older adults are more likely to turn to a primary care physician, or to use natural remedies over psychotropic medications or psychotherapy for symptoms of depression [73]. Most adults who have crossed the threshold to initiate mental health treatment report awareness of the existing stigma [74][75] (Preliminary Data C3b). Perceived public stigma at the initiation of care predicts poor medication adherence and higher rates of mental health treatment discontinuation among depressed elderly three months later [45, 46]. Perceptions of stigma are associated with feelings of social exclusion and poorer quality of life in older adults [76]. Anticipated stigma (expected personal costs from one’s own family or social network related to taking an antidepressant for depression) is higher among depressed elders. Adults in outpatient mental health treatment who perceive their social network as supportive of mental health care are significantly more likely to remain in treatment [77, 78].

Beliefs about depression and its care: Individuals hold beliefs about the etiology, course and treatment of depression that influence their treatment adherence. Skepticism about the efficacy of antidepressant medications has been associated with reluctance to accept a diagnosis of depression [51] and was the sole predictor of early discontinuation in one study [79]. In primary care, up to half of older adults reported concerns about the long-term effects of antidepressants and becoming dependent on them [80]. Many older adults misattribute depressive symptoms as a consequence of aging or medical illness, and therefore do not seek care. Other elders may feel responsible for causing their illness [81] (Preliminary Data C2) or express concerns about the personal and social impact of treatment [67, 82, 83]. Alternatively, receptivity to mental health care is associated with positive health behaviors such as filling an antidepressant prescription, receiving guideline concordant therapy or counseling [84]. Increased confidence in mental health treatment appears to diminish the negative impact of stigma [85]. A greater perceived need for antidepressant therapy, relative to the concerns about care, predicts medication adherence [79]. Among depressed adults, endorsement of the presence of an illness was a better predictor of antidepressant adherence than objective depression severity ratings [45].

Illness-Related barriers: These barriers include those factors related to comorbid medical and psychiatric illness. The complexity of a medication regimen necessitated by medical comorbidities may be associated with
decreased adherence to depression treatment in the elderly [86]. Medication adherence problems increase with the total number of drugs prescribed [87]. The average older American takes three prescription and four over-the-counter medications daily, and those with depression may take more medications than those without depression [88]. Key risk factors for non-adherence related to poor outcomes in the elderly include: lack of a medication administration routine, therapeutic duplication, hoarding, confusion over generic and trade names, discontinued medications retained, and multiple storage locations [89]. Overwhelmed by medication regimen complexity, patients may also decide to limit the total number of medications taken, with the view that continuing their antidepressant is discretionary, whereas taking medications for other medical illnesses is necessary or more important [90]. Worries about adverse effects may also prevent depressed patients with comorbidities from adhering to medication regimens [91]. In turn, such worries may be multidimensional because: 1) the likelihood of adverse drug reactions increases with increasing numbers of medications in a potentially exponential fashion [92]; and 2) worries about adverse effects may also be anticipatory and relate to comorbid anxiety and somatization [93]. As with tangible barriers, medical comorbidities themselves may not be mutable, but the problems created by medication regimen complexity are not insurmountable with the assistance of a personalized intervention for depression adherence.

Other illness factors that may impact later-life depression medication adherence include: comorbid somatic anxiety, comorbid moderate alcohol use, and mild cognitive impairment. Somatic anxiety: Depression associated with clinically significant anxiety, primarily generalized anxiety disorder or subsyndromal anxiety is found in 30-60% of older outpatients with depression [94-98]. In the recent PROSPECT study using care management for later-life depression, the intervention was more effective than usual care in patients with low anxiety but added little benefit for patients with higher anxiety severity [99]. Anxious individuals may be hyper-vigilant regarding their bodily sensations, and overestimate the danger of medications or the severity of side effects [94]. Older patients with anxious depression frequently misattribute somatic symptoms of anxiety to adverse medication effects, contributing to both drop-out and poor response in antidepressant trials [93]. Additionally, older adults with anxiety/somatic focus may tend to discount psychological explanations for psychiatric symptoms and refuse treatment [100]. The potential negative effect of somatic anxiety on adherence is especially concerning as anxious depression is associated with higher rates of suicidality in older patients [93]. However, comorbid anxiety is also modifiable; one study [101] found that symptoms of psychic anxiety and somatic symptoms/anxiety were among the symptoms showing greatest change during adequate antidepressant treatment of later-life depression. Cognitive difficulties with mild cognitive impairment: Even in older adults without dementia, mild cognitive impairment is a uniquely burdensome influence on adherence to depression treatment in a significant number of older adults. Medication adherence involves taking a prescribed medication at the appropriate time in the correct amount and manner [102]. Thus, adhering to medications requires intact executive function, working memory, and encoding and storage of information. While there is evidence for specific cognitive deficits associated with nonadherence among both mixed-aged and older adults with schizophrenia [103] and with HIV [104], there is less research regarding specific cognitive deficits associated with nonadherence in later-life depression. Cooper et al [105] found that while decreased adherence in older adults was associated with cognitive impairment, the relationship was not linear; adherence was lowest in those with less than severe impairment. The researchers hypothesized that those with very mild impairment were able to use memory aids such as pillboxes, while those with more severe impairment had caregivers assisting them. Thus, patients with mild but clinically significant cognitive impairment may need external assistance in creating a treatment plan that can be personalized to enhance their ability to adhere to depression treatment. Alcohol use: Alcohol misuse is a growing concern for older adults, particularly primary care patients [106]. In a large-scale primary care study of elderly patients, investigators found that 22% were moderate drinkers (1-7 drinks per week), 4% were at-risk drinkers (8-14 drinks per week), with 4.5% heavy (>14 drinks per week) or binge drinkers. It is common in clinical settings to observe older patients escalating their alcohol use in response to depressive symptoms such as insomnia. Unfortunately, studies of comorbid depression, alcohol abuse and treatment adherence are virtually non-existent for patients of any age. However, the limited existing data suggest a negative relationship between problem alcohol use and adherence to depression treatment. One study of nearly 4000 older adults in 11 countries [105] found that non-adherence was associated with problem drinking. More studies are needed to determine the relationship between problem drinking and adherence to depression treatment in older adults.

In sum, we propose to test of the usefulness of a brief, novel intervention, the Treatment Initiation and Participation (TIP) program, to improve antidepressant adherence and depression outcomes at two primary
care centers with diverse older adult populations (Michigan and NY). The TIP program is innovative in its approach to the problem of nonadherence to antidepressant treatment among older adults in primary care settings. TIP targets early adherence as the foundation of early pharmacotherapy efficacy. TIP is unique in its emphasis on the psychological barriers that may undermine adherence behaviors, such as stigma and health beliefs, and its focus on techniques to address these potential obstacles. Unlike other interventions, TIP personalizes the antidepressant treatment by helping the older adult set a goal and develop an individualized antidepressant adherence strategy that is tailored to his/her lifestyle. The strategy will address the three levels of barriers described above and will define a specific plan for remembering to take the medication. Finally, the target is an aging population that has traditionally been underrepresented in adherence studies of depressed patients. The proposed research will have impact because of the growing proportion of individuals in the U.S. who are in later life and are at increased risk for the negative consequences of depression, the most common mental health disorder in the U.S. in this age group. While rates of diagnosis and treatment of later-life depression are improving, a treatment gap remains due to nonadherence, from older patients never initiating recommended treatment, erratic medication-taking or discontinuing treatment prematurely. Research to understand better nonadherence and to test interventions to improve adherence are important components of the NIMH Strategic Plan. If the proposed intervention improves antidepressant initiation and adherence, it could decrease the deleterious effects of and reduce the unnecessary burden of untreated later-life depression. As a brief, manualized psychosocial intervention, TIP is designed to fit easily within primary care practices and to be delivered by non-MD staff.

C. PRELIMINARY STUDIES

In Section C, we provide data on: 1) the combined experience and history of successful research with older patients with depression and with adherence behaviors in older patients as well as; 2) the feasibility and impact of the TIP intervention. The data summarized have been generated from both the Weill Cornell and University of Michigan groups. The collective experience of the investigators demonstrates the capability to successfully undertake and complete the proposed study.

C1. Initiating Antidepressant Therapy

Guidelines recommend that patients with new episodes of major depression receive continuous antidepressant treatment during the acute treatment phase. Using performance measures developed with the VA Office of Quality and Performance, the number of VA patients receiving adequate antidepressant treatment during the acute treatment phase was examined \[107\]. VA patients with new episodes of depression were identified (N=20,575). In separate multivariate logistic regressions, the influence of age, gender, race, marital status, distance to VA providers, region, psychiatric/medical comorbidities and treatment location at the time of initial diagnosis were evaluated. Results indicated that 31% percent of depressed older veterans did not receive adequate antidepressant coverage (>12 of 16 weeks following diagnosis) during the acute treatment phase. More recent analyses by our group (unpublished data) calculating medication possession ratios (MPRs) using the National Registry for Depression (NARDEP) indicate that 40% of older depressed patients have poor (<80%) MPRs. While data from these analyses cannot define causality, it is likely that poor medication adherence (e.g. never filling, discontinuing or failing to refill antidepressant scripts) likely plays a large role in inadequate medication coverage for many older patients.

Early Treatment Risks: Collaborators at UM have recently established that VA patients in depression treatment had higher suicide rates during two readily identifiable treatment periods: the 12 weeks following psychiatric hospitalization and following new antidepressant starts, with risks highest following inpatient hospitalization\[87\]. In a recent study (Kales et al, submitted Journal of General Internal Medicine), we examined whether certain patient characteristics were associated with disparities in levels of outpatient monitoring. We found that the sole patient characteristic associated with significantly lower rates of monitoring for both high-risk treatment periods was age \( \geq 65 \). This is of concern, given that older patients appear to be at higher risk for suicide, particularly following inpatient stays, and may need particular attention in this time frame. Again, as with antidepressant coverage, we cannot determine causality, but we suspect that the low rates of follow-up visits found in older patients with depression have in part to do with patient-level barriers (e.g. refusal for more frequent visits, no-shows, cancellations, and medical comorbidity). We concluded that adapted interventions and proactive outreach may be needed that target this elderly population with depression.

C2. Barriers, Treatment Participation and Adherence. Data collected in both study sites provide complementary information about patient-level barriers to later-life antidepressant treatment. These will be summarized sequentially:
Prior work by the UM group on racial disparities in later-life depression \cite{108, 109} including examinations of provider-side factors on depression diagnosis/management strongly suggested the need to study the patient-side determinants of depression care. The current R21 (R21MH073002) “Racial Differences in Antidepressant Care Adherence” being conducted at the University of Michigan is using a mixed-methods approach to identify the key modifiable determinants of depression treatment adherence among older African-American and white patients. This includes a baseline survey with particular attention to possible factors that may differ across racial groups with depression as well as a series of focus groups held with a subset of subjects to obtain more in-depth qualitative information. Views from a series of focus groups held with older African-American subjects yielded themes including:

1) **fears about treatment and treatment efficacy**
   - “I just wonder what these depression pills are made of? Where do they come from? Why would a pill of some kind be made to help us?”
   - “I don’t think doctors really understand…they just give you something to cover it over…they don’t get to the root of it.”

2) **stigma**
   - “You don’t come out and say it [that one is depressed]…if you speak your mind they say, don’t pay any attention to her, she’s crazy”
   - “People judge you”

3) **conflicting views of religion and psychiatric care**
   - “You have to pray, cry, get up, wipe your eyes and come out fighting”
   - “My husband said to me, ‘do you believe in God?’ Well, then, ACT like it’…and we prayed and I didn’t take the medication anymore”

Preliminary findings from the baseline survey for subjects recruited to date (n=144, with n=42 African American and n=102 white patients) also appear to confirm that a number of psychological barriers may be even more problematic for African-American subjects. These included perceived stigma on the Stigma Coping Scale with African-American subjects endorsing significantly greater concerns with stigma than white subjects (t=2.19, p<0.03). As in the focus groups, African-American subjects also had acknowledged significantly greater fears about treatment and treatment efficacy on the Patient Attitudes and Ratings of Care for Depression scale (p<0.03). In addition, s<br>ignificantly more African-American than white subjects cited problems with transportation (28.6% vs. 14%, X^2=4.43, p<0.04) and finances (45.2% vs. 23.5%, X^2=6.69, p<0.01) as tangible barriers to depression care. Conversely, the percent of African-American subjects who endorsed drinking alcohol was significantly lower than white subjects (34.1% vs. 59.4%, X^2=7.46, p<0.007). While the number of prescription medications taken by subjects did not differ by race, it should be noted that a majority of subjects were taking five or more medications.

In a parallel fashion, data on patient-level barriers has been collected by Dr. Sirey and her group at Cornell: **Lack of knowledge about depression**: In a sample of 66 older adults with depression being prescribed antidepressant treatment in primary care, both logistical and psychological barriers to adherence were evident at treatment initiation. Fifty-four percent of older adults indicated that they believed that ‘depression is an expected part of growing old’. Most (82%) felt it would eventually ‘go away by itself’. However, only 13% indicated that they believed it is a ‘natural reaction to loss’. When prescribed antidepressant therapy, only 45% knew the name and dose of their antidepressant medications and 34% knew both the dose and timing. These two sets of ideas (treatment is helpful vs. treatment is unnecessary or harmful) reflect the ambivalence presented by many older adults who are recommended antidepressant therapy. **Stigma concerns and ambivalence about antidepressant treatment**: Among a sample of 35 older adults with depression identified in primary care, 50% indicated that they believed that most people ‘would not accept a person with depression as a close friend’ and ‘could not be open about their own illness’. Twenty-three percent felt to blame for their illness. At the same time, 79% felt depression is ‘helped by treatment’. However, 81% indicated that they would prefer to handle emotional problems ‘by themselves’, and 62% ‘felt bad taking an antidepressant’. Most (75%) were worried about side effects. These two sets of ideas (treatment is helpful vs. treatment is unnecessary or harmful) reflect the ambivalence presented by many older adults who are recommended antidepressant therapy. **Stigma predicts treatment discontinuation among older adults**: A two-stage sampling design identified 92 outpatients with major depression. Sixty-three patients were 18–64 years old; 29 patients were 65 years old or older. Perceived stigma was assessed at baseline, and discontinuation of treatment was recorded at 3-month
follow-up. The hypothesized age difference in the effect of stigma on treatment discontinuation was tested in a logistic regression model that controlled for baseline severity of depression. In this model, the interaction between age and stigma was significant, and the main effect of age was marginally significant. In older, but not younger patients, greater perceived stigma was associated with a greater likelihood of treatment discontinuation. To illustrate the effect, we calculated the adjusted odds ratio of a mean stigma score 3 points (half the standard deviation) above the mean stigma score for young and old age groups. Older adults had a 1.7 greater likelihood of drop out with a stigma score 3 points above the mean. Sirey, J.A., et al., Perceived stigma as a predictor of treatment discontinuation in young and older outpatients with depression. Am J Psychiatry, 2001. 158(3): p. 479-81.

**Perceived stigma and self-rated illness severity predict medication nonadherence.** 134 adult outpatients with major depression were interviewed at baseline and in follow-up three months later. They were classified as adherent or nonadherent to recommended antidepressant therapy. In a subgroup of the sample, we investigated the relation between self-reported adherence and nortriptyline plasma concentrations and found reasonable concordance. A logistic analysis revealed that overall high perceived stigma (OR=.92, p=.05) was associated with medication nonadherence. While depression severity on the HDRS was not predictive of adherence, higher self-rated illness severity was (OR=1.22, p=.05). These findings indicate that among patients who have sought treatment, higher overall perceived stigma and the perceived need for care at baseline predicted antidepressant nonadherence 3 months later. Sirey, J.A., et al., Predictors of antidepressant prescription and early use among depressed outpatients. Am J Psychiatry, 1999. 156(5): p. 690-6.

**C3. Intervention Pilot Studies:**

**C3a. The Treatment Initiation and Participation (TIP) Program:**
The Treatment Initiation and Participation program is an intervention program designed to reduce barriers and improve treatment initiation and participation in depression care. TIP develops an individualized profile of barriers collaboratively with the participant and uses a variety of techniques (e.g. psychoeducation, problem-solving, motivational interviewing) to address barriers and improve treatment participation. This approach has been piloted with older depressed adults to identify barriers and improve antidepressant adherence in two settings (mental health clinics and primary care). In addition, a modified version of the TIP program is being tested to improve engagement in mental health care (R01 079265, PI:Sirey).

**C3b. TIP in a Mental Health Setting:** Older adults (N=52) with major depression seeking outpatient mental health treatment were randomized to either pharmacotherapy alone or pharmacotherapy with the TIP intervention. A Mixed Effects model demonstrated a group effect on depression outcome such that the intervention group showed a greater improvement in depression than the non-intervention group (F=8.67, df=1,61.54, p=.005). The intervention group had significantly lower hopelessness scores (F=8.12, df= 1, 49.92, p=.006). Only 14% (3/21) of the TIP patients reported any hopeless ideation at study completion as compared to 63% (15/24) of the non-intervention group. At the study completion (28 weeks), 71% (15/21) of the TIP group achieved remission, (HDRS score <10), as compared to 42% (10/24) of the Treatment as Usual (TAU) group ($\chi^2=4.10$, df=1, p=.04). At both 12 and 24 weeks after admission, more TIP patients remained in treatment than patients in the non-intervention group (Fisher’s Exact Test = p.05, and Fisher’s =p.04). Sirey, J.A., M.L. Bruce, and G.S. Alexopoulos, The Treatment Initiation Program: An Intervention to Improve Depression Outcomes in Older Adults. Am J Psychiatry, 2005. 162(1): p. 184-186.

**C3c. TIP in Primary Care:** Adherence: Older adults (N=64) who were newly prescribed an antidepressant by their primary care physician were randomized to either PCP visits alone or PCP visits with the 3-session TIP intervention. Most patients (75%) who met criteria and were contacted for participation were willing to participate. Participants had research assessments at study entry, and 6, 12 and 24 weeks after entry to assess adherence and depressive symptoms. Both groups had adequate 24 week study completion (84% TIP and 76% TAU) with no differences between groups in attrition rates (1K23MH68638, PI: Sirey).
Adherence was rated at follow-up assessments on a scale of 1-6 where a score of 5 or greater equals 15%-20% nonadherence (scale validated in Sirey et al., 2001). At the 12 week follow-up, 82% of TIP patients were 80% adherent whereas only 43% of the TAU patients were adherent. A mixed effect model of adherence found significant group differences at 6 weeks that were maintained at 12 and 24 weeks. The TIP group was significantly more adherent (F=10.89, df=55.1, p<.001). There was no effect of group over time. There were no differences associated with age or gender, or depression severity.

Reduction of depressive symptoms: Both TIP and TAU had comparable levels of depressive symptoms on the 24 item HAM-D at study entry (TIP=20.6, sd=6.6 vs. TAU=20.8, sd=5.0). We examined changes in depressive symptoms over time using a mixed effects model controlling for entry depression severity. We found that older adults in the TIP group showed a greater decrease in depressive symptoms than those elders receiving usual care. The change occurred during the early treatment period (during the intervention visits weeks 1-6) and was sustained until 24 weeks.

Adherence and Depression: To explore the relation of adherence to depression outcome in a preliminary way, we combined TIP and TAU groups and divided the sample into those participants who were fully adherent at the 6- and 12-week follow-up assessments and those who reported variable adherence or nonadherence. In a mixed-effects model, the adherent participants (across both groups) had both lower HDRS scores at follow-up comparison points and over time (adherence group by week F=3.92, DF=3, 154 p= <.01).

D. RESEARCH DESIGN AND METHODS

D1. Overview: The objective of the proposed study is to conduct a randomized controlled trial of the effectiveness of the Treatment Initiation and Participation (TIP) program in a sample of 260 older adults drawn from two primary care sites. Specifically, the aims are: 1) to test the impact of the TIP intervention on adherence to antidepressant treatment; and 2) to test the impact of the TIP intervention on depressive symptoms. Consentig older adults (N=260, 130 from each site) who are newly prescribed an antidepressant for depression and meet inclusion criteria will be randomized to either the intervention condition (pharmacotherapy treatment with their primary care physician and the TIP program) or the TAU control condition (pharmacotherapy treatment with their primary care physician as usual). Research assessments will be conducted in-home at study entry, and 6, 12 and 24 weeks after entry to test the study hypotheses. The in-home assessments reduce study attrition among older participants who are burdened by mobility problems, transportation difficulties, and winter weather-related concerns.

The study will test the hypotheses that depressed older adults who participate in the intervention (TIP) will be: 1) More adherent to the recommended antidepressant regimen at the 6 and 12 week follow-up assessments, and 2) Less depressed at 6, 12 and 24-week follow-ups. We propose to conduct three exploratory analyses to identify characteristics of nonadherence, the mediating impact of adherence on depression outcomes and the moderating impact of common clinical factors that co-occur with later-life depression. The proposed study will be conducted at primary care centers with diverse older adult populations located in two complementary geographical settings (Ann Arbor, Michigan and New York City) and will generate samples that can “strengthen the public impact of NIMH-supported research” (NIMH Strategic Plan).

In the following sections we will describe first describe the intervention and control conditions. These descriptions will be followed by the study design, methods and data analysis plan.

D2. Treatment Initiation Program in Primary Care (TIP): The TIP program is a brief, individualized intervention designed as an adjunct to pharmacotherapy for depression prescribed by a primary care physician. The key to the intervention is the involvement of the older adult in creating an adherence strategy tailored to his/her barriers and needs. TIP is different from other interventions in two ways. First, the target barriers have been empirically identified in earlier research. Secondly, the individualized profile of barriers addressed in the TIP program is personalized based on an assessment conducted with the older adult. Each participant identifies the barriers or challenges that are relevant to him/her. TIP goes beyond rational decision-making by helping the older adults articulate a treatment goal, identify underlying beliefs and concerns that guide treatment adherence decisions, and develop an adherence strategy that fits his/her lifestyle. Often the barriers to adherence are not well formulated. The TIP intervention helps the senior articulate the often ‘irrational’ fears that s/he may be self-conscious about admitting to the PCP or him/herself, but become the
D2a. TIP Intervention Protocol: The intervention consists of three in-person meetings (30 minutes each) at the primary care office and an additional telephone follow-up with a trained TIP counselor. Meetings at the primary care site allow for ‘real life’ implementation of the TIP intervention. Three sessions allow the TIP Counselor and older adult participant to establish an alliance and work on barriers together. However, the brevity keeps: 1) independence as the goal; 2) contrasts with psychotherapy; and 3) decreases potential dependency. There are six steps to the TIP intervention: 1) review symptoms and antidepressant therapy regimen, and conduct a barriers assessment; 2) define a personal goal that could be achieved with adherence, 3) provide education about depression and antidepressant therapy; 4) address collaboratively barriers to treatment participation; 5) create an adherence strategy; and 6) facilitate and empower the older adult to talk directly with the PCP about the treatment. While the order of the steps may vary for different individuals, we will present the most common format:

1. The first step is to review symptoms and antidepressant therapy regimen, and conduct a barriers assessment. Review of depressive symptoms includes eliciting symptoms that may be distressing, assessing depression severity and monitoring the presence of suicidal ideation. Any suicidal ideation will be followed by our suicide risk assessment protocol[110].

   In older adults, depression frequently co-exists with other clinical symptoms such as somatic anxiety, mild cognitive impairment, and potentially, increased alcohol consumption. Where applicable, the counselor will discuss these symptoms as part of the depression review. Somatic anxiety poses a special challenge to early antidepressant adherence. Worries about side effects, body changes and long-term consequences of treatment can undermine initial openness to treatment. For older adults with somatic anxiety, special attention will be taken to elicit concerns. Identifying anxiety symptoms and concerns that exist prior to treatment can help untangle side effects from pre-existing anxiety.

   The review of symptoms and the antidepressant recommendation usually elicits spontaneously a first set of barriers. The counselor then identifies potential barriers with the older adult by reviewing barriers listed in the TIP Intervention Guide. The identified barriers will then become the focus of the intervention. In our pilot work, we found that older adults are sometimes initially willing to accept antidepressant therapy when their doctor recommends treatment, but may become aware of concerns later and discontinue treatment [46]. Sometimes older adults are reluctant to admit they have concerns about the recommended treatment. In the barrier assessment, stigma concerns are elicited by asking how others (spouse, adult child, friends, etc.) view the participant’s depressive symptoms, and what, if anything, the older adult has done about their stigma concerns. These questions seek to elicit the older adult’s perceptions of how those in their social network view depression and its treatment. It is important to ask specific and direct questions about prior mental health care and knowledge of anyone else who sought care. Barriers are reviewed in a gentle, supportive, non-confrontational manner.

2. After barriers are identified, the counselor works with the client to define a personal goal that might be achieved if depression treatment is successful. Helping the older adult choose a goal is a chance to identify the most problematic symptom, or depression-related impairment from the older adult’s perspective. Sometimes goals are very general, like “I want to have more energy”. Other times they are very specific, such as “I want to make plans to see my friends more often”. Choosing a goal helps both to personalize the antidepressant treatment, to increase treatment participation and to orient the participant towards the future. Working to achieve the goal may help the older adult persist in the face of difficult aspects of adherence (e.g. remembering doses, early side effects). In our exploration of community depressed elders referred for treatment, participants who could articulate a goal were more likely to accept mental health treatment (p=0.02, \( \chi^2 = 5.412 \)) (Unpublished data, Sirey & Mateo, 2008).

3. Once barriers and a goal are identified, the counselor provides education on depression and antidepressant therapy. This discussion goes beyond the basic explanation of depression. It includes dispelling the common myths (e.g. depression is a natural part of aging, or an inevitable response to the death of a loved one) and linking the participant’s symptoms to the criteria for depression. This step allows the older adult to link ‘clinical symptoms’ with the distress or impairment he/she is experiencing. For many adults, the etiology of their distress is viewed as something that cannot be changed (e.g., aging, chronic illness). Reframing symptoms as illness-related allows the older adults to recast intractable obstacles as treatable problems. This is an important aspect of improving the acceptance of antidepressant therapy.
Brief psychoeducation prior to beginning mental health treatment has been found to decrease missed appointments and drop out for both minority and non-minority adults\cite{111, 112}. A psychoeducation intervention to improve knowledge about care and reduce concerns among African-American elderly referred for psychotherapy demonstrated an increase in mental health sessions attended\cite{67}. Similarly, while there are no tried and true stigma interventions, education appears to be useful to allay stigma concerns\cite{68}. Providing education may address knowledge deficits, even in older adults who have had prior treatment for depression.

To support the education process, a packet of material is provided that can be read at home. The packet includes: information on depression, treatment and suicide in older adults from the Geriatric Mental Health Foundation; New York Times articles by public figures about their experiences with depression (e.g., Tipper Gore, Mike Wallace); \textit{Stop the Stigma} by Mary Hopkins; and a note pad to write questions for the PCP prior to each visit. To accommodate vision difficulties that are common in older adults, all materials are provided in large print format and have been used in the pilot studies.

4. The Treatment Initiation and Participation program counselor then goes on to address collaboratively the barriers or challenges to treatment participation and adherence that are identified. The TIP orientation relies on the ‘spirit’ of Motivational Interviewing (MI) to help in exploring and resolving any ambivalence\cite{113}. The stance is directive, but empathic and promotes the individual’s wish to change based on what they find problematic and the personal goal set. Motivations to change are translated into commitments to change with a behavioral plan. It is the strength of commitment to this behavioral plan that is associated with behavior change. TIP uses techniques from MI to help mobilize the older adult who suffers from low energy and anhedonia associated with depression. The TIP counselor elicits both sides of the ambivalence (or pros and cons in decisional terms) and takes an empathic stance to encourage consideration of a shift in the decisional balance towards change. The TIP counselor uses empathic listening and helps to elicit motives for change and resistance/barriers. The counselor then supports a decision and assists in creating an action plan.

The TIP counselor is sensitive to the beliefs and concerns that may have their roots in culture or religion. To identify potential solutions, TIP draws on problem-solving interventions. Using brainstorming techniques, the participant and the TIP counselor will collaboratively identify potential solutions to barriers and evaluate the pros and cons of each solution to choose the best one. The counselor can help the older adult identify alternative perspectives for each of the barrier domains. To guide the counselor, the Intervention Guide with frequent cited participant barriers and effective interventions is used during meetings.

Below is an example of barriers, associated activities and techniques and outcomes:

<table>
<thead>
<tr>
<th>Psychological Barrier</th>
<th>TIP intervention activity</th>
<th>Source of technique (PS, MI, or PE*)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal stigma concern: My neighbor will not include me if she thinks I’m crazy.</td>
<td>Validate concern (stigma is real!); Define disclosure options; Emphasize personal choice; Review pros and cons of each option</td>
<td>MI: Reflective listening and empathy; PS: Brainstorming; MI: Collaboration; PS: Identify Pros and Cons and compare</td>
<td>Support; More hope; Less helplessness; Action plan</td>
</tr>
<tr>
<td>Treatment efficacy concerns What’s medication going to do? Nothing can change.</td>
<td>Identify hopeless as symptoms of depression; Identify what s/he wishes to change; Link goal with treatment outcome</td>
<td>PE: Education about depression; PS: Identify a goal; PE: Review antidepressant efficacy data and discuss the importance of adherence</td>
<td>Increase in knowledge; Increased motivation; Engagement</td>
</tr>
<tr>
<td>Attribution of depression symptoms It’s the diabetes and my age that cause my troubles</td>
<td>Validate overlap of medical &amp; psychological symptoms; Describe symptoms of depression; Review myths &amp; misattribution</td>
<td>PE: Depression symptom and medical symptom overlap; PE: Information on depression; PE: Discuss myths and stereotypes</td>
<td>Increased knowledge; Increased perceived need for treatment</td>
</tr>
</tbody>
</table>

\*PE=Psychoeducation \ PE-Discuss myths and stereotypes \ PS-Problem-solving \ MI=Motivational Interviewing

\textbf{Stigma:} It is not uncommon for older adults to have concerns about shame or stigma when their depressive symptoms are framed as mental illness symptoms and treated with antidepressant therapy. They worry that ‘others’ will see them as weak or vulnerable, and fear that stigmatizing views may jeopardize their autonomy. They worry that their friends will treat them differently, exclude them or avoid them. Stigma is a complex barrier. It is true that individuals discriminate against and devalue adults with psychiatric difficulties. We present stigma as “real”-- as real as transportation barriers. Often stigma is perceived as a “scarlet letter” that is permanent and visible. To address stigma, TIP works with the participant to increase a sense of control and to empower the older adult by providing education and offering the possibility of judicious disclosure. There is evidence that education about mental illness improves attributions about depression and increases views on treatment efficacy\cite{114}. Combining education about depression and its treatments with the ability to make a choice about disclosure in personal situations increases the individual’s sense of control and mastery. When a situation requires disclosure, we review the pros and cons of disclosure and select the best solution.
5. The TIP intervention is based on the assumption that a successful adherence involves perceived need, overcoming barriers, and a realistic well-defined plan for adherence. Creating an adherence strategy involves reviewing what medications are taken and when. Discussion of previous instances of non-adherence helps to identify challenges to adherence. The TIP counselor and patient collaboratively develop strategies to foster adherence including developing a list of medications with generic and brand names, using pill boxes, cueing (e.g. linking medication taking with another activity\[^{115}\]) timing of doses and careful placement of medicines. During this process the older adult can raise concerns about forgetting doses, potential side effects, and duration of treatment. Often addressing the barriers, setting a personal goal and creating an adherence routine will be ‘threshold’ events that will help the older adult feel more empowered, that may result in greater adherence and reduction in depression. They will have collaboratively worked with the counselor on their concerns and difficulties. This increases a sense of personal mastery and medication self-efficacy around taking care of themselves. For older adults who are passively adherent, the TIP process can build an increased sense of commitment to the treatment by addressing unspoken concerns and collaboratively creating an adherence plan.

6. The TIP Counselor will work with the older adult to maintain, facilitate, and empower the older adult to talk directly with the PCP about the treatment. TIP patients are encouraged to monitor their progress and communicate with their PCP. Just as with the TIP intervention, we encourage the participant to view antidepressant therapy as collaborative. Physicians are aided by careful observation of symptoms by knowledgeable patients. Note pads are provided for questions or notes assembled prior to the next visit. If the participant is experiencing intolerable side effects, the TIP counselor works with the older adult on how to describe them and their duration, and to generate a question regarding the side effects for the PCP. Simple guidance on when to contact the PCP and what to say in the message, can help an older adult who is reluctant to ‘bother the doctor’ obtain help rather than simply discontinuing the medication.

The TIP intervention works specifically with the older adult to manage his/her treatment. The counselor uses discretion to decide what interventions should be used. In some cases more education will be required. In others, ambivalence will resolve more slowly, requiring greater definition of a personal goal. Additionally, some older adults will be better at problem-solving than others. While multi-level interventions such as IMPACT and PROSPECT have become increasingly more popular and have demonstrated positive results in trials, it has been harder to integrate them into routine practice\[^{116}\]. The TIP intervention is patient-oriented and designed to empower the patient to manage their antidepressant therapy. It is the simplicity of direct work with the older adult in the primary care setting that increases the potential for sustainability.

**D2b. Who will conduct the Treatment Initiation Program?**

The interventions will be administered by a counselor who has a Master’s degree in Psychology, Social Work or Mental Health Counseling. While we believe it is possible to have TIP delivered by a less skilled interventionist, the research on care manager interventions suggests using individuals with more mental health training may improve outcomes due to the expertise available to deliver different psychological skills and handle personality pathology\[^{117}\]. Thus, for this effectiveness study and consistent with our pilot study, the TIP counselors will have mental health training. If TIP improves adherence, the primary care site could consider adaptation of this service for a nonmedical staff member, such as a physician’s assistant or social worker.

**D2c. Is this a hybrid therapy or a service delivery intervention?**

TIP is a mental health service delivery intervention. It is not a psychotherapy designed to reduce depression per se, but an intervention to augment antidepressant pharmacotherapy. Combining effective techniques used by some psychotherapies does not make the TIP itself a psychotherapy. While these techniques have been used effectively in the context of some psychotherapies, they are also used in other types of interventions to assist individuals, groups and organizations work through the change process.

**D2d. Will a caregiver be involved?**

Older adults may be accompanied by a family member to primary care visits. Caregivers or other supportive individuals can facilitate adherence. However, the TIP intervention specifically targets the older adult to manage medications and enhance their relationship with the PCP. Given variability across elders in caregiver participation, we will deliver the TIP intervention to the older adult participant alone. For all participants, we will document the presence of someone who helps the older adults when s/he is sick, financially or gives advice. In our exploratory analyses, we will examine the impact of an involved caregiver (as defined by support on the Duke Social Support Index) on treatment adherence.

**D2e. TIP Training for Counselors:** Training on TIP will be provided in person at each site by both Drs. Sirey and Kales. Training will include pre-training activities, face-to-face training and follow-up training. We expect face-to-face training to take two days with a follow-up one month later. The face-to-face training will include classroom didactics, role-play and experience providing the TIP intervention with supervision.
Prior to the face-to-face training: Study Counselors will complete training in protection of human subjects online. We have provided online training on Human Subjects to community staff in both our Network Core (P30 MH68638) and as part of the Cornell Homecare Partnership (R24 MH064608).

Day One: Study Orientation, Identification of Barriers: During the first day of training, the emphasis will be on training to elicit depressive symptoms, and beliefs and attitudes assessment (using the Intervention Guide). Counselors will observe a video which illustrates assessment of depression in the context of medical symptoms and suicide risk assessment (Suicide Risk Assessment in the Appendix [110]). Illustrative cases will be reviewed and counselors will discuss their own experiences encountering stigma, ageism and depression before they address these concerns with older adults. This training increases their sensitivity to commonly reported barriers. Counselors will observe a brief tape of motivational interviewing and be provided additional reading. They will engage in role-playing of ‘typical’ scenarios generated from the pilot study.

Day Two: Treatment Initiation Program Intervention Techniques: The second day will focus on intervention techniques. Dr. Sirey will introduce barriers, motivational interviewing and problem-solving techniques. Counselors will review the Intervention Contact Guide (In Appendix). The intervention guide serves as a “play book” for the intervention. It provides the steps of the intervention and a guide to commonly cited barriers. It uses a checklist format so that interventions (e.g. anticipated stigma → explore scenario, review pros and cons of disclosure) and statements (e.g., ‘depression is not an expected part of aging’) that apply are linked to barriers. Guides are used for supervision and to record counselor activities. Role play will be continued using presentations from the previous training and counselors will practice the intervention.

After the classroom training, the counselors will begin their field training to administer TIP. The counselors will observe a videotape of an intervention conducted by Dr. Sirey. Afterwards, they will each have 3 training cases with video-conferenced supervision with both Dr. Sirey and Dr. Kales (visits 1-3). Dr. Sirey will supervise the TIP principles and techniques, and Dr. Kales will provide supervision on medication and comorbid medical issues. TIP competency is based upon: identifying barriers; successful goal-setting; skillful use of techniques; and display of appropriate manner with participants (the fidelity measure is included in the Appendix).

D2f. TIP Fidelity: After the training period, separate supervision will be provided monthly across sites with Dr. Sirey and Dr. Kales. Each counselor will ‘present’ study cases. Dr. Sirey will review the TIP techniques and administration of the intervention with attention to personalizing it for each patient. Dr. Kales will provide consultation on the adequacy of pharmacotherapy proposed, side effects and other health issues relevant to depression care. After competency is established, Dr. Sirey will review tapes quarterly of two participant’s series of meetings with the Counselor (all three visits) to assure fidelity. If fidelity is inadequate, feedback will be provided and an additional two sets of tapes (visits 1-3) will be reviewed.

D3. The Control Condition: The control condition will be ‘treatment as usual’ provided by the PCP with the addition of the TIP literature packet. We chose usual care as our control condition as it remains the standard of care. To date, there is little evidence in the literature that brief adherence interventions augmenting pharmacotherapy improve adherence outcomes [110]. Therefore, the burden of demonstrating an effect above and beyond usual care remains the first step in adherence research. Both study groups will receive comparable literature packets and participate in the follow-up visits as recommended by their PCP.

D4. Study Sites: The study will be conducted at two primary care sites, one in NYC and one in Michigan.

The New York City site (Weill Cornell Internal Medical Associates, WCIMA) is a large, urban primary care clinic conducting 60,000-70,000 visits annually. The clinic serves a full range of adults with 25% older adults. The population served is from a mix of ethnic and racial groups (25% African American, 22% Latino, 5% Chinese American, and 5% other South Asian Americans). The clinic uses the EPIC medical record system which can be programmed for chart reviews to identify a new antidepressant prescription.

The Michigan site (The Turner Clinic) is the outpatient primary care program of the University of Michigan Geriatrics Center, specializing in the assessment and treatment of older adults. The clinic provides care for over 26,000 older adult outpatient visits annually. The clinic uses the Careweb medical record system allowing for easy programming of chart reviews and identification of new prescriptions of antidepressants. The Michigan site draws patients from rural and urban areas with mix of racial and ethnic groups (15% African American, 3% Asian, 2% other minorities).

D5. Study Sample & Eligibility: Eligibility criteria have been selected to produce a sample of 260 older adults (age ≥65) who have been newly prescribed antidepressant medication by a primary care physician for depression at one of the two participating clinics (130 from New York City and 130 from Michigan).
To maximize generalizability to older adult patients of other large primary care sites, we have set broad inclusion criteria and expect significant variability in disability, medical comorbidity, social support and functioning consistent with the diversity seen in this type of setting. We selected 65 as the cut-off to select a group of elders with at least minimal medication insurance coverage (as all older adults age >64 are eligible for Medicare Part D). While there is variability in Medicare Part D co-payment, all elders will have at least some insurance for prescriptions. This potentially decreases the impact of medication costs on adherence. Recent work has found an increase of antidepressant prescriptions and decrease in out-of-pocket expenses since implementing Medicare Part D [65].

Older adults who receive a new prescription for depression and have not been on antidepressants in the previous 6 months will be eligible. Because antidepressants are widely prescribed, and the TIP intervention targets adherence among depressed older adults, we verify with all prescribing physicians that the antidepressant is to target depression. We recognize this broad criterion will generate a heterogeneous sample and will test the impact of the TIP intervention among participants whose physicians define clinical necessity.

We have elected to exclude older adults: who are suffering from a psychotic or bipolar disorder (as observed on the SCID); require immediate attention due to high suicide risk (i.e. intent or plan in immediate future); or suffer from significant cognitive impairment (MMSE <24). There are no pilot data indicating that TIP will be useful for older adults with depression in the context of these additional problems. Elders suffering from these symptoms may require more intensive intervention and may not be able to complete reliably research assessments. We will exclude elders with alcohol or substance dependence, but will include elders who may be considered ‘moderate’ drinkers (defined as ≤14 drinks a week, or less than 4 on the AUDIT-C). We will exclude elders who do not have the ability to understand or communicate in English. While we recognize that this may exclude monolingual Spanish-speaking elders who seek care at the NYC site, given the complexity of the barrier constructs (stigma, attitudes), and potential variability across ethnic and racial groups, we opted not to add the additional dimension of language to this first effectiveness study. This study will recruit bilingual elders of any ethnic group.

D6. Recruitment and Consent Procedure: To maximize recruitment potential, study participants will be identified by two methods: physician referral and chart review. In both sites, physicians will have the opportunity to refer patients directly to the study by paging the study staff. Study personnel will be available to meet with a potential subject after the physician’s appointment at the primary care site.

We recognize that primary care physicians may be very supportive of the study, but may not have time in their visits to consider and discuss the study. At both sites we will use chart review to identify patients who may be eligible for the study. In NYC, WCIMA uses the EPIC medical system for patient charts. The system can be programmed to identify patients based on demographics, diagnosis, or medications. For this study, Dr. Cherif, a collaborating WCIMA physician, will update and maintain a screening program to identify eligible patients with a new diagnosis of depression and/or new prescription of an antidepressant among all older adults (age >65). The screening, which was used for the pilot project, will be conducted on a daily basis. Similarly, the University of Michigan has a system-wide electronic medical record that can be reviewed for potential subjects. We will use "EMERSE" (Electronic Medical Record Search Engine [119, 120], a kind of “Google” system for the electronic medical record, developed by David A. Hanauer MD, a collaborator who has a Master’s in medical informatics from MIT. This is a secure system that maintains an audit trail. It is an easy to use, intuitive search engine for free-text documents. One creates search bundles of terms and this system searches the record for these and produces context-sensitive search results or “hits”. This method is currently being used for recruitment in an NIMH-funded study (R21 MH073002). Once a potential subject is identified at either site, the primary physician will be paged to obtain consent to contact the patient and verify that the patient is receiving antidepressant treatment for depression. Both groups of physicians have expressed willingness to be paged to review potential subjects and establish the need for depression treatment.

In both recruitment methods, the study personnel will meet with any eligible older adult, review study procedures, and obtain informed consent for study participation (screening, randomization, audiotaping, research assessments, and authorization for medical records to be obtained at the final follow-up). In the pilot project, we found comparable rates of agreement (75% of eligible) for older adults referred by PCPs and identified through the medical record.

D6a. Study Randomization and Entry: Location of study encounters: Research contacts for both TIP and TAU participants will take place in the participant’s home and TIP intervention visits will be conducted at the primary care site or nearby research office. The TIP intervention is delivered in an office to simulate ‘real world’ circumstances. Conversely, research assessments are an artifact of the proposed study. While there is an added cost to the study, in-home assessments reduce subject burden and attrition by facilitating scheduling
and eliminating transportation difficulties and weather-related cancellations. Conducting research assessment in the home also helps clearly separate the ‘research’ from the ‘intervention’.

Inclusion and randomization: If the older adult consents to participate, the study research assistant will administer the baseline assessment. Using the physician criteria of ‘in need of depression treatment’ (based on prescription and telephone verification), we have not set specific depression diagnostic or severity criteria. This sampling strategy will potentially generate a heterogeneous sample of elders with varying degrees of depressive symptoms. However, we will define our sample as ‘clinically significant depression’ as defined by their primary care physician and retain our focus on adherence and our goal to be as consistent with primary care prescribing practices as possible. The research assistant (RA) will review the baseline data with the coordinator and the PIs to determine if the older adult meets inclusion and exclusion criteria. All older adults who meet criteria will be randomized by the study coordinator based on a random number sequence generated by Dr. Leon, the study statistician (Randomization described in D19). If the older adult is to receive TIP, the counselor will contact the participant and arrange to deliver the TIP intervention at either the primary care or nearby research office.

D6b. Recruitment Rates: We plan to enroll 7-8 subjects per month for 36 months (see study timetable) to meet our target goal of 260 subjects. We expect to have a start up period of six months during while time we will meet with the primary care physician and staff, set up study procedures and monitoring meetings. Recruitment will take place from month 7 through month 42, leaving 6 months (months 43-58) for final follow-up and 12 months (months 52-60) for data management, data analyses, interpretation and write-up.

Study Timetable

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<th>Study activity/Month</th>
<th>Year 1 Months 1-6</th>
<th>Year 1 Months 7-12</th>
<th>Year 2 Months 13-18</th>
<th>Year 2 Months 19-24</th>
<th>Year 3 Months 25-30</th>
<th>Year 3 Months 31-36</th>
<th>Year 4 Months 37-42</th>
<th>Year 4 Months 43-48</th>
<th>Year 5 Months 49-54</th>
<th>Year 5 Months 55-60</th>
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<tbody>
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<td>Start up</td>
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<td>Data analyses &amp; write up</td>
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Recruiting depressed older adults in a primary care setting is labor intensive and requires readily available staff. Ease of referrals and quick follow-up is essential to fitting research into a busy primary care setting. Many eligible elders will not carry a formal diagnosis of depression due to concerns about stigma. Thus, we will need to review the medical records for daily prescriptions of antidepressants, then identify who may be eligible by contacting their physicians for medical clearance and if cleared, speaking to the potential subject. At times, potential subjects request study personnel to speak with family members about study protocol information. We will follow-up daily with potentially eligible elders to allow us to recruit as close to the new prescription date as possible. We recognize that some elders may initiate antidepressant treatment prior to being contacted given that: 1) conducting research in medical settings ‘with other people’s patients’ requires that we obtain physician medical clearance prior to contacting potential subjects; and 2) elders may be likely to have family participating in their care that they wish to consult with prior to consenting to participation in the study.

To meet the study goal of enrolling 7-8 subjects each month, or 87 per year for three years, we expect to review at least 20 subjects per month or 240 per year who meet initial inclusion criteria (a new antidepressant prescription, age 65 or older). Of those patients who are reviewed, we expect 30% to be excluded due to exclusion criteria (e.g., more than mild cognitive impairment, non-English speaking). Of those elders who are approached, we have estimated a 25% refusal rate. This rate is consistent with the pilot data, and our previous research conducted with depressed, medically compromised elders (73% agreed, R01 MH59366 and in our current depression treatment study with older adults with COPD (76% agreed, R01 HLB71992) [121]. Based on our experience using this recruitment method in a current study (R21 MH073002), we expect the majority of older adults who consent to screen positive for clinically significant depression.

D7. Research Assessments

D7a. Goal of Research Assessments: The purpose of the research assessments is to obtain information on participant’s adherence, depressive symptoms, functioning, attitudes, mental health service utilization, and sociodemographic factors. The research assessments are designed to minimize participant burden and increase study participation. The assessments will be conducted by the RA in person in the participant’s home. The RA will not know the study hypotheses or the assigned condition for each subject. While there is an added cost, in-home assessments reduce research burden and attrition by facilitating scheduling and eliminating
transportation difficulties and weather-related cancellations. Conducting research assessment in the home also helps clearly separate the ‘research’ from the ‘intervention’. While the TIP intervention will take place at either the primary care site or adjacent research office to simulate ‘real world’ circumstances, research assessments are an artifact of the proposed study. We considered in-home TIP intervention meetings, but felt it reduced the potential for future sustainability as it is inconsistent with typical primary care practice.

During the in-person research assessments, we will ensure that the senior is using any assistive devices they have. Hearing problems are common among older adults, but it is a rare older adult who cannot be helped with hearing devices. It has been our experience that in-person interviews decrease confusion for older adults with impairments in communication.

### Study Contact Table: Timing and Location of Research Visits and Intervention Meetings

<table>
<thead>
<tr>
<th>Study week</th>
<th>1-10 days</th>
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<th>4</th>
<th>6</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
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<td>PC office</td>
<td>PC office</td>
<td>PC office</td>
<td>Phone call</td>
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<tr>
<td>Research Assessments</td>
<td>Baseline at home</td>
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#### D7b. Timing of Research Assessments: As soon as an eligible subject is identified, the consent process and baseline assessment will be scheduled. For research assessment, the RA will schedule the visit ahead of time, call to confirm the appointment with the subjects, and then visit the home and conduct the research interview. Baseline assessments will be conducted as soon as possible after the eligible subject is identified (no later than 10 days after identification). Follow-up research assessments will be administered at 6, 12, and 24 weeks after baseline assessment. These time points were chosen both to capture the impact of the intervention, and to balance the need for accurate assessment with the untoward impact of frequent research visits. The timing of the initial 6-week follow-up was chosen to measure adherence directly after completion of the TIP intervention visits have ended (weeks 1, 2, and 4 and phone call at 6 weeks after baseline completed). The second follow-up visit (12 weeks after baseline) allows us to assess the degree of continued adherence and depression outcomes. The final 24-week assessment will provide an assessment of depressive symptoms for the secondary depression hypotheses and exploratory adherence mediation hypothesis.

**Will adherence be captured with only three follow-up assessments?** We recognize that more frequent research assessments (e.g. monthly) might capture nuanced changes in adherence. However, we have tried to balance assessment accuracy with potential untoward effects of assessment on the impact of the TIP intervention. Research interviews about symptoms, functioning and adherence can increase the attention to depressive symptomatology, offer a mental health language for symptoms and associated impairments, and are perceived as supportive interactions by elders.[122] The goal of the intervention is to increase an understanding of depression, its impact, and its treatment, as well as develop a personalized strategy for successful treatment participation. As a result, we have chosen three follow-up visits. This follow-up schedule is consistent with other studies of depressed geriatric primary care patients (IMPACT).

#### D8. Baseline Assessments: Baseline assessment will include measures of depression diagnosis, symptom severity, somatic anxiety, alcohol use, cognitive functioning, ADL and IADL functioning, prior mental health treatment and contact, economic hardship, insurance, mobility and psychological barriers, such as perceived need for care, anticipated stigma and public stigma, knowledge deficits and depression knowledge. All of the measures selected have been administered in prior and current research by the participating research groups and have been found to be well tolerated by our older adult population.

**Follow-up Research Assessments:** Follow-up assessments will take place 6-, 12- and 24-weeks after baseline and should take 45 minutes. All assessments will be conducted in-person in the participant’s home. In-home assessments decrease missed appointments due to weather, transportation, or inconvenience and are preferred by the majority of older adults. Any elders who do not wish to have an in-home assessment can be seen either at the PCP office or nearby.

### D9. Outcome Measures

**Measurement of adherence:** The choice of an adherence method should be based on the study objectives and sample population.[123] While MEMS caps may be considered the ‘gold standard’ for some studies, MEMS caps are problematic in studies of adherence as they themselves function as an adherence intervention.[124] MEMS caps are also too costly for larger, community-based studies.[123] Pharmacy data is a less useful method because many elders use more than one pharmacy, and refill information may underestimate unintentional nonadherence. Self-report is frequently used in community studies due to ease and cost. Our own research has documented concordance between self-reported adherence and chart recorded blood levels.[49] Others have found good concordance with pharmacy records.[125] However, with self-report alone, there is less of an
opportunity to document nonadherence among elders who are either unaware of their nonadherence or minimize their nonadherence.

For this study, we will follow the recommendation of several investigators to couple a self-report adherence with an additional objective measure of adherence, a pill count\cite{126, 127}. There is no ideal way to measure adherence in a community-based effectiveness intervention study. We have sought to balance the ease of administration and the limitations of self-report with a pill count conducted at home to verify the adherence report. This combination of measures has adequate reliability, takes advantage of our in-home research visits, does not overly burden elders (as unannounced counts would be likely to do) and will not modify natural pill-taking behavior like MEMs caps.

Adherence will be recorded using the **Brief Medication Questionnaire (BMQ)**. The Brief Medication Questionnaire (BMQ) is a 9-item self-report measure of medication adherence and barriers to adherence. The BMQ captures both sporadic and repeat nonadherence and has been used with older adults\cite{128}. The BMQ has been validated against MEMS data and has an 80% sensitivity and 100% specificity for identifying patients with MEMs data indicating poor adherence. These signal detection indices suggest that the BMQ outperforms most existing measures in terms of simple non-adherence detection. Additionally, the BMQ was recently validated in a study using HMO automated pharmacy data with significant correlations found between self-reported adherence using BMQ and pharmacy records\cite{125}. The BMQ elicits the number of doses in the past week the antidepressant was taken as prescribed. It will also provide information on how many missed doses occur.

**Pill counts** have been used to verify self-report measures of adherence. Pill counts can be completed during in-home assessments with older adults\cite{129}. At each in-home assessment, we will examine the antidepressant pill bottle to extract information on the prescription date, quantity and dosing. We recognize that participants will vary in the number of pills prescribed and refills completed by each follow-up assessment. Using the prescription filled date and assessment date, we will record the number of pills prescribed and the number of pills taken. The number of pills removed divided by the number of pills prescribed to the assessment date will provide the proportion of doses taken. This will serve as the measure of observed adherence. While we recognize that pills removed do not necessarily translate into pills taken, this pill count method administered at the 6- and 12-week follow-ups will provide us with a verification of the subject’s adherence behavior. **Definition of Adherence**: Subjects will be classified as adherent if they are taking 80% or greater of their prescribed antidepressant doses. We have chosen to use the emerging standard of 80% as our adherence goal as it reflects the goal of improving the quality of care. On the BMQ, adherence is defined as the number of doses taken divided by the number of doses prescribed. Nonadherence will be calculated in two ways based on the suggestion of its authors: (1) subject report of non-adherence on the Regimen subscale (where a score of >1 indicates a positive screen); and (2) subject report of >20% of prescribed daily antidepressant doses omitted in the past week. Participants who have dropped out of the study will be classified as nonadherent.

Utilizing and comparing different measures of adherence will allow us to examine adherence behaviors more comprehensively. However, using two adherence measures requires plans for determining a final adherence outcome for hypothesis testing. Agreement across the two non-adherence measures will be assessed using Kappa statistics, and the direction of over- or under-estimation between the measures will be assessed. For analyses, we will use the lowest proportion of doses taken (from our two measures) as the adherence outcome measure.

As stated in the Aims, we have not included hypotheses about adherence at 24 weeks because we believe that adherence reports at 24 weeks or 6 months after prescription may be a function of clinical response, physician prescribing procedures, and sustained side-effects. While continued adherence is important, the TIP intervention targets specifically early treatment initiation and adherence.

**Depression – Depression Diagnosis**: We use the **SCID diagnostic interview**\cite{130} to make DSM-IV diagnoses for all participants. We expect that many participants will meet criteria for major depression, but we will not exclude any participants who meet eligibility criteria. We recognize that not setting severity criteria will generate a heterogeneous sample with variations in depression severity. We will explore the impact of the TIP intervention among participants whose physicians deem the medication to be clinically necessary (‘clinically significant depression’).

The SCID will allow us to assess symptoms using all information, to document prior episodes and the existence of comorbid conditions. Reliability results of the SCID have shown this instrument to have adequate reliability, with a test-retest coefficient equaling 0.69 and inter-rater reliability of 0.64. Given the complex relationship between medical-neurological comorbidity and disability, this study will use the “all-inclusive approach” by having RAs record all symptoms and signs of depression, and document evidence of possible medical contributors to symptoms of depression. Each SCID interview will be reviewed by a geriatric psychiatrist (Dr. Kales) or clinical psychologist (Dr. Sirey) to make the final diagnosis. We will screen for
exclusion characteristics such as psychosis and other psychiatric disorders (e.g. bipolar disorder) using the SCID screening questions. We recognize that this is a limited assessment, but a full diagnostic evaluation is beyond the goal of this study as it would create unnecessary burden for the majority of study participants.

**Depression severity:** Change in severity of depression is one of the outcomes of this study. A 24-item [Hamilton Depression Rating Scale (HDRS)](49) was chosen as the interviewer-rated instrument because of its extensive use in clinical trials. Using the HDRS will provide treatment outcome data that can be compared with other studies. While the MADRAS has become more widely used, the assessments of hopelessness, worthlessness, and helplessness in the 24-item HDRS may reflect change related to the empowering and support provided by the TIP intervention. HRSD inter-rater reliability will be assessed by the use of audiotapes of a random sample of 20% of all interviews. The interviews will be rated independently by all research assistants across the two study sites using digital recordings transferred in secured email transfers.

**Training for RAs:** Training and credentialing for study Research Assistants across sites will be overseen by Dr. Kales and her staff. Training in clinical interviewing and diagnostic assessments consists of several components: 1) observation and discussion of the SCID and HDRS training tapes; 2) in-person observation of interviews conducted by experienced clinicians with patients exhibiting a range of depression severity; 3) role plays of the interviews; and 4) conducting patient interviews with in-person supervision. These efforts have produced excellent reliability for clinical assessments conducted by Cornell RAs. For example, study reliability of assessors in the PROSPECT study was 0.97 for HRSD ratings and 0.92 for diagnoses of major depression.

**D10. Moderators**

**D10a. Anxiety**

There are a number of sensitive measures of anxiety. We have chosen the [Anxiety Sensitivity Index-Revised (ASI-R)](131), which was developed to measure anxiety-sensitivity, the fear of anxiety-related sensations based upon beliefs of their harmful consequences. The construct validity of anxiety sensitivity is supported by a large body of research documenting its role in the genesis of anxiety and panic. The ASI-R has been found to be highly internally consistent and composed of psychometrically acceptable items assessing the fears of somatic, social, and cognitive anxiety symptoms.

**D10b. Cognitive Assessment**

Overall cognitive dysfunction will be assessed with the [Mini Mental State Examination (MMSE)](49). Because the study goal is to examine the usefulness of the intervention in a wide range of elders without significant cognitive impairment, we will rely on the MMSE for exclusion of such impairment (MMSE<24). If the counselor has specific concerns about cognitive deficits that impact on the participant’s inability to participate, these concerns will be reviewed with the Investigators and a clinical decision will be made about study inclusion.

Recent research has found that mild memory difficulties and executive dysfunction are more common among community elderly who have MMSE scores >24 (132). However, the literature does not provide clear evidence of specific cognitive dysfunction and medication nonadherence among depressed elders, unlike those impairments documented among adults with schizophrenia and bipolar disorder (103, 139). A full neuropsychological battery is beyond the scope of the proposed study. To examine the relationship of cognitive functioning to adherence, we will administer the [Mattis Dementia Rating Scale (DRS)](130). The DRS is organized in such a way that the most difficult items are given first. It has adequate sensitivity and specificity to detect early impairments (134). The DRS is widely used and tolerated by depressed elders seen in research by the Cornell group. The DRS was useful in identifying cognitive impairment among older adults with Bipolar Disorder (135) and associated with missed visits among elders in primary care (136).

**D10c. Alcohol Use**

The AUDIT-C (137) will be administered to determine alcohol consumption. This is a shortened version of the full 10-item AUDIT (138). It can reliably identify at-risk and moderate drinkers (those individuals who consume <14 drinks per day).

**D11. Barriers To Care**

**D11a. Public and Anticipated Stigma**

To examine the impact of stigma, we will use two measures that capture public and anticipated stigma. To measure the awareness of public stigma towards depression, we will use the [Link Stigma Coping Scale](69). This has good psychometric properties and we have used it successfully in prior studies with elders. It provides an assessment of the older adult’s perception of community stigma (e.g. what they believe they have to contend with in the public). To measure anticipated stigma, we have developed a brief 7-item scale called the [Anticipated Stigma Inventory](69). This scale was designed for older adults specifically to measure the types and intensity of reactions they would expect from people if they were depressed. The stem for the items is: “If I were depressed, I would be concerned that others would...” This stem is followed by a review of possible responses, such as ‘exclude me’, ‘distrust me’, and ‘criticize me’.
This scale provides data on stigma expectations. In previous work with a large sample of depressed and non-depressed older adults (N=503), the scale had good consistency (Chronbach’s alpha = .91).

**D11b. Perceived Need For Treatment:** To measure perceived need for mental health care, we will use the General-practice Users Perceived-need Inventory (GUPI). The GUPI is a shortened version of the Perceived Need for Care Questionnaire which was widely used the beyondblue study beginning in 2002. The measure has good consumer validity and was easy to understand and complete [139]. We will measure perceived necessity and concerns about antidepressant therapy using Horne’s Beliefs about Medications Questionnaire. This measure has been used with psychiatric patients, including in our own research. Reporting more concerns about medications has been linked to antidepressant nonuse among depressed primary care patients [141] and lower perceived necessity predicts nonadherence measured with blood levels among psychiatric patients [142]. Self-reliance will be assessed using a single item used previously to measure this construct [143]. We know of no other brief validated scale of self-reliance used to predict service need or use. This item has been used in our previous studies (K23 MH68638).

**D11c. Prior mental health contact and support for treatment:** To assess prior mental health contact, each participant will be asked about prior mental health treatment, antidepressant use and outcome (duration, satisfaction, resolution of symptoms). To assess social support for mental health treatment we will use a simple two-item rating of the number of people who support mental health treatment and the number of people who discourage it. This assessment was found to predict longer-term follow-up among depressed mixed-age adults who sought outpatient mental health care [78].

**D11d. Knowledge about depression and its treatment:** To measure knowledge we will assess both the presence of ‘myths’ about depression and self-rated assessment of education, and information and understanding of depression. To measure myths about the etiology and course of depression, we have adapted a scale developed by Wills et al. to assess the presence of myths. Five items ask about commonly held ideas such as “depression is a normal and expected part of aging” and “depression will go away by itself”. These items have been used in our prior research with depressed older adults. In addition, we will assess the perceived level of education using the two items that constitute the Patient Education scale from the PARC-D [145]. As with our other measures, this scale has been previously used in prior studies by both groups.

Because patient preference can influence adherence, we will include a measure to capture dissatisfaction with antidepressant therapy as a treatment option. We will ask subjects if they would have preferred an alternative treatment. This question has been used by Britten et al. to document preferences not met and is associated with nonadherence [146]. We recognize that there are a number of other measures of preference available, but have chosen this measure for its brevity and relation to adherence behavior.

Resignation will be assessed using the Beck Hopelessness Scale. The BHS is a 20-item scale used to evaluate hopelessness in depressed individuals by measuring an individual’s expectations about the future. The BHS consists of 20 true/false items that either endorse or deny pessimistic and optimistic statements.

Self-efficacy will be assessed using the General Perceived Self-Efficacy Scale (GPSE). The GPSE is a 10-item psychometric scale designed to assess an individual’s ability to cope with new and difficult tasks. The GPSE consists of 10 items rated on a 4-point scale with responses ranging from not at all true to exactly true.

**D12. Patient Characteristics**

**D12a. Sociodemographic Variables:** Information on date of birth, gender, country of origin, ethnicity/race, marital status, current living status (alone or with someone), presence of adult children in the home, and educational level will be obtained using a demographic form we routinely use in our research. We will use education as a proxy measure for health literacy as recommended by Zarcadoolas [147]. To assess current financial situation, we ask for both total income and a self-rated financial assessment.

**D12b. Functioning:** Limitations in Activities in Daily Living, Instrumental Activities of Daily Living, and Mobility will be assessed using Multilevel Assessment Instrument (MAI) [148]. We have used the MAI successfully in frail populations with high levels of disability warranting an instrument that can differentiate the degree of limitations and ‘objectively’ assess ability. We will also use SF-12 [149] to assess perception of functioning.

**D12c. Health Status:** To quantify the level of medical burden, we will use the MAI Illness list [148]. This list is easily and reliably administered and provides the number of chronic illnesses. This will be compared to the information obtained from the medical chart to minimize underreporting or lack of subject knowledge. Other options such as the CIRS-G or Charlson, are too time consuming for this study. At follow-up, we will collect additional information on health events (e.g., injuries).

**D12d. Social Support:** Depression outcomes in older adults are associated with low perceived social support. To assess social support in this sample we will use Duke Social Support Index [150]. The Index yields scores on 3 categories: subjective social support, social interaction, and instrumental social support. It has been well
received by seniors participating in our studies.

**D13 Treatment Adequacy and Service Utilization**

**D13a. The Composite Antidepressant Scale (CAD)** uses information on dose and duration of antidepressant therapy over time to construct weekly ratings of treatment adequacy ratings. We have used this measure successfully with older adults to document the adequacy of antidepressant therapy in other community studies\(^{[45, 49]}\).

**13b. Cornell Service Index:** The Cornell Services Index (CSI) will be used to collect and catalogue self-reported information on health and mental health services use, including the purpose, setting, and type of provider. The CSI will be used to record the mental health visits attended during the follow-up. The CSI has excellent inter-rater reliability (ICC .97-1.0) and good test-retest reliability (Phi correlations: .54-1.0) for reported service use across a range of services and provider types \(^{[151]}\). Self-report of service use on the CSI has been validated against claims data and found to be a reliable. In addition, we have recorded recommended treatment from subjects in prior studies and found them to be reliable reports \(^{[152, 153]}\).

**D14. Reimbursement of Participants:** Participants will receive $40 as a compensation for their time during the baseline assessment and $25 for each follow-up assessment. There will be no reimbursement for time with the counselor, because these meetings are free services.

**D15. Procedures Aimed to Improve Adherence to Research, Reduce Attrition and Burden:** Common to this type of intervention research with older adults are missed assessments or assessments not occurring at exactly the time of the scheduled appointment. This population is at particular risk of missing assessment appointments because of health complications and transportation. We will conduct in-home assessments to follow-up with all participating subjects. Assessments are scheduled one week to 10 days before the due date, and participants are then called 24 hours before to reconfirm.

*Intent to Attend* \(^{[154]}\) will be administered at each study visit, where each subject rates his or her intent to attend the next assessment session on a Likert scale. If a subject expresses low intent (i.e., < 5), a blinded assessor will query as to the reasons for low intent and attempt to accommodate that subject’s needs (e.g., more convenient time of day for appointment) to decrease the chance of losing the subject during study follow-

<table>
<thead>
<tr>
<th>CONSTRUCT</th>
<th>MEASURE</th>
<th>Time length</th>
<th>Baseline</th>
<th>6 wk</th>
<th>12 wk</th>
<th>24 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depression Severity</strong></td>
<td>Depression diagnosis</td>
<td>SCID</td>
<td>15 mins</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td></td>
<td>Severity rating</td>
<td>HDRS (with SCID interview)</td>
<td>5 mins</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td><strong>Antidepressant Treatment</strong></td>
<td>Adherence self-report</td>
<td>Brief Medication Questionnaire</td>
<td>7 mins</td>
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<td>X</td>
<td>X</td>
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<td></td>
<td>Adherence verification</td>
<td>Pill counts</td>
<td>7 mins</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Dose and duration of antidepressant</td>
<td>Composite Antidepressant Data</td>
<td>5 mins</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Barriers to Care</strong></td>
<td>Perceived need for care</td>
<td>GUPI</td>
<td>2 mins</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>Overall need for help, Prior treatment</td>
<td>Review of prior care</td>
<td>3 mins</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>Preference for self-reliance</td>
<td>Ortega self-reliance item</td>
<td>1 min</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Concerns about treatment</td>
<td>Beliefs About Medications Questionnaire</td>
<td>7 mins</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Beliefs about depression &amp; its care</td>
<td>Myths (5 item) PE scale from PARC-D</td>
<td>2 mins</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Belief in myths</td>
<td>Britten preference item</td>
<td>1 min</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Information and understanding</td>
<td>Beliefs for other treatment</td>
<td>1 min</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Preference for other treatment</td>
<td>Link Stigma Scale</td>
<td>7 mins</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Public stigma</td>
<td>Anticipated stigma</td>
<td>4 mins</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Anticipated stigma</td>
<td># of encouraging &amp; discouraging (2 items)</td>
<td>1 min</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Clinical, Cognitive and Health Status</strong></td>
<td>Alcohol use</td>
<td>AUDIT C</td>
<td>3 mins</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>Somatic anxiety</td>
<td>ASI</td>
<td>10 mins</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>Functioning</td>
<td>MAI IADL, mobility &amp; ADL scales</td>
<td>10 mins</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>ADL, IADL, mobility</td>
<td>SF-12</td>
<td>10 mins</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>Perceived functioning</td>
<td>Duke Social Support Index</td>
<td>8 mins</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Social interaction, support</td>
<td>Medical list</td>
<td>4 min</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Health Status</td>
<td>Chronic Disease Score</td>
<td>3 mins</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>MAI illness list</td>
<td>MMSE</td>
<td>7 mins</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Illnesses being treated</td>
<td>Mattis Dementia Rating Scale</td>
<td>10 mins</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Cognitive functioning</td>
<td>Overall status</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Cognitive impairment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
At each assessment, we will forecast the next assessment date to anticipate any difficulties. Any problems with the next appointment can be resolved with problem-solving. We ask all participants for a contact person who may be called if we are unable to reach the participant/subject. This contact is called when a participant is unable to be contacted after frequent attempts. This tracking method helps us locate participants and classify the reason for attrition. Participants can have intervening medical events or hospitalizations that make them difficult to contact. Whenever possible, if the elder cannot be visited in person, we complete a minimum assessment by telephone to gather data on the primary outcome. In our prior research protocols, we have had a low attrition rate (R21MH073002: Kales & R01526591:Sirey). We have estimated an attrition rate of 12%.

Based on the time estimates for the proposed measures, we expect the baseline to take 2 hours and follow-ups to be 45 minutes. This battery of measures is used in other research studies conducted with depressed, frail older adults in diverse setting by the Cornell Center (e.g. COPD rehabilitation patients (R01 MH65539), homecare patients (5R24 MH064608), and home-delivered meal recipients (R01 MH075897). If there are participants who become tired, we will use several breaks and/or schedule a follow-up visit.

D16. Data Analytic Procedures:
D16a. Preliminary Analyses: The clinical and demographic characteristics at the time of randomization will be examined. Frequency distributions will be calculated for all variables. The mean, median, standard deviation, minimum and maximum will be calculated on each continuous measure. Graphical displays including histograms and box plots will be produced. Transformations will be used when distributional assumptions are not fulfilled.

The two randomized intervention groups will be compared on baseline demographic and clinical variables. The groups will be compared on continuous or ordinal variables with t-tests or Mann-Whitney tests, respectively. Chi-square tests will be used for categorical variables. For example, analyses will evaluate whether randomly assigned groups are balanced by comparing the two groups on baseline variables, such as age, gender, ethnicity, severity of depression, disability, overall cognitive impairment, and health status, which have been found to be related to depression and may influence its outcomes [27, 152, 155]. If a between group difference is identified and that variable is correlated with the outcome at a level of $r \geq 0.30$, it will be included as a covariate in the analyses of the primary and secondary Hypotheses (described below). Interpretation of the results will incorporate the adjustments.

D16b. Hypotheses Testing: The inferential analyses will involve tests of the primary and secondary hypotheses. Our approach for testing these hypotheses will adhere to the intent-to-treat principle, analyzing subjects classified as they have been randomized. Each test will use a two-tailed alpha-level of 0.05.

Primary Hypothesis
Adherence Hypothesis: Participants randomized to the TIP intervention will be significantly more likely to be adherent to antidepressant treatment at 6-week follow-up (just after intervention) and 12-week follow-up (6 weeks after the intervention ends) as compared to participants randomized to the TAU condition. Subjects will be classified as adherent only if they meet criteria (defined in Section D9) at both 6 and 12 weeks. All others will be non-adherent. Logistic regression analyses will compare adherence rates across groups, controlling for site, the stratification variable. The models will include any covariates identified (in analyses described above) if group imbalance is detected. In a subsequent model, a likelihood ratio test will examine the incremental contribution of the intervention by site interaction, which will be retained if statistically significant.

Secondary hypothesis
Depression Hypothesis: Participants randomized to the TIP intervention will have a significantly lower severity of depressive symptoms (on the HDRS) [16] over the 24-week follow-up than older adults who are randomized to the TAU control condition.

A mixed-effects linear regression model will examine the 24-item HDRS (dependent variable) at baseline and weeks 6, 12 and 24. The model will include 2 random effects, a subject-specific intercept and slope. The fixed effects will be intervention and site. Subsequent models will examine the incremental contribution of the intervention by site interaction and the contribution of intervention by time with likelihood ratio tests. Each statistically significant interaction will be retained in the final model. We hypothesize faster decline in depression severity for the TIP intervention.

D16c. Statistical Power Analyses: The sample size determination was primarily motivated by the sample size required for the primary hypothesis. Nevertheless, power analyses were also conducted for the secondary hypothesis to assure a sufficient sample size.
Adherence hypothesis: The power analyses examined the statistical power to detect clinically meaningful effects. Calculations were performed using Power and Precision software \(^{[156]}\) and assumed a two-tailed alpha level of 0.05. The sample size of 130/group will provide sufficient statistical power (>80%) to detect clinically meaningful differences between intervention groups using the logistic regression model described above. For example, the following differences in adherence rates would be detected with power >80%: 55% (TIP) vs. 35% (TAU) with 84% power; 60% (TIP) vs. 40% (TAU) with 89% power; 70% (TIP) vs. 50% (TAU) with 90% power; 80% (TIP) vs. 64% (TAU) with 81% power.

Depression Hypothesis: A simulation study was conducted to examine statistical power to detect group differences in slopes of the HDRS. In order to examine power for the proposed sample size, the simulations varied the intraclass correlation coefficient (ICC: .50 and .60) and the standardized effect size at the end of the study (.35 and .40) that would result from differences in slopes between two randomized groups. Assumptions included 3 (out a possible 4) observations (i.e., assessment times) over time per subject and a two-tailed alpha level of .05. For each combination of specifications, 1000 datasets were generated and SAS PROC MIXED was used for the mixed-effects linear regression models. Based on these simulations, the statistical power for the proposed N of 130 subjects per group was calculated. The empirical statistical power for various combinations of simulation specifications is as follows. With an ICC of .50, the statistical power will be .88 for a standardized effect of .40 and power will be .79 for a standardized effects of .35. With an ICC of .60, the power will be .89 for an effect of .40 and power will be .82 for an effect of .35. To put these hypothesized treatment effects in perspective, we expect that the HRSD standard deviation (sd) will be about 8.0, based on follow-up data from the PROSPECT study conducted with depressed older adults in primary care \(^{[40]}\). Thus, 40 sd units is 3.2 units on the HRSD and that represents a clinically meaningful group difference. Similarly, .35 sd units is about 2.8 units on the HRSD, which again represents a meaningful difference.

D16d. Exploratory Hypotheses

1. Moderator analyses: We will explore the moderating impact of participant race and depression severity as well as clinical factors prevalent in older adults with later-life depression (baseline somatic anxiety, mild cognitive impairment and alcohol use) on the effect of the intervention on adherence (the dependent variable).  

2. Mediator analysis: We will explore early antidepressant adherence (at 6 weeks) as a mediator of the effect of the intervention on depressive symptoms. We hypothesize that the effect of TIP versus TAU will be much greater on subsequent depressive symptoms (decrease in depressive symptom severity from 6 to 24 weeks) among those participants who are adherent at 6 weeks.

Analyses of moderators and mediators are exploratory and, as recommended by \(^{[157]}\), will focus on the magnitude of the effect. They will not involve significance testing. Furthermore, in contrast to repeated dependent measures proposed for Hypotheses 2, we will use fixed-effects logistic regression and fixed-effects linear regression approach for the exploratory analyses. Separate analyses will examine each exploratory hypothesis. The independent variables will include treatment and the respective hypothesized moderator (from baseline) or mediator (from week 6). Initially, the main effects will be tested. Then, in subsequent models, the incremental contribution of the interaction of treatment with each of the respective hypothesized mediating or moderating effects will be examined. To demonstrate evidence of the effect of a moderator, there must be a treatment by moderator interaction. One way to examine this interaction is to compare, in a descriptive fashion, the between intervention group effects on adherence for each level of the moderators (e.g., Number Needed to Treat based on adherence rates separately for those with and without baseline somatic anxiety). In contrast to our moderator analysis, either a main effect of the mediator or a treatment by mediator interaction would provide evidence of a mediator effect, but our specific hypothesis is that we will observe a mediator by treatment condition interaction. Once again, based on the recommendations of Kraemer et al. \(^{[157]}\), these analyses will focus on the magnitude of the effect and not on significance testing. (For that reason, power analyses have not been presented for Exploratory Hypotheses.) We will consider medium effect sizes noteworthy (as delineated in Kraemer and Kupfer)\(^{[158]}\). Results from these exploratory hypotheses guide the design of future RCTs (e.g., inclusion/exclusion criteria from the moderator results).

3. Patterns of nonadherence: In the Primary Adherence Hypothesis, patients who did not initiate treatment, or took less than 80% of prescribed doses will be considered nonadherent. In exploratory analyses, we will initially characterize the patterns of adherence. For example, using information from the follow-up interviews at 6 and 12 weeks, these patterns might include: 1) never initiating antidepressant therapy; 2) brief adherence followed by discontinuation; 3) early nonadherence, followed by discontinuation; and 4) complete adherence during the trial. Exploratory analyses will compare the adherence groups that are identified on hypothesized barriers to adherence (e.g., stigma, necessity versus concern, self-reliance) using between adherence group effect sizes (Cohen’s d).
D16e. Strategies for Attrition. Intervention studies with the elderly are vulnerable to attrition over time. This can introduce bias and reduce power, precision and generalizability [159]. Although we will make every effort to prevent attrition, some attrition is inevitable. The analyses will include all available observations (i.e., from the various assessment times) from each subject. No imputation processes will be used to replace missing data. In the logistic regression model for the Adherence Hypothesis, the dependent variable model will be classified as non-adherent for all who do not complete the first 12 weeks. (The rationale for this was provided above: Section D9.) In addition, the Intent to Attend variable will be used as a covariate to account for attrition in sensitivity analyses that examine the assumption of ignorable attrition. The proposed mixed-effects model (Depression Hypothesis) will incorporate all available HRSD data from subjects, even those who do not complete the 24-week follow-up. Mixed-effects models yield valid inferences assuming ignorable attrition (i.e., attrition is accounted for by covariates or the dependent variable measured prior to dropout [160]). Two strategies will be used to examine the sensitivity of the assumption of ignorable attrition. First, a pattern mixture model [161] will be used to examine response to treatment among participants with various dropout patterns. This will be implemented in the mixed-effects framework described by Hedeker and Gibbons [162] in which subjects are classified by attrition pattern (e.g., early dropout, middle dropout, completer). Second, the Intent to Attend covariate will be used in sensitivity analyses. The estimates of the treatment effect from the models described above will be compared with models that also include the main effects of either dropout pattern or Intent to Attend. In addition, in keeping with the Intent to Treat Principle, we will make every effort to continue assessments for the entire course of randomized treatment, even among those who fail to adhere to randomized intervention assignment or must leave study assigned treatment [163].

D17. Randomization: We plan to randomize subjects in a ratio of 1:1, 130 subjects to each group. Randomization will be stratified by site. In order to reduce the probability that a disproportionate number of subjects is assigned to one of the treatments, a blocking strategy will be conducted with Dallal software.

D18. Data Management: Data management for both sites will be coordinated by the Cornell data management staff that are part of the Biostatistics Data Management Unit (BDM) of the ACISR. Database design will be developed by the Cornell Data Manager, Eros Papademetriou in consultation with the study statistician, Dr. Leon. Design decisions will be discussed during the weekly Operations meeting. Once the database is finalized, data entry will be conducted at each site. The data will be merged annually for DSMB reporting. A final study database will be developed at the study conclusion for analyses by both Principal Investigators.

Enrollment and Randomization, Scheduling and Tracking, Auditing of Data and Data Entry and Storage. A single enrollment and randomization application will be developed to assign identification codes to patients during the pre-enrollment period, track eligibility status and subsequently randomize eligible patients. Initially, a screening form with preprinted subject codes will be generated based on contact from identification of an eligible study subject. Once an eligible participant is screened, completes baseline and is randomized, the screening forms will be entered daily to provide updated eligibility information. The Tracking System will be developed to assist research personnel in managing follow-up interviews. Reports of scheduled visits, overdue contacts and pending contacts will be generated to ensure adherence to the protocol. The Auditing System will generate reports for: a) data quality control (% of scales returned for corrections); b) rate of data entry; and c) backlog of data that have not been entered. All scales will be audited for identifiers, item completeness, and consistency of major clinical indicators. A standard data entry system has been developed for each assessment instrument that performs immediate checks for valid ranges specified for each item. The Data System is developed in Access for this study. Every scale is kept in a separate table and each record is flagged according to time point of administration. Data entry errors will be minimized by using menu-driven modules that are designed to accept only the valid range of values for each variable to reduce risk of erroneous data. In addition, in an effort to minimize keypunch errors, data will be entered independently into two separate files. Programs will be written to compare each entry across files and identify inconsistencies. The inconsistent entries will be verified and corrected in the database. The Data Manager, Mr. Papademetriou, will be responsible for providing Progress Reports weekly in the study meeting. These reports will include recruitment, participation/retention rates and information on protocol adherence. Backups and Security: Procedures will be followed that protect the confidentiality of subject information. Access to the study databases will be limited to appropriate study personnel using password protection. Study identification numbers are used on all research instruments and all completed assessments are kept in locked file cabinets. Daily backup of all study files will be performed.

D19. Summary: We propose to conduct a randomized controlled trial to test the effectiveness of a novel intervention, the Treatment Initiation Program in Primary Care, designed to improve adherence and depression
outcomes among depressed older adults identified in primary care. The intervention targets psychological barriers to care such as stigma and beliefs about depression and its care, to overcome mutable obstacles to adherence depression treatment. If effective, this intervention could be integrated into the primary care services and be sustained. Future work would extend this intervention to other older adult populations and venues, such as Spanish-speaking populations.
E. HUMAN SUBJECTS

E1. Selection: Our objective is to study 260 (130 from New York City and 130 from Ann Arbor, MI) older adults (age ≥ 65) prescribed a new antidepressant medication for depression by their primary care physician (PCP).

E1a. Inclusion Criteria:
1. Age: 65 years and older;
2. Receiving newly prescribed antidepressant medication at a participating primary care site.
3. Prescription is provided by PCP for clinically significant depression.

E1b. Exclusion Criteria:
1. Presence of significant alcohol (>13 drinks per week) or substance abuse (defined by DSM IV) or psychotic disorder (e.g., psychotic depression, bipolar disorder, schizophrenia);
2. High suicide risk, i.e. intent or plan to attempt suicide in near future (based on Suicide Risk Protocol in Appendix);
3. Significant cognitive Impairment defined as MMSE < 24;
4. Inability to speak or understand English;
5. Aphasia interfering with communication.

E1c. Rationale for Inclusion Criteria:

Age: Subjects 65 years old or older are included because this study focuses on treatment adherence among older adults. The barriers to adherence that are the foundation for this intervention were identified among older subjects.

Use of recently prescribed antidepressants: PCP’s provide the majority of treatment for later-life depression and antidepressant therapy is the evidenced-based treatment in the primary care setting. The study tests the impact of the TIP intervention on antidepressant treatment adherence.

PCP-defined depression: Since our investigation examines the impact of TIP on antidepressant treatment adherence, we wish to intervene with a broad group of elders suffering from depression. We will be able conduct post-hoc exploratory analyses to look at differences in severity of depression across the diagnostic groups using scores on the HDRS-24.

E1d. Rationale for Exclusion Criteria:
Presence of significant alcohol or substance abuse or psychotic disorder: Other psychiatric disorders or substance abuse disorders may require care, but will present with different barriers. To test the impact of this intervention, we have restricted the sample to depressed older adults whose barriers were identified in our prior research. If an individual is identified who is in need of services, we will work with the adult to make a referral.

High Suicide Risk: Anyone who expresses suicidal ideation is administered our suicide risk assessment protocol. This allows us to determine the nature and severity of the suicide risk. We define suicide risk as intent or plan to attempt suicide within a month. We will include in the study patients with passive or vague, and transient, active suicidal ideation because such suicidal ideation is often part of the depression syndrome. Complete exclusion of patients with any suicidal ideation would result in a mildly depressed sample and limit the clinical significance of the proposed intervention. Anyone identified as being at high risk for suicide will be referred for clinical treatment to appropriate services based on our risk profile (See
Suicide Risk Assessment in Appendix). If previously undetected serious psychiatric symptoms emerge over the course of study participation, research staff will follow standard risk procedures (e.g. notify supervisor and PI, arrange for emergency services if necessary), and help link the individual to care.

**Significant Cognitive Impairment:** These patients are excluded because such cognitive impairment may interfere with assessment of depressive symptomatology and the delivery of the proposed interventions. Additionally, older adults with significant cognitive impairment may require an intervention that more directly includes a caregiver to be effective in linking them to care. Patients with more mild cognitive impairment (MMSE>24) will be included in the study.

**Inability to Speak or Understand English:** We have excluded older adults who cannot speak or understand English because the intervention was developed in English. While we considered translation to Spanish, the complexity of the barrier constructs (stigma, attitudes) and potential variability across ethnic and racial groups, would add an additional dimension to this first effectiveness study. This study will recruit bilingual elders of any ethnic group.

**Aphasia Interfering with Communication:** This exclusion is necessary because these subjects cannot participate meaningfully in the interventions offered by the study and the assessment procedures.

### E2. Subject Availability

Subject availability is crucial for this study. We believe that we are in a favorable position to recruit the sample required for the proposed study. Potential subjects are identified through physician referrals and chart reviews.

In NYC, WCIMA uses the EPIC medical system which can be programmed to identify patients based on demographics, diagnosis, or medications. A screening program will be developed to identify eligible patients with a new diagnosis of depression and/or new prescription of an antidepressant among all older adults (age >65). The screening, which was used for the pilot project, will be conducted on a daily basis. The University of Michigan has a system-wide electronic medical record that can be reviewed for potential subjects. We will use the "EMERSE" search engine to input specific criteria and identify potential subjects. Once a potential subject is identified at either site, the primary physician will be paged to obtain consent to contact the patient and assure that the potential subject is appropriate. Both groups of physicians have expressed their willingness to be paged for study participation. Both sites treat adequate numbers of patients to be screened for this protocol.

### E3. Sources

Source of research material will include interviews with participating subjects and review of medical records.

### E4. Recruitment

**E4a. Inclusion of women and minorities**

Written consent will be obtained by study personnel who will inform the patient about the study as discussed below in section E5b. The New York City site (Weill Cornell Internal Medical Associates, WCIMA) is a large, urban primary care clinic conducting 60,000-70,000 visits annually. The clinic serves a full range of adults with a quarter of population being older adults. The population served is from a mix of ethnic and racial groups (25% African American, 22% Latino, 5% Chinese American, and 5% other South Asian Americans).

The Michigan site (The Turner Geriatric Clinic) is the outpatient program of the University of Michigan Geriatrics Center, specializing in geriatric assessment and treatment of older adults. The clinic provides care for over 26,000 older adult outpatient visits annually. The Michigan site draws patients from rural as well as urban areas as well as treating as mix of racial and ethnic groups (15% African American, 3% Asian, 2% other minorities).

Women are included in the proposed project. Given that the gender prevalence in prior studies of depression is higher in women than men (multiple studies showing gender ratio of 2:1) we expect that greater than 50% of patient participants will be women.
E4b. Inclusion of Children
Children will not be included as this study tests hypotheses related to adherence to antidepressant therapy for depression among older adult participants.

E5. Protection of Human Subjects

E5a. Potential Risks
There are two potential risks associated with this research. The first is the burden of standardized research assessments. The second risk is the potential for distress resulting from discussion of personal issues during the research assessment. To address participant burden, we will inform the subjects in advance of the time commitment. In addition, we allow for breaks and are sensitive to participant fatigue. A second measure employed to reduce the risk of distress is the training of research personnel. All staff are trained to be sensitive to discussing difficult topics and to provide appropriate support should a subject become distressed.

E5b. Precautions
The following safeguards have been developed to reduce the risks of the project:

Procedures Related to Subject Safety: The following procedures have been developed to increase the safety of our subjects:

Suicide Risk: We will use in this study the Suicide Risk Management Protocol developed by the Cornell group and used by the PROSPECT Study. The triggers to administer the Protocol's Assessment Form by Research Assistants will be identification of “suicidal thoughts”. The trigger for administering the suicide risk assessment form by counselors is the report of suicidal ideation. Once the research assistants or counselors complete the suicide risk assessment form, an action plan for high-risk patients will be implemented based on the risk assessment guide.

Burden by Research Assessment: This study requires a careful assessment of a number of domains. To reduce subject burden, we selected the most parsimonious battery that permits testing of the proposed hypotheses. Only trained and clinically-experienced interviewers will be used to minimize risks.

Informed Consent: Informed consent will be obtained by trained study personnel. Subjects will discuss with personnel the study procedures and sign a consent form approved by the IRB at each participating site. Through the consent process, the subjects will become aware of the required time commitment, the potential risks and benefits, their right to refuse participation in the study and to terminate participation at any moment without prejudice, and the name and telephone number of the Principal Investigator (Dr. Sirey at Cornell and Dr. Kales at UM).

Confidentiality of Subjects: The consent form will stipulate that information provided by the subjects will remain strictly confidential, with access limited to the research staff and, if applicable, State or Federal regulatory personnel. No one but the project staff will have access to the master list linking subjects’ names to code numbers, and all information obtained will be coded. The master list will be locked. Publications or presentation of findings will not include information identifying the subjects.

E5c. Risk-Benefit Ratio
The benefits to subjects will be free of cost:

1. Psychiatric evaluation
2. Ongoing monitoring of their clinical state;
Potential benefits to society by the study are:
1. The likelihood of identifying an effective intervention to improve adherence to treatment for older adults;
2. The likelihood of identifying whether improved adherence is associated with improved depressive symptoms.

With the precautions taken, in our view, the likely benefits of this study outweigh the potential risks.

E6. Data Safety and Monitoring Board (DSMB) Duties
We will establish a DSMB to oversee our activities in order to ensure the safety of participants in our study, the validity of our findings, and the need for further data collection. We propose to include a geriatric psychiatrist, a psycho-interventions investigator, a primary care physician and a consumer from one of the practices. We will identify a biostatistician available for review of data. The DSMB Board will review the study design, the IRB protocols of UM and Cornell, adverse events, and interim reports of the ongoing study. The Study Coordinating Center will be responsible for preparing data and data analyses requested by the DSMB Board. The Study Steering Committee will hold teleconferences with the DSMB Board throughout each year and, when needed, in-person conferences. Drs. Sirey and Kales will interact with the DSMB at the DSMB’s discretion, providing them with material to facilitate fulfillment of the functions detailed below. DSMB functions include:

1. Review of protocols, informed consent procedures, and safety plans;
2. Monitoring the progress of the study, i.e. participant recruitment and retention, risk/benefit ratio for participants, adherence to timetable, and quality of data;
3. Evaluation of the impact of new treatment developments on the risk/benefit ratio of our study;
4. Making recommendations to the PIs and NIMH about continuation, modification, or termination of the ongoing study based on adverse events or beneficial outcomes;
5. Requesting interim analyses;
6. Monitoring the confidentiality of trial data and results of monitoring;
7. Offering consultation to the investigators on procedures likely to increase participants’ burden, to raise ethical concerns, or to give the appearance of conflict of interest.

The following data will be available to the DSMB Board:

1. All adverse events: We propose to submit individual adverse events, as well as summary tables every six months to the DSMB, but we would respond to the DSMB recommendation if a higher frequency of reporting is desirable.
2. All interim data analyses planned by the investigators.
3. Analyses requested by the DSMB Board.
4. All reports to NIMH and all publications.

We plan to have at least one teleconference per year and when needed in-person conferences.

All adverse events will be reported to the respective site IRBs. These reports will be made available to the DSMB and to NIMH.
**F. Vertebrate Animals:** Not applicable

**G. Select Agent Research:** Not Applicable

**H. Literature Cited**


48. Datto, C.J., MD; Thompson, R., PhD; Horowitz, D., MD; Disbot, M., RN; Bogner, H., MD, MSCE; Katz, I, MD, PhD, Do Clinician and Patient Adherence Predict Outcome in a Depression Disease Management Program? JCOM, 2003. 10(2): p. 6.


I. Multiple PI leadership Plan: Not applicable

J. Consortium/Contractual Arrangements: Not Applicable

K. Resource Sharing: Not Applicable

L. Letters of Support

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