

[\[reviewer notes→\]](#)

Provide a short title for this study (200 characters or less):

Prevention of Depression: Impact on the Transition to Early Adulthood

T1.0

Select the type of application:

New Research Study

T2.0

Is the proposed research study limited to the inclusion of deceased individuals?

* No

T2.1

Are any research activities being conducted at the VA Pittsburgh Healthcare System or with VA funds?

* No

[\[reviewer notes→\]](#)

T3.0

What is the anticipated risk to the research participants?

Minimal Risk

T3.1

Why do you feel that all aspects of this research study, including screening and follow-up, involve no more than minimal risk to the research subjects?

Subjects will participate in research interviews, provide saliva samples for DNA, and measurements of height, weight, BMI, waist and hip circumference, and blood pressure.

The probability and magnitude of harm or discomfort from these study procedures are not greater in and of themselves than those ordinarily encountered in daily life.

T4.0

Does the proposed study qualify for 'exempt' IRB review or for a determination of either 'not research' or 'no human subject' involvement?

* No

T5.0

Does the proposed research study qualify for 'expedited' IRB review status?

* No

[\[reviewer notes-\]](#)**CS1.0 What is the reason for this submission?**

New Research Protocol Submission

CS1.1 Has this research study been approved previously by the University of Pittsburgh IRB?

* No

CS1.1.1 Has this research study (or a substantially similar research study) been previously disapproved by the University of Pittsburgh IRB or, to your knowledge, by any other IRB?

* No

[\[reviewer notes-\]](#)**CS2.0 Title of Research Study:****Prevention of Depression: Impact on the Transition to Early Adulthood****CS2.0.1**

Requested approval letter wording:

CS2.1 Research Protocol Abstract:

This is a four site study that proposes to examine the long term effects of a Cognitive Behavioral Program (CBP) which was previously provided to a cohort of adolescents when they were 13-17 years old. The sample is at high risk for depression by virtue of familial (parental depression) and individual factors (past history of depression and/or current subsyndromal depressive symptoms). In the original study, across all 4 sites, we successfully enrolled 99% (N=316) of our proposed target recruitment of 320 adolescents, with equal recruitment across the 4 sites. Participants were randomized into either CBP or treatment as usual (TAU), with equally high retention (92%) in both conditions. Results through the 8-month follow-up indicated a significant prevention effect of CBP with regard to depressive episodes. The aims of the current proposal are to (a) study the longer term impact of CBP on preventing depression during the critical developmental transition to early adulthood, a period of multiple new life challenges and stressors; (b) assess potential biological (e.g., genetic) and psychosocial (e.g., childhood abuse, stressful life events) moderators of response to the intervention; (c) examine the broader impact of the CBP program on sequelae of depression including other mental and medical health problems, health risk behaviors, and impairment in the attainment of developmental competencies; and (d) assess the long-term cost-efficacy of CBP, identify markers of the impact of CBP on key economic outcomes (e.g., workplace productivity), and examine the longer-term economic benefits of preventing or delaying the onset of mood disorders in adolescents with CBP.

[\[reviewer notes-\]](#)

CS3.0 Name of the Principal Investigator:

[David Brent](#)

Note: Adjunct faculty of the University, including lecturers and instructors, are not permitted to serve as a PI or Faculty Mentor but may serve as co-investigators.

CS3.1 Affiliation of Principal Investigator:

UPitt faculty member

If you chose any of the Pitt options, please indicate the specific campus:

[Main Campus - Pittsburgh](#)

If you chose the UPitt faculty member option, provide the PI's University Faculty Title:

CS3.2 Address of Principal Investigator:

WPIC - Room 311 Bellefield Towers
3811 O'Hara Street
Pittsburgh, PA 15213

CS3.3 Recorded Primary Affiliation of the Principal Investigator:

U of Pgh | School of Medicine | Psychiatry

CS3.4 Identify the School, Department, Division or Center which is responsible for oversight of this research study:

[U of Pgh | School of Medicine | Psychiatry](#)

CS3.5 Telephone Number of Principal Investigator:

412-246-5282

CS3.6 Recorded Current E-mail Address of Principal Investigator to which all notifications will be sent:

brentda@upmc.edu

CS3.7 Fax Number:

412-246-5344

CS3.8 Does this study include any personnel from Carnegie Mellon University, and/or use any CMU resources or facilities (e.g., Scientific Imaging and Brain Research Center (SIBR))?

* No

CS3.9 Is this your first submission, as PI, to the Pitt IRB?

* No

[\[reviewer notes→\]](#)**CS4.0****List of Co-Investigators:**

Last First Organization

Iyengar Satish U of Pgh | Faculty of Arts and Sciences | StatisticsMelhem Nadine U of Pgh | School of Medicine | Psychiatry[\[reviewer notes→\]](#)**CS5.0 Name of Primary Research Coordinator:**Candice Biernesser**CS5.1****Address of Primary Research Coordinator:**WPIC - 312 Bellefield Towers
3811 O'Hara St.
Pittsburgh, PA 15213**CS5.2****Telephone Number of Primary Research Coordinator:**

412-586-9064

CS6.0**Name of Secondary Research Coordinator:****CS6.1****Address of Secondary Research Coordinator:**WPIC - 328 Bellefield Towers
3811 O'Hara St.
Pittsburgh, PA 15213**CS6.2****Telephone Number of Secondary Research Coordinator:**

412-586-9064

CS6.3**Key Personnel/Support Staff (Only list those individuals who require access to OSIRIS):**Last First Organization
There are no items to display[\[reviewer notes→\]](#)**CS7.0****Will this research study use any [Pediatric PittNet](#) or Clinical and Translational Research Center (CTRC) resources?**

No

[\[reviewer notes-\]](#)

CS8.0 Select the entity responsible for scientific review.

WPIC SRC - Western Psychiatric Institute and Clinic Scientific Review Committee. Note: Please upload the Research Committee approval notification in the "Supporting Documentation" section.

[\[reviewer notes-\]](#)

CS9.0 Does this research study involve the administration of an investigational drug or an FDA-approved drug that will be used for research purposes?

* No

CS10.0 Is this research study being conducted under a University of Pittsburgh-based, sponsor-investigator IND or IDE application?

* No

If YES, you are required to submit the IND or IDE application and all subsequent FDA correspondence through the Office for Investigator-Sponsored IND and IDE Support (O3IS). Refer to applicable University policies posted on the O3IS website (www.o3is.pitt.edu).

[\[reviewer notes-\]](#)

CS11.0 Use the 'Add' button to upload one or more of the following:

- the sponsor protocol (including investigator initiated studies) and/or other brochures
- the multi-center protocol and consent form template, *if applicable*

Name	Modified Date
POD.2_FINAL.1_ALL_3-09-2010	3/9/2010 3:47 PM

Is this research study supported in whole or in part by industry? This includes the provision of products (drugs or devices).

* No

Is this a multi-centered study?

* Yes

[\[reviewer notes-\]](#)

CS12.0 Does your research protocol involve the evaluation or use of procedures that emit ionizing radiation?

*

CS13.0 Does this research study involve the deliberate transfer of recombinant DNA (rDNA) or DNA or RNA derived from rDNA into human subjects?

* No

Upload Appendix M of NIH Guidelines:
 Name Modified Date

CS14.0 Are you using UPMC facilities and/or UPMC patients during the conduct of your research study?

* No

If Yes, upload completed Research Fiscal Review Form:
 Name Modified Date

[\[reviewer notes-\]](#)

CS15.0 Indicate the sites where research activities will be performed and/or private information will be obtained.

Choose all sites that apply and/or use Other to include sites not listed:

Sites:

UPMC

Other

UPMC
 Sites:

 UPMC Western Psychiatric Institute & Clinic

If you selected School, International or Other, list the sites:
 Subjects will be given the choice of a home visit or coming in to research office in Bellefield Towers.

This study will also be conducted in independent parallel protocols at Harvard, Kaiser Permanente, and Vanderbilt under the direction of their own site PIs.

*For non Pitt or UPMC entities, upload documents granting permission to conduct research at that site:
 Name Modified Date

CS15.1 Have you, [David Brent](#) , verified that all members of the research team have the appropriate expertise, credentials, and if applicable, hospital privileges to perform those research procedures that are their responsibility as outlined in the IRB

protocol?

* Yes

CS15.2

Describe the availability of resources and the adequacy of the facilities to conduct this study:

* Resources and support are provided by the NIMH Grant and the Department of Child Psychiatry at UPMC. The offices at Bellefield Towers are appropriate for conducting research interviews with study subjects. The study interviewers have access to personal automobiles that they use to travel to subjects' homes to conduct interviews and are reimbursed for mileage.

[\[reviewer notes→\]](#)

CS16.0 Special Research Subject Populations:

Categories

Children (age < 18 years old)

[\[reviewer notes→\]](#)

CS17.0 Does your research involve the experimental use of any type of human stem cell?

* No

[reviewer notes-]

- 1.1** Objective: What is the overall purpose of this research study? (Limit response to 1-2 sentences.)
The overall purpose of this research study (POD 2) is to follow-up the cohort of subjects who participated in the original prevention study (POD)(IRB# 0208118). Having successfully met the recruitment, implementation, and short-term outcome goals of POD.1, we now seek to follow this sample as they move from adolescence into young adulthood, collecting new data on individual, familial, and environmental risk factors and a broader set of long-term outcomes in order to more fully describe the potential public health impact of our initial prevention findings (i.e., to promote the adoption of such a prevention program).
- 1.2** Specific Aims: List the goals of the proposed study (e.g., describe the relevant hypotheses or the specific problems or issues that will be addressed by the study).
Aim 1. To assess the long-term impact of this prevention program across the critical developmental transition to young adulthood, a period of high risk for incident and recurrent mood disorders.
Hypothesis 1: Compared to youth in the TAU control condition, youth in the CBP program will continue to demonstrate a lower burden from depression during emerging adulthood across multiple indices of depression (e.g., cumulative incidence of depressive episodes, depression-free-days).
Secondary Aims
Aim 2. To collect new data to examine potential individual (e.g., genetic, personality) and contextual (e.g., child abuse, stressors) moderators of CBP response and long-term course. We will obtain DNA from the proband, index parent, and two other family members, and assess polymorphisms in candidate genes that have been shown to be associated with unipolar depression and with cardiovascular risk [e.g., the serotonin transporter promoter gene (5-HTTLPR), angiotensin convertin enzyme (ACE)]. We will obtain data about depression and other mental health history of these other relatives, as well as probands' early abuse exposure, stressful life events during young adulthood, and neuroticism. These new data will let us better characterize this sample, assist in the public health targeting of this program, and guide the development of the next generation of preventive interventions aimed at those adolescents who were less responsive to the current program.
Hypothesis 2: Within this sample, the long-term effect of CBP will be moderated by the level of individual (e.g., genetic) and environmental (e.g., stress) risk, with the greatest impact of CBP compared to TAU seen in those youth at the lowest relative risk.
Aim 3. To examine the broader impact of the CBP program on sequelae of depression likely to emerge during this transition period, such as impairment in attainment of developmental benchmarks (e.g. financial independence, establishment of romantic relationships), and increased risk of other mental and physical health problems and health risk behaviors (e.g., substance abuse, anxiety, overweight, high blood pressure).
Hypothesis 3: Compared to those in TAU, young adults who had been in the CBP program will show greater developmental competence, better self-reported and interview-assessed physical health (e.g., global health, BMI, blood pressure), lower levels of psychological traits related to cardiovascular risk (hostility, threat appraisal), and fewer and less severe health risk behaviors (e.g., physical activity, diet, smoking, sleep); and effects will be mediated by lower levels of inter-current depressive symptoms and episodes.
Aim 4. To estimate the long-term cost-effectiveness of the CBP program and to quantify long-term economic benefits of preventing or delaying the onset of mood disorders in adolescents. In addition, we will examine markers of the impact of CBP on key economic outcomes important in the transition to adulthood, including human capital accumulation (e.g., engagement in and completion of secondary and post-secondary education) and improved workplace productivity (e.g., lower levels of unemployment, absenteeism, and presenteeism).
Hypothesis 4.1: The long-term cost per outcome (e.g., cost per depression-free day) achieved will be lower for young adults in the CBP intervention than in TAU.
Hypothesis 4.2: Compared to TAU participants, young adults who had been in the CBP program will show better educational attainment and workplace productivity.

1.3

Background: Briefly describe previous findings or observations that provide the background leading to this proposal.

In POD.1, the primary outcome was prevention of depressive episodes and symptoms during adolescence. We were successful in accomplishing this aim (see Progress Report), both as a main and moderated short-term effects. Note that in the model, all POD.1 results and variables are labeled POD.1 and are displayed in yellow. The additional boxes represent the new contributions of POD.2, and the overall figure depicts the relation between the original study and the proposed new work.

Outcomes in emerging adulthood. In keeping with the aims of POD.1, the primary outcome of POD.2 is the prevention of depressive episodes during emerging adulthood (Aim 1). Furthermore, we predict that the impact of the CBP program on reducing depression during adolescence will mediate the link between the intervention and depression in early adulthood, developmental milestones during this transition period, and a broader set of mental and physical health outcomes (Aim 3). Moreover, this joint effect on depression, functioning, and other health outcomes will impact economic indicators (Aim 4). Below we review the literatures relevant to each component of the model, presented in order of each Specific Aim of POD.2.

3.3. Depression during Emerging Adulthood (Aim 1). Adolescence and emerging adulthood are "sensitive periods" for depressive disorders (Reinherz et al., 1999). Depression often begins as depressed mood or minor depression during early adolescence (Ge, Conger, & Elder, 2001; Pine, Cohen, Cohen, & Brook, 1999), with the average age of first onset MDD being 15 years (Hankin et al., 1998). The National Comorbidity survey found that individuals ages 15-24 were the most likely to have had an affective illness in the past year (Kessler et al., 1994). Lifetime prevalence rates of depressive disorders increase linearly from mid-adolescence to young adulthood, from 15% at ages 15-16 to 21% at ages 21-22 (Kessler & Walters, 1998), with a cumulative prevalence rate for MDD by the end of adolescence of 25% (Kessler, Avenevoli, & Merikangas, 2001). Among offspring of depressed parents, the peak age of MDD onset appears to be between 15-20 years old, and 44% have had an MDE by age 24 (Weissman, Warner, Wickramaratne, Moreau & Olfson, 1997). Thus, early adulthood is a critical period for the occurrence of MDD, particularly among high risk offspring.

In terms of follow-up, other prevention trials (e.g., Sandler et al., 2003; Wolchik et al., 2002) have shown that effects actually may increase over long-term follow-up. For example, in their two trials of children exposed to parental bereavement or divorce, Sandler (a consultant on the present proposal) and colleagues have (a) found increasing differences between those who received the intervention and those who did not, for periods of follow-up as long as 6 years later, (b) identified likely mechanisms of change of this long-term impact, and (c) determined sub-groups most likely to benefit from the intervention. Given the parallels between our studies, and the positive effect of our program over the first 8 months of follow-up, we expect to be able to make similar contributions to the understanding of processes underlying the prevention of depression.

3.4. Biological and Psychosocial Moderators of CBP Depression Effects (Aim 2). Our preliminary analyses (see 4.2 in the Progress Report) showed that both adolescent and parent risk factors moderated the effects of CBP. Youth in the CBP program with the lowest relative risk of mood disorders had the best outcome compared to TAU youth at the same level of risk and to youth at higher risk. A host of interrelated variables may account for this finding. In our sample, associations were found between current parental depression, earlier age of parental depression onset, high youth depressive and anxious symptoms, more stressful life events, and lower SES. The new data collection in POD.2 provides a unique opportunity to evaluate both genetic and environmental moderators of the longer-term effects of a psychosocial intervention program. In particular, we will examine genetic liability, neuroticism, and child abuse and neglect as potential diatheses in the presence of more proximal environmental stressors. We consider each of these below.

Genetic contributions to depression. Evidence of the contribution of genes to the etiology of depression has been found using family, adoption, and twin studies. Twin studies have reported heritability estimates of depression ranging from 37% to 43% (e.g., Bierut et al., 1999; Kendler et al., 1995). Family studies have found a 2.5 to 4 fold risk for depression in first-degree relatives of individuals with depression (Craddock & Forty, 2006; Kovacs & Devlin, 1998). Familial transmission from parent to child is greater if the parental depression is early-onset (age less than 20), recurrent, or comorbid with anxiety (Beardslee et al., 1998; Weissman et al., 1988) all of which characterized a considerable portion of our sample of parents in POD.1. Indeed, our main parental moderator of CBP effects – current parental depression – was significantly associated with an earlier age of onset for parents' first

depression and a more chronic life course of depressive illness.

Shared risk for depression and cardiovascular disease. The comorbidity between depression and cardiovascular disease is well documented (Glassman, 2007). Medically healthy depressed individuals are at higher risk for cardiovascular morbidity and mortality, even after controlling for the relation between depression and smoking (Wulsin & Singal, 2003). This comorbidity may be explained by common psychosocial antecedents such as family adversity (Fellitti et al., 1998) as well as shared genetic influences (Bondy, 2007). A twin study of male veterans found a substantial genetic correlation between the occurrence of cardiovascular disease and depression ($r=.42$) with no contribution due to shared environment. This finding is plausible in terms of possible shared etiological mechanisms such as increased emotional reactivity in response to stress, hyper-reactivity of the hypothalamic-pituitary axis and hypersecretion of cortisol, alterations in the renin angiotensin system, and in immune response and inflammatory pathways (Bondy, 2007). Candidate depression genes. Genome-wide linkage studies to identify markers linked to depression, anxiety, and neuroticism have converged on broad chromosomal regions (e.g., Camp et al., 2005; Crowe et al., 2001; Fullerton et al., 2003; McGuffin et al., 2005). In addition, whole genome association studies will be reporting results in the near future, which should guide the selection of candidate genes beyond the existing literature. We review here possible candidate genes based on extant data, but recognize the limitations of current association studies, especially those based in single-nucleotide polymorphisms (SNPs) (Gelernter et al., 2003). Methodological problems that have been identified include variability in phenotyping, population stratification, inappropriate control groups, and failure to consider the role of gene by environment interactions. In the proposed study, we will guard against these difficulties by careful phenotypic assessment of participants and their families, obtaining DNA from family members as well as probands to allow for Family Based Association Tests (FBAT) that are not vulnerable to effects of population stratification, and characterization of stressful life events and the family environment that may influence genetic expression. In addition to examining the genes outlined herein, we will store the DNA and await further research that clarifies which genes are particularly worth studying in the future. Therefore, we describe several possible candidate genes for illustrative purposes. These genes were chosen because of their potential functional significance for the pathogenesis of depression and evidence of replication, especially with meta-analyses (Lin & Tsai, 2004; Lotrich & Pollock, 2004; Serretti et al., 2007), associating variations of the gene with depression, related phenotypes (e.g., suicidal behavior), and either cardiovascular disease, or a risk factor thereof.

(a) Serotonin Transporter Promoter Gene (5-HTTLPR). Serotonergic function has been shown to be altered in depression (Lotrich & Pollock, 2004). The most consistent genetic polymorphism associated with depression has been a 44 bp insertion-deletion in the serotonin transporter promoter region (5-HTTLPR). The deletion and insertion are referred to as the short and long alleles, with the former showing less *in vivo* transcriptional activity (Heils et al., 1996). A tri-allelic form has been reported in which one long form has lowered transcriptional activity, similar to the *s* allele (Holmans et al., 2004; McGuffin et al., 2005). The *s*-allele has been shown to be associated with high emotional reactivity to frightening stimuli as documented on fMRI (Hariri et al., 2005), neuroticism, anger, and depression in interaction with stressful life events (Anguelova et al., 2003; Caspi et al., 2003). Recent meta-analyses have shown an association between the less functional variant of 5-HTTLPR and the following phenotypes relevant for this study: response to antidepressants (Serretti et al., 2007), suicidal behavior (Lin & Tsai, 2004), and depression ($OR=1.16$) (Lotrich & Pollock, 2004). An increased risk of depression has been found in those with the *S* allele and increased exposure to stressful life events and family adversity (Caspi et al., 2003; Kaufman et al., 2006; Kendler et al., 2005; Zalsman et al., 2006). Increased blood pressure and heart rate in response to mental stress (risk factors for cardiovascular disease) also have been associated with the *s/s* genotype (McCaffery et al., 2003).

(b) Tryptophan Hydroxylase (TPH): TPH-1 expressed in the brain during neurodevelopment but not later in life is the rate-limiting enzyme for the synthesis of serotonin. Several haplotypes have been associated with depression; the strongest association was attributed to a 2-SNP haplotype comprising A779C polymorphism (Gizatullin et al., 2006). A meta-analysis showed an association between the A218 allele (in linkage disequilibrium with the A779C allele) and suicidal behavior ($OR=1.33$; Rujescu et al., 2003). A brain-specific expressing TPH gene variant, TPH-2, has been described, but has not been as extensively studied as TPH-1. A 1463G-A transition in the TPH-2 gene, a functional SNP replacing arg441 with this (R441H), results in about 80% loss of function in serotonin production. This loss of function may represent an important risk factor for unipolar depression (Garriock et al.,

2005; Zhang et al., 2005). The same allelic variation in TPH-1 associated with suicidal behavior also has been linked with increased likelihood to respond to provocation with anger, a known risk factor for cardiovascular disease (Manuck et al., 1999). More recently, fMRI-documented increased emotional reactivity has been associated with the G844T polymorphism of TPH-2 (Brown et al., 2005).

(c) Serotonin 5-HT_{2A} receptor gene is a post-synaptic receptor. Association studies have shown that variants of this gene predict antidepressant response, including a statistically significant association between the A allele of rs7997012 and antidepressant response to citalopram in 1,953 patients who participated in the STAR-D study (18% better response in those with the A allele, p 's < .00004) (McMahon et al., 2006). Other polymorphisms in linkage disequilibrium with this polymorphism have been associated with increased liability to anger and aggression, which are known risk factors for cardiovascular disease (Giegling et al., 2006).

(d) Brain Derived Neurotrophic Factor (BDNF) is a protein that appears to protect against the neurotoxic effects of stress. In animal models of stress-induced depression, BDNF levels decline; this decline is reversed with antidepressant treatment (Berton et al., 2006). A G to A SNP at nucleotide 196 results in a val66-to-met (V66M) change in the BDNF protein (Egan et al., 2003). Early-onset depression is associated with the met66 genotype in some studies, and the val66 genotype in others both as a direct effect, and in interaction with a history of early child abuse (Berton et al., 2006; Kaufman et al., 2006; Strauss et al., 2004). The met66 polymorphism has been associated with HPA hyperactivity (Schule et al., 2006) and BDNF also has been implicated in metabolic syndrome, both known risk factors for cardiovascular disease (Hristova & Aloe, 2006).

(e) Dopamine Receptor D4 (DRD4). Dopamine has been implicated in the pathogenesis of mood disorders. A significant association between DRD4 and mood disorders, especially MDD, has been reported (Manki et al., 1996) such that 4-repeat allele was significantly lower and 5-repeat allele was significantly higher in persons with unipolar depression compared to controls. A meta-analysis of 12 studies (Lopez et al., 2006) found a significant association between a 48-bp polymorphism and unipolar depression such that the higher repeat polymorphisms (longer) were associated with a higher risk of depression. Although this candidate gene has not been as extensively studied with regard to cardiovascular risk, this polymorphism also has been found to be associated with increases in diastolic and systolic blood pressure (Sen et al., 2005).

Candidate cardiovascular genes. Angiotensin-converting enzyme gene (ACE) is responsible for the generation of angiotensin II and bradykinin, which are important for the maintenance of vascular tone. The most extensively investigated polymorphism is the insertion (I) or deletion (D) of a 287 bp Alu repeat within intron 16 of the gene. The D allele is associated with increased levels of ACE, increased risk for hypertension, left ventricular hypertrophy, myocardial infarction, higher basal and stimulated cortisol levels, and onset of depression and slower response to antidepressant treatment (Arinami et al., 1996; Baghai et al., 2001; Bondy, 2007; Rigat et al., 1990). A second SNP polymorphism in the promoter region of the ACE gene (rs4921) with an A/T transition has been associated with major depression as well as hypercortisolism and increased levels of C-reactive protein, which are risk factors for cardiovascular disease (Baghai et al., 2006).

Candidate genes in the stress response pathway. Alterations in the hypothalamic-pituitary axis (HPA) are thought to be central to the pathogenesis of mood disorders (Young, 2004). In addition to its role in depression, hypersecretion of cortisol has been reported in young adults at familial risk for depression (Mannie, Harmer, & Cowen, 2007). The number of studies that have been conducted does not allow for meta-analysis, so these findings must be considered suggestive. Polymorphisms in the glucocorticoid receptor (GR) have been reported to be associated with altered GR sensitivity and increased risk for unipolar depression (BcII, ER22/23EK) (Ising & Holsboir, 2006; Vam Rossum & Binder 2006). A polymorphism in a GR modulator also has shown altered HPA activity, increased risk for recurrent unipolar depression, and differential response to antidepressants (FBK 5, Binder et al., 2004).

Neuroticism. In addition to direct assessment of genes, we plan to examine genetically-linked marker variables, such as neuroticism. Neuroticism is a personality trait defined as emotional reactivity, or the general tendency to experience negative affect, with heritability ranging between .30 and .60 (Eaves et al., 1999). Particularly relevant to the present proposal is that neuroticism is a potential intermediate phenotype for depressive disorders. Intermediate phenotypes can help dissect or decompose complex phenotypes such as depression into simpler ones because they are located closer to genes in the pathway from genes to behavior. Moreover, intermediate phenotypes are believed to lead to a more

successful search for the genes involved in the development of complex disorders.

Individuals who score high on measures of neuroticism are prone to have irrational ideas, to be less able to control their impulses, and to cope poorly with stress (Costa & McCrae, 1992). Kendler, Gardner, and Prescott (2002) showed that, after stressful life events, neuroticism was the strongest predictor of onset of major depression. We will examine whether neuroticism moderates the relation between the intervention and subsequent depression, and mediates the link between genes and depression.

Early abuse and neglect and stressful life events. The assessment of abuse and neglect during childhood is salient to the proposed study for three main reasons. (1) Hostile and withdrawn parent-child interactions have been shown to partially mediate the relation between parent and child depression and to influence course (Goodman & Gotlib, 1999). A better assessment of childhood maltreatment, even retrospectively reported, can help identify which offspring of depressed parents are most likely to experience recurrence or persistence of their depressive disorder as they move into adulthood. Moreover, history of abuse predicts earlier onset of depression, longer episode length, and more recurrences (Barbe et al., 2005). In several large systematically sampled studies, childhood sexual abuse was associated with an increased risk for depression and other disorders, especially among women (MacMillan et al., 1997; Molnar, Buka, & Kessler, 2001). (2) A history of abuse may moderate the treatment effects of psychotherapy for depression. In a large, multi-site study of the treatment of chronic depression, individuals with a history of early abuse were much more likely than those without such a history to show a better response to psychotherapy and a less vigorous response to antidepressants (Nemeroff et al., 2005). (3) There is growing evidence of a gene-by-environment interaction with regard to risk for early-onset depression. Kaufman et al. (1998) reported that children and adolescents who were abused and develop depression were much more likely to do so if they also had a positive family history of mood disorders. Subsequently, studies have shown that depression is most likely to ensue when a lower expressing polymorphism (either s or L^g) of the serotonin transporter gene is present in individuals who also have a history of abuse (Caspi et al., 2003; Kaufman et al., 2006). Similarly, the lower expressing form of BDNF (val66) in combination with a history of abuse is more likely to result in early-onset depression (Kaufman et al., 2006). The assessment of more proximal stressful life events also is warranted because of the well-known relation between stressful life events and depression onset (e.g., Brown & Harris, 1989; Kendler et al., 2002), and evidence of an interaction between genotype and life stressors with regard to the incidence of early-onset unipolar depression (Caspi et al., 2003; Kendler et al., 2005; Zalsman et al., 2006).

3.5. Sequelae of Depression among Young Adults (Aim 3). In addition to the distress caused by depressive symptoms in adolescence, early mood disorders increase the risk of secondary adverse outcomes (e.g., substance abuse, suicidality, lower educational attainment, early pregnancy, stressful life events), the effects of which persist even after the primary illness has remitted (Kessler et al., 2001). We broadly classify these secondary effects in terms of (a) role functioning and attainment of developmental benchmarks, and (b) physical and mental health outcomes, including health risk behaviors. We recognize that each of these broad domains could be split into much finer distinctions or outcomes could be grouped differently. In keeping with the original aims of POD.1, we view the primary outcome of the proposed project as prevention of depression, and we have designed POD.2 to have the greatest precision and power to test the mood disorder effects. We have synthesized these multiple, secondary outcomes in a more global manner to reflect the exploratory nature of these analyses.

Role functioning. Adolescent depressive symptoms and disorders have been associated with a range of negative functional outcomes in adulthood. In a longitudinal study of unipolar depressed adolescents, Rao et al. (1995) found deficits in extra-familial relationships, life satisfaction, and overall functioning seven years later, even after the depressive disorder had remitted. No psychosocial deficits, however, were found in young adults who did not experience a recurrence of depression from adolescence to young adulthood. Similarly, Lewinsohn et al. (2003) found that adolescent MDD was associated with "pervasive impairments" during young adulthood including reduced life satisfaction, poor relationship quality, and environmental adversity.

Youth who attend college may be given a reprieve from adult responsibilities and thereby experience psychological benefits (Aseltine & Gore, 2005; Raymore, Barger, & Eccles, 2001). Nonetheless, the career path of young adults is often unstable, marked by enrollment in various levels of higher education and/or frequent job changes and periods of unemployment (Bernhardt et al., 1999; Starr, 1986). Both job changes and unemployment are more prevalent in individuals ages 18-21 compared to older age groups (Bureau of

Labor Statistics, 2006), and unemployment during emerging adulthood has been linked to depression (Dooley, Prause, & Ham-Rowbottom, 2000; Galambos, Barker, & Krahn, 2006). Young adult males who are depressed are twice as likely to have difficulty supporting themselves financially, and four times as likely to report a lack of access to health care due to costs; young adult depressed females are more likely than nondepressed females to cite financial difficulties as interfering with their career progress (Reinherz et al., 1999).

Emerging adulthood also is when young people (ages 19-29) spend more of their leisure time alone than any other age group besides the elderly (Larson, 1990). Although family of origin can be an important source of support, conflicts also often arise (e.g., Goldscheider & Goldscheider, 1993). Indeed, many depressed young adults report poor relationships with their parents (Reinherz et al., 1999). Progression through adolescence into adulthood includes an increased pursuit of close relationships and intimacy within those relationships (Savin-Williams & Berndt, 1990). However, the development and maintenance of romantic relationships may be particularly stressful for high-risk young adults who exhibit poorer relationshiping in marriage (Weissman et al., 1997) and less intimate romantic relationships (Ensign, Scherman & Clark, 1998; Scharf & Mayselless, 2001).

Mental and physical health. Depression in adolescence is associated with a range of negative mental and physical health outcomes. Youth with a history of depression are at increased risk for conduct disorder, personality disorders, and suicidal behavior (Brent et al., 1988; Fergusson & Woodward, 2002; Lewinsohn, Rohde, & Seeley, 1998). Alcohol, drug, and tobacco abuse are linked with depression, and longitudinal studies suggest a bi-directional relation, with substance abuse both preceding and following the onset of depressive episodes (Rohde, Kahler, Lewinsohn, & Brown, 2004). Anxiety is frequently a precursor of mood disorders and also may occur simultaneously with depression, across the lifespan (e.g., Pine et al., 1998).

Mental and physical health problems are closely inter-related during adolescence and emerging adulthood. The leading causes of mortality (reckless driving, homicide, suicide) during this age period have links to psychopathology (Eaton et al., 2006; Hingson et al., 2005; Merrick et al., 2004). Social and emotional problems are associated with such negative health behaviors as substance abuse, sexual risk taking [sexually transmitted diseases (e.g., HIV)], as well as unhealthy dietary behaviors and physical inactivity contributing to obesity and concomitant morbidity such as early onset type 2 diabetes, hypertension, endocrine and pulmonary problems (Dietz, 1998; Field, Cook & Gillman, 2005; Weiss et al., 2004).

In addition to this indirect effect of psychopathology on physical morbidity through health behaviors, social and emotional problems may directly influence physical morbidity through psychophysiological mechanisms such as stress reactivity. For example, asthma and other respiratory symptoms have been found to be reciprocally related to depression (Goodwin, Jacobi, & Thefeld, 2003; Goodwin, Lewinsohn, & Seeley, 2004). Further, a longitudinal study following individuals from middle childhood through young adulthood showed that of all psychiatric disorders, MDD had the strongest and most consistent prospective association with subsequent physical illness independent of prior health problems (Cohen et al, 1998).

These links were particularly strong between MDD and medical problems associated with immunological disorders (e.g., allergic and infectious illnesses). Cardiovascular disease (CVD) may be linked to depression via shared psychological traits such as bias toward threat, hostility, and cynicism that may reflect increased stress reactivity.

Physical health morbidity during young adulthood also may result from the concomitant indirect effects of health behaviors coupled with direct psychophysiological mechanisms. Depression in adolescence predicts elevated body mass index (BMI) and obesity in early adulthood even when taking prior BMI into account (Franko et al., 2005; Richardson et al., 2006; Stice et al., 2005). The association between depression and subsequent CVD also appears to be at least partially mediated through the effects of depression on BMI (Kabir et al., 2006). Further, deleterious health behaviors such as binge eating and physical inactivity are associated with the subsequent development of obesity (Bulik & Reichborn-Kjennerud, 2003; Jakicic & Otto, 2005; Pender & Pories, 2005; Yanovski, 2003) which, in turn, is associated with higher risk for cardiovascular disease (Lee et al, 2007; Loria et al, 2007). Increased blood pressure is a significant risk factor for cardiovascular disease (Kannel, 1996), and past history and current symptoms of depression predict hypertension due to shared health risk behaviors (e.g., low physical activity), shared psychosocial etiology (Felliti et al., 1998), and (potentially) shared genes that contribute to both conditions (Davidson et al., 2000; Scherrer et al., 2003).

Thus, decreasing early depressive symptoms among high risk youth through preventive interventions such as the one provided in POD.1 may result in substantially lowered

morbidity and improved mental and physical health as adolescents move into the young adult years (Aim 3 of POD.2). The proposed follow-up assessment will include an inquiry about mental health (anxiety, substance use, suicidality), health related and health behaviors, body mass index, waist-to-hip ratio, and blood pressure.

3.6. Economic Impact of the Depression Prevention Program (Aim 4). Little is known about the cost-effectiveness of youth mental health treatment (Lynch & Clarke, 2006; Romeo et al., 2005). One economic evaluation of a youth depression prevention program showed short-term cost-offsets in social service use for participants (Lynch et al., 2005). POD.2 would provide the first long-term evaluation of the cost-effectiveness of any youth depression intervention and be the only mental-health cost-effectiveness analysis reaching across the divide of adolescence into young adulthood. Our POD.2 follow-up interviews will be, on average, 6 years post-randomization. With this assessment window, we will be able to assess long-term benefits of the program, including cost-offsets to other service sectors. In addition to service cost savings, the preventive intervention also could improve labor market outcomes for youth who participated in the program. Large epidemiologic and workplace studies have shown that depression is associated with poor labor market outcomes in adults such as reduced likelihood of employment (Dooley et al., 2000; Ettner et al., 1997; Marcotte & Wilcox-Gok, 2001), decreased earnings (Berndt et al., 2000; Ettner et al., 1997, Marcotte & Wilcox-Gok, 2001), increased absenteeism (Dewa et al., 2004; Kessler et al., 2006; Stewart et al., 2003), and reduced productivity while at work (i.e., presenteeism) (Adler et al., 2006; Dewa et al., 2004; Kessler et al., 2006; Wang et al., 2004). These labor market effects of depression are comparable to other chronic health conditions (Adler et al., 2006; Wang et al., 2004). Effective depression treatments in adults have improved maintenance of employment (Dewa et al., 2003; Schoenbaum et al., 2002, 2005; Simon et al., 2000) and reduced absenteeism (Kocsis et al., 2002; Schoenbaum et al., 2001; Simon et al., 2002). A meta-analysis (Timbie et al., 2006) found small labor supply effects of depression treatment programs, although most of the studies had short follow-ups, and longer follow-ups showed larger gains in labor supply. Notably, none of these studies measured reduced productivity while at work (presenteeism), despite evidence from epidemiologic studies that presenteeism accounts for the majority of work time loss due to depression (Dewa et al., 2004; Kessler et al., 2006; Stewart et al., 2003).

Examination of labor market productivity in adolescence and emerging adulthood is a methodological challenge. Young adults participate in a variety of activities that help them develop financial independence and accumulate human capital, which will increase their probability of future workplace productivity and earnings (Becker, 1964; Berndt et al., 2000). Young adults work for pay, volunteer, intern to gain new skills, and, perhaps most critically, pursue higher education (Becker, 1964). An overall measure of educational engagement (e.g., mean hours of productive engagement in educational activities) provides a useful gross index of young adult development (Brown et al., 2003; Rowe, & Kahn 1997; Kosterman et al., 2005), and such measures predict long-term outcomes (e.g., substance abuse). Mental health problems have been found to specifically influence such educational outcomes as high school graduation, college attendance, GPA, and history of suspension or expulsion from high school (Currie & Stabile 2006; Fletcher & Wolfe 2007; Kessler et al. 1995; Stoep et al. 2003). The current revised proposal now includes both general (e.g., productive engagement) and specific measures (e.g., high school graduation) of school outcomes to index this construct.

In summary, reducing early onset depression through effective prevention may improve human capital accumulation and workplace productivity as individuals move from adolescence into young adulthood. The proposed application will enable us to collect new data on labor market outcomes not included in POD.1, and will extend current knowledge about the impact of depression on labor market productivity for young adults. We will also be able to extend our knowledge on the long-term cost-effectiveness of the CBP program.

- 1.4** Significance: Why is it important that this research be conducted? What gaps in existing information or knowledge is this research intended to fill?
 This competitive renewal builds on the broad base of developmental psychopathology research and the findings from POD.1 with regard to both breadth and depth. (a) POD.2 would be the longest follow-up of a targeted sample in a randomized controlled depression prevention trial. (b) POD.2 will allow an examination of the impact of the intervention on the transition to early adulthood, which is when young adults are encountering multiple new life challenges and potential stressors. (c) We will obtain broad and developmentally-informed

Section: Section 1 - Objective, Aims, Background and Significance

assessments of physical and mental health, competence and functioning during this important transition period, and will explore the role of depression in mediating those outcomes. (d) We will assess the impact of family psychopathology (genotyping and psychiatric histories) on the development of depression in young adults. The proposed study will be the first to examine the moderating role of these diatheses in relation to a preventive intervention. For example, we will explore whether genetically vulnerable individuals respond more or less well to the CBP program. (e) We will study putative mechanisms by which these moderators may influence outcomes, thereby guiding future intervention development to address the needs of youth who, by virtue of their risk status, may not respond to the CBP program as it is currently structured. (f) Both short- and long-term cost-effectiveness of the program will be evaluated. We will examine markers of the impact of CBP on key economic outcomes important in the transition to adulthood including educational attainment and workplace productivity (e.g., lower levels of unemployment, absenteeism, and presenteeism). (g) Finally, POD.2 is consistent with the recommendation made by Kessler et al. (2001) in a discussion of future directions for research on mood disorders in adolescence, that "genetically informative designs that include measures of both biological and environmental risk factors would be ideal, along with follow-ups of experimental designs that evaluate the long-term effects of innovative outreach and treatment strategies" (p.1010). Moreover, the current proposal is in line with the highest priority for the NIMH Division of Services and Intervention Research by testing long-term and broader effects of an innovative prevention strategy, and evaluating its cost-efficacy. POD.2 will inform us about the potential of the CB program to reduce the burden of depression and its sequelae, and will aid in both the personalization of the intervention and the identification of new prevention targets through studying biological and psychosocial moderators of the intervention effects.

[\[reviewer notes-\]](#)

2.1 Does this research study involve the use or evaluation of a drug, biological, or nutritional (e.g., herbal or dietary) supplement?

* No

[\[reviewer notes-\]](#)

2.2 Will this research use or evaluate the safety and/or effectiveness of one or more devices?

* No

[\[reviewer notes-\]](#)

2.3 Summarize the general classification (e.g., descriptive, experimental) and methodological design (e.g., observational, cross-sectional, longitudinal, randomized, open-label single-blind, double-blind, placebo-controlled, active treatment controlled, parallel arm, cross-over arm) of the proposed research study, as applicable.

This is a longitudinal descriptive study assessing the long term benefits of a cognitive behavioral intervention in the prevention of depression.

2.3.1 Does this research study involve a placebo-controlled arm?

* No

[\[reviewer notes-\]](#)

2.4 Will any research subjects be withdrawn from known effective therapy for the purpose of participating in this research study?

* No

[\[reviewer notes-\]](#)

2.5 Will screening procedures (i.e., procedures to determine research subject eligibility) be performed specifically for the purpose of this research study?

* No

[\[reviewer notes-\]](#)

2.6 Provide a detailed description of all research activities (e.g., all drugs or devices; psychosocial interventions or measures) that will be performed for the purpose of

this research study.

This description of activities should be complete and of sufficient detail to permit an assessment of associated risks.

At a minimum the description should include:

- **all research activities**
- **personnel (by role) performing the procedures**
- **location of procedures**
- **duration of procedures**
- **timeline of study procedures**

The research procedures involved in this study are: interviews, questionnaires, measurements of height, weight, BMI, waist and hip circumference, and blood pressure, and collection of saliva samples for DNA.

(1) Research interviews and questionnaires:

The proposed new interviews will be scheduled to be at least 3 years beyond the final, 32-month interview from POD.1 (median = 4 years), but no sooner than the proband's 20th birthday. The expected median proband age at the time of the proposed assessment will be 22 years old.

In the proposed study (POD.2), we will assess the proband and index depressed parent about the period of time since their 32-month evaluation, thereby yielding continuous psychiatric diagnostic information spanning a range of 5 to 7 total years of follow-up. Proband will be interviewed about developmental transitions that first emerge in early adulthood such as the shift to independent living, significant romantic relationships, school, and employment. Two additional family members will be interviewed regarding their lifetime psychiatric histories of key diagnoses (mood disorders, anxiety disorders, alcohol and drug use disorders). Please see table in Section 2.8- Assessment Battery for a listing of specific assessments.

These interviews will be conducted at time that is most convenient for the participant and can be conducted either in the subject's home or at Bellefield Towers. The entire assessment is expected to take approximately 3 hours for probands and about 2 hours for the other participants.

All interviewers (Independent Evaluators (IE)) will be trained in performing psychiatric assessments. Current IEs have had extensive experience with administering the KSADS, SCID, and LIFE/DSR, and have had good inter-rater reliability (e.g., LIFE/DSR; 90% agreement; diagnoses of depressive disorders, 97.6 % agreement). New interviewers also will have had past experience with clinical interviews and will undergo training in the SCID, KSADS, LIFE, CDRS-R, HDRS, and GAS during the first 3 months of the project; current interviewers will participate in this training as both a review and to assure that current and new IEs are consistent. Some assessments will be audiotaped for reliability purposes.

(2) Saliva samples for DNA will be collected using the Oragene™ DNA Self-Collection Kit, which provides a median DNA yield of 110 µg per 2 ml sample of saliva. Participants will be asked to open the collection vial and deliver 2 ml of saliva into the vial. Capping the container releases DNA-preserving fluid which then mixes with the saliva and preserves the DNA for long-term storage at room temperature. Saliva samples from all sites will be sent to Dr. Robert Ferrell's laboratory at the Human Genetics Department, University of Pittsburgh, where DNA extraction and storage will occur. Saliva sample will be collected by the research interviewer at the time of the interview either in the subject's home or Bellefield Towers.

(3) Young adult probands will provide measurements of height, weight, BMI, waist and hip circumference, and blood pressure. These measurements will be done using portable scales, stadiometers, tape measures, and a portable Omron Blood Pressure Monitor. These measurements will be performed by the research interviewer at the time of the interview either in the subject's home or Bellefield Towers.

Height and weight measurements will be obtained in stocking feet without shoes. BMI will be calculated based on height and weight. Waist and hip circumference will be obtained using a non-stretching fiberglass tape at the narrowest point or the umbilicus (in the absence of a

clear narrowest point) and hips at the widest part of the buttocks. Measures will be taken by staff members who are the same sex as the participant.

For blood pressure, participants will be seated for five minutes before the first reading. Three measurements will be taken from the seated participant's right arm at two-minute intervals. The first reading will be discarded because it may reflect an initial reactivity to the measurement procedure. Averages of the second and third measurements will be used in the analyses.

In this multicenter study, oversight is divided among the investigators across all sites. Please see the federal grant which is uploaded to this application for division of responsibilities.

Dr. Garber and Vanderbilt University function as the overall coordinating center. All data and genetic material is sent to the University of Pittsburgh. Pittsburgh is the data coordinating center and a separate data coordinating center protocol will be submitted to the IRB.

2.6.1

Will blood samples be obtained as part of this research study?

* No

If Yes, address the frequency, volume per withdrawal, the total volume per visit, and the qualifications of the individual performing the procedure:

Study Flow Chart:

Name	Modified Date
------	---------------

[\[reviewer notes→\]](#)

2.7

Will follow-up procedures be performed specifically for research purposes? Follow-up procedures may include phone calls, interviews, biomedical tests or other monitoring procedures.

* No

[\[reviewer notes→\]](#)

2.8

Does this research study involve the use of any questionnaires or survey instruments?

* No

Upload a copy of all unpublished surveys/questionnaires. Also upload any published materials that may include questions, images, video, or sound recordings that may be especially disturbing to subjects:

Name	Modified Date
------	---------------

List the name and publisher for commercially available materials (Note: these materials do

not need to be uploaded):

[\[reviewer notes→\]](#)

2.9

If subjects are also patients, will any clinical procedures that are being used for their conventional medical care also be used for research purposes?

* no

If Yes, describe the clinical procedures (and, if applicable, their frequency) that will be used for research purposes:

2.10 The blood sample question was moved to 2.6.1.

[\[reviewer notes→\]](#)

2.11 **What is the total duration of the subject's participation in this research study across all visits, including follow-up surveillance?**

* up to 4 weeks to complete all procedures

[\[reviewer notes→\]](#)

2.12 **Does this research study involve any type of planned deception?**

If Yes, you are required to request an alteration of the informed consent process (question 4.7)

* No

[\[reviewer notes→\]](#)

2.13 **Does this research study involve the use of UPMC/Pitt protected health information that will be de-identified by an IRB approved "honest broker" system?**

* No

[\[reviewer notes→\]](#)

2.14

Will protected health information from a UPMC/Pitt HIPAA covered entity be accessed for research purposes or will research data be placed in the UPMC/Pitt medical record?

* No

2.14.1 Will protected health information from a non-UPMC/Pitt HIPAA covered entity be obtained for research purposes or will research data be placed in the non-UPMC/Pitt medical record?

* No

[\[reviewer notes-\]](#)

2.15 Does this research study involve the long-term storage (banking) of biological specimens?

* Yes

2.15.1 Broadly describe the intended future use of the banked biological specimens:

Genetic analyses of genes related to depression, cardiovascular disease the stress response pathway. This is a rapidly advancing field. Currently, the following are potential areas of study :

Candidate Genes for Depression

- (a) Serotonin Transporter Promoter Gene (5-HTTLPR)
- (b) Tryptophan Hydroxylase (TPH)-1 and TPH
- (c) Serotonin 5-HT_{2A} receptor gene
- (d) Brain Derived Neurotrophic Factor (BDNF)
- (e) Dopamine Receptor D4 (DRD4).

Candidate cardiovascular genes:

Angiotensin-converting enzyme gene (ACE) the insertion (I) or deletion (D) of a 287 bp Alu repeat within intron 16 of the gene. A second SNP polymorphism in the promoter region of the ACE gene (rs4921) with an A/T transition

Candidate genes in the stress response pathway:

Alterations in the hypothalamic-pituitary axis (HPA) are thought to be central to the pathogenesis of mood disorders. In addition to its role in depression, hypersecretion of cortisol has been reported in young adults at familial risk for depression. Polymorphisms in the glucocorticoid receptor (GR) have been reported to be associated with altered GR sensitivity and increased risk for unipolar depression (BcII, ER22/23EK). A polymorphism in a GR modulator also has shown altered HPA activity, increased risk for recurrent unipolar depression, and differential response to antidepressants (FBK 5).

2.15.2 Indicate the planned length of storage of the banked biological specimens:

* Samples may be stored indefinitely.

2.15.3 Will biological specimens be stored **without identifiers or linkage codes?**

* No

[\[reviewer notes-\]](#)

2.15.4 Will subjects (including family members, if applicable) be informed of their personal results from analyses performed on their biological specimens?

* No

[\[reviewer notes→\]](#)

2.15.4.1 Justify why the personal results will not be disclosed to the research subjects at this time. Under what conditions, if any, might personal results be disclosed to research subjects in the future?

Genetic analyses will be performed in a research lab (not CLIA certified). In terms of predictive testing, any positive result pointing to a genetic test would have to be extensively replicated, validated, and standardized by relevant regulatory committees before it could be used in a clinical setting. Therefore, no individual test results will be given to participants.

Note: If the personal results of analyses performed on the banked specimen will not be disclosed to research subjects, the informed consent document corresponding to this research study should address why this information is not being provided. If the personal results of such analyses may be disclosed to research subjects in the future, the conditions for such disclosure should also be addressed in the informed consent form.

[\[reviewer notes→\]](#)

2.15.4.7 Describe the procedures that will be employed to protect the confidentiality of subjects' private information associated with use of biological specimens:

Genetic data are kept confidential within the research team (including the investigators at all sites). Genetic material is coded by ID number with no personal identifiers. The code linking the identification numbers will be kept under lock and key and only study personnel will have access to it.,

2.15.4.8 Will the banked biological specimens or data derived from them be provided with subject identifiers to any secondary investigators or external entities?

* No

2.15.4.9 Will research subjects be remunerated in the event of the future commercial development of inventions or products based on the research use of their biological specimens?

* No

[\[reviewer notes→\]](#)

2.16 Will research participants be asked to provide information about their family members or acquaintances?

* No

[\[reviewer notes→\]](#)

2.17 What are the main outcome variables that will be evaluated in this study?

Primary endpoint will be depression free days comparing those who received the CBT group as an adolescent vs. those who did not.

2.18 Describe the statistical approaches that will be used to analyze the study data.

* Refer (if applicable) to the statistical section of the protocol or grant that accompanies this IRB submission. Specify the page number below.

Please see the statistical section of the multicenter grant - beginning on page 24

[\[reviewer notes→\]](#)

2.19

Will this research be conducted in (a) a foreign country and/or (b) at a site (e.g., Navajo Nation) where the cultural background of the subject population differs substantially from that of Pittsburgh and its surrounding communities?

* No

Note that copies of training records, licenses, certificates should be maintained in the study regulatory binder and are subject to audit by the Research Conduct and Compliance Office (RCCO).

In addition, individuals planning to conduct human subject research outside the United States must complete an optional module on the CITI training website: International Studies. [Click here](#) to access the instruction sheet for accessing optional CITI modules.

[\[reviewer notes→\]](#)

2.21

Will this research study be conducted within a nursing home located in Pennsylvania?

* No

[\[reviewer notes-\]](#)

Section 3 - Human Subjects

3.1 What is the age range of the subject population?

All probands will be young adults. However, some siblings may be as young as 6 years of age. Therefore, the age range is 6 and older

3.2 What is their gender?

* Both males and females

Provide a justification if single gender selected:

3.3 Will any racial or ethnic subgroups be explicitly excluded from participation?

* No

If Yes, identify subgroups and provide a justification:

3.4 For studies conducted in the U.S., do you expect that all subjects will be able to comprehend English?

* Yes

[\[reviewer notes-\]](#)

3.5 Participation of Children: Will children less than 18 years of age be studied?

* Yes

3.5.1 Specify the age range of the children to be studied. (Check all that apply below:)

*

Choices

0-6 years of age

7-13 years of age

14-17 years of age

3.5.2 Provide a rationale for the specific age ranges of the children to be studied:

Siblings of the probands will be recruited into this study and will undergo psychiatric assessment and provide a saliva sample. The KSADS-PL is validated in children age 6 and older. Therefore, siblings age 6 and older will be eligible to participate in this study.

3.5.3 Describe the expertise of the study team for conducting research with children within this age range:

Dr. Brent is the Academic Chief of Child Psychiatry and is the Director of the Services for Teens at Risk (STAR) Clinic. He and his staff have vast experience in the assessment and treatment of childhood and adolescent depression and suicidality.

3.5.3.1

Have you obtained the following clearances from all research staff who may have direct contact with children under the age of 18? Direct contact under the law includes face-to-face, and telephonic or electronic, contact with minors. Please see the [Child Clearances](#) guidance document for further explanation?

Pennsylvania Department of Public Welfare Child Abuse History Clearance; Pennsylvania State Police Criminal Record Check; and FBI Criminal Background Check

Yes

Note: If No, once all clearances are obtained, a modification must be submitted.

If you selected N/A, please explain:

It is important to note that "direct contact" refers not only to face-to-face meetings but also extends to communication via phone (including text messaging), social media or internet. Direct contact also includes the care, guidance, supervision or control, or routine interaction with, minors. Conversely, a participating investigator or support staff member who does not have direct contact, either electronically or in person, with children does not need to obtain clearances (e.g., statistician, non-clinical laboratory personnel, etc.). If your research study provides babysitting services, the babysitters must have the required child clearances.

*** Note:** It is the **responsibility of the principal investigator** to ensure that all research staff have these clearances prior to any interaction with children. Contact Human Resources at 412-624-8150 for assistance with this process.

3.5.4

Describe the adequacy of the research facilities to accommodate children within this age range:*
Addressed below:

We anticipate that most research visits will be conducted as home visits in the child's normal environment. However, visits may be conducted in our research offices if the family prefers. In these cases, visits will be conducted in Dr. Brent's research staff offices in Bellefield Towers.

3.5.5

Permitted Categories of Research: The Federal Policy and FDA regulations governing human subject protections specify that research involving children must fall into one of the following permitted categories.

The research does not involve greater than minimal risk [45 CFR 46.404/21 CFR 50.51].

<p>45 CFR 46.406</p> <ul style="list-style-type: none"> • The risk represents only a minor increase over minimal risk. • The research procedures present experiences to the subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations. • The research procedures are likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for understanding or amelioration of the subjects' disorder or condition. <p>45 CFR 46.407</p>

- The risk is justified by the anticipated benefit to the subjects; and the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches.

Provide a justification which **must address all considerations** related to the designated category of research:

Subjects under age 18 (siblings of probands) will undergo a psychiatric interview and will provide a saliva sample. The magnitude of harm or discomfort for these procedures are not greater in and of themselves than those encountered in daily life.

[\[reviewer notes-\]](#)

3.6 Does this research study involve prisoners, or is it anticipated that the research study may involve prisoners?

* No

[\[reviewer notes-\]](#)

3.7 Will pregnant women be knowingly and purposely included in this research study?

* No

[\[reviewer notes-\]](#)

3.8 Does this research study involve neonates?

* No

[\[reviewer notes-\]](#)

3.9 Fetal Tissues: Does this research involve the use of fetal tissues or organs?

* No

[\[reviewer notes-\]](#)

3.10 What is the total number of subjects to be studied at this site, including subjects to be screened for eligibility?

Note: The number below is calculated by summing the data entered in question 3.11. Any additions or changes to the values entered in 3.11 will be reflected in 3.10.

* 320

3.11

Identify each of the disease or condition specific subgroups (include healthy volunteers, if applicable) that will be studied.

Click on the "Add" button and specify for each subgroup:

- 1) how many subjects will undergo research related procedures at this site; and
- 2) if applicable, how many subjects will be required to undergo screening procedures (e.g., blood work, EKG, x-rays, etc.) to establish eligibility. **Do Not include subjects who will undergo preliminary telephone screening.**

*

Subgroup	Number to undergo research procedures	Number to undergo screening procedures
View Depressed parent (previously participated as target parent)	80	80
View Additional family members with the closest possible biological relationship to the proband adolescent. In order of descending preference, the additionally enrolled relatives will be (described in terms of their relationship to the adolescent proband): biological parents, full siblings, grandparents, aunts/uncles, and half siblings.	160	160
View Probands (previously participated as teens)	80	80

3.12

Provide a statistical justification for the total number of subjects to be enrolled into this research study at the multicenter sites or this site.

* If applicable, refer to the statistical section in the protocol or grant. Specify the page numbers in the textbox.

Please refer to multicenter grant - beginning on page 26.

[\[reviewer notes-\]](#)

3.13

Inclusion Criteria: List the specific criteria for inclusion of potential subjects.

1. Adolescent and depressed parent participants of POD 1 along with 2 additional family members with the closest possible biological relationship to the proband adolescent. In order of descending preference, the additionally enrolled relatives will be (described in terms of their relationship to the adolescent proband): biological parents, full siblings, grandparents, aunts/uncles, and half siblings.

3.14

Exclusion Criteria: List the specific criteria for exclusion of potential subjects from participation.

Only those subjects who participated in POD1 and their family members are eligible to participate.

3.15

Will HIV serostatus be evaluated specifically for the purpose of participation in this research study?

* No

	Section: Section 3 - Human Subjects
--	-------------------------------------

If Yes, provide a justification:

[\[reviewer notes-\]](#)

- 4.1 Select all recruitment methods to be used to identify potential subjects:
Recruitment Letters and/or Scripts

Recruitment Letters and Scripts

Upload recruitment letters/scripts/text:

Name	Modified Date
Phone script for previous participants-PROBANDS 2008.doc	11/21/2008 4:53 PM
Phone script for previous participants-DEP PAR 2008 rev.doc	12/9/2008 11:18 AM
Phone script for new participants OTHER PARENT 2008.doc	12/9/2008 11:20 AM
Phone script for new participants SIBLING 2008.doc	12/9/2008 11:22 AM
recruitment letter.doc	9/17/2008 8:52 PM

- 4.2 **Provide a detailed description of your recruitment methods, including identifying and initiating contact with participants:**

1. A recruitment letter will be sent to all previous participants (proband and parents) of the POD 1 study thanking them for their previous participation and explaining this new study. The letter will be followed up with a phone call to the proband and depressed parent from the study team. See phone script below - a summary of the study will be given and, if interested, the proband and/or parent will be scheduled for an interview. The depressed parent will be asked to introduce the study to other family members and ascertain their interest. After the family member has provided permission contacted by the study team, they will be contacted and have the study explained to them. If they are interested, they will be scheduled for an interview.

2. We will attempt to locate previous participants based on the information they provided at the last interview. If the letter is returned with address unknown, the following methods will be used to attempt to locate previous participants: (1) use telephone directories; (2) use the contact information provided at the last assessment; (3) obtain voter registration information, and (4) search Google, "MySpace," "Facebook," and similar Internet resources.

[\[reviewer notes-\]](#)

- 4.6 **Are you requesting a waiver to document informed consent for any or all participants, for any or all procedures? (e.g., a verbal or computerized consent script will be used, but the subjects will not be required to sign a written informed consent document. *This is not a waiver to obtain consent.***

* No

[\[reviewer notes→\]](#)

4.7 Are you requesting a waiver to obtain informed consent or an alteration of the informed consent process for any of the following?

* No

4.7.1 If Yes, select the reason(s) for your request:
There are no items to display

General Requirements: The Federal Policy **[45 CFR 46.116 (d)]** specifies in order for a waiver of consent to be approved, the request must meet four criteria. For each request, you will be asked to provide a justification addressing how each of these criterion is met.

[\[reviewer notes→\]](#)

4.8 Are you requesting an exception to the requirement to obtain informed consent for research involving the evaluation of an 'emergency' procedure?

Note: This exception allows research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent.

* No

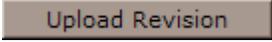
[\[reviewer notes→\]](#)

4.9

Upload all written informed consent documents.

The FDA requires a new element of consent for "applicable" clinical trials: These are clinical trials registered on clinicaltrials.gov AND are conducted under a U.S. IND or are otherwise subject to FDA regulations.
[Click here for more information.](#)

The  button is *only* to be used to upload a **new consent form**.

Click on the  button next to the form name to upload a **revised consent form**.

Draft Consent Forms for editing:

Name	Modified Date
POD2.proband.consent 12.9.2008	3/25/2010 9:25 AM
POD2.adult family member 12.9.2008	3/25/2010 9:12 AM
POD2.child family member 12.9.2008	3/25/2010 9:15 AM

Approved Consent Form(s):
 Name Modified Date

[\[reviewer notes→\]](#)

4.10 **Will all potential adult subjects be capable of providing direct consent for study participation?**

*

Yes

[\[reviewer notes→\]](#)

4.11

At what point will you obtain the informed consent of potential research subjects or their authorized representative?

Prior to performing any of the research interventions/interactions

4.11.2

Taking into account the nature of the study and subject population, indicate how the research team will ensure that subjects have sufficient time to decide whether to participate in this study. In addition, describe the steps that will be taken to minimize the possibility of coercion or undue influence.

Subjects will be sent a letter which will be followed up a week later with a phone call - at which time an appointment will be scheduled. They will have approximately 2 weeks to think about participation in this study. Subjects will be informed that participation is voluntary.

[reviewer notes-]

4.12 Describe the process that you will employ to ensure the subjects are fully informed about this research study.

* Addressed below:

This description must include the following elements:

- who from the research team will be involved in the consent process (both the discussion and documentation);
- person who will provide consent or permission;
- information communicated; and
- any waiting period between informing the prospective participant about the study and obtaining consent

When an interview is due (based on the age of the proband entering young adulthood), letters describing the study will be mailed to the proband and index parent approximately two weeks prior to when the interview is due. Interviewers then will follow this with telephone calls to participants to brief them about the interview purpose, length, and rationale, and to schedule an appointment with those interested. The proband or target parent also will be asked for the contact information for other family members from whom they have received permission for us to contact. These potential participants also will be informed about the purpose, length, and rationale of the interviews and an appointment will be scheduled for those who interested. These interviews will be conducted at a place and time that is most convenient for the participant. At the interview appointment, research staff will administer the consent and assent forms to participants.

4.13**Are you requesting an exception to either IRB policy related to the informed consent process?**

- For studies involving a drug, device or surgical procedures, a *listed physician* investigator is required to obtain the written informed consent unless an exception to this policy has been approved by the IRB
- For all other studies, a *listed* investigator is required to obtain consent (Note: In order to request an exception to this policy, the study must be minimal risk)

* Yes

If Yes, provide a justification and describe the qualifications of the individual who will obtain consent:

This is a minimal risk study. We are requesting permission for the project coordinator and research interviewers be permitted to obtain informed consent and to sign the Certification of Informed Consent.

4.14**Will you inform research subjects about the outcome of this research study following its completion?**

* No

If Yes, describe the process to inform subjects of the results:

[reviewer notes-]

5.1

Describe potential risks (physical, psychological, social, legal, economic or other) associated with screening procedures, research interventions/interactions, and follow-up/monitoring procedures performed specifically for this study:

*

View	Research Activity:	Audiotaping
	Common Risks:	No Value Entered
	Infrequent Risks:	Experimental Interventions: Potential risk of breach of confidentiality
	Other Risks:	No Value Entered

View	Research Activity:	measurement of height, weight, waist and hip circumference, and blood pressure.
	Common Risks:	No Value Entered
	Infrequent Risks:	No Value Entered
	Other Risks:	Experimental Interventions: These measurements may potentially be upsetting or cause embarrassment to participants, particularly to individuals who might have concerns about their body image. Taking blood pressure might be slightly uncomfortable for some participants

View	Research Activity:	Participation in genetic studies
	Common Risks:	No Value Entered
	Infrequent Risks:	Experimental Interventions: A risk of providing genetic material is the potential for breach of confidentiality, which could impact future insurability and employability or have a negative impact on family relationships, and/or result in paternity suits.
	Other Risks:	No Value Entered

View	Research Activity:	Providing saliva samples for DNA
	Common Risks:	No Value Entered
	Infrequent Risks:	Experimental Interventions: This procedure is quite non-invasive. A possible risk for this method of sample collection might be embarrassment to the subject at being asked to deliver a specimen of saliva into a cup.
	Other Risks:	No Value Entered

View	Research Activity:	Research assessments
	Common Risks:	Experimental Interventions: Some individuals might feel uncomfortable answering questions of a sensitive nature.
	Infrequent Risks:	Experimental Interventions: Potential for emotional distress due to the types of questions being asked.
	Other Risks:	Experimental Interventions: There is a small risk that research records (questionnaires, interviews, audio-recordings) might be obtained by persons not authorized to do so. There is a slight risk that research data files might be compromised, and obtained or viewed by unauthorized persons

5.1.1 Describe the steps that will be taken to prevent or to minimize the severity of the potential risks:

Experimental Interventions:

Protection for risks associated with research assessments. The interviews involve no specific risk or discomfort beyond those of a standard clinical interview; all probands and target parents have completed similar interviews without problems as part of POD.1. All interviewers are trained clinicians with extensive experience in mental health; they know how to recognize and handle participant distress if it occurs. Therefore, they can pace the interview and interrupt or terminate it if a participant becomes too distressed or fatigued. The interview will only recommence when and if the participant reports feeling capable of doing so. Participants are clearly informed that they are free to not respond or to terminate involvement at any time, with no adverse consequences.

All audio-recordings are digital, and are stored as password-protected files on computer networks. Only authorized staff with appropriate network- and file-level passwords will have access to these files. Recordings will be coded by subject identification number, date, study name, and initials of the interviewer.

Protection for risks associated with potential loss of confidentiality. All participants are assigned a numerical code for identification. Names and other identifiers linking the identifying information to the numbers will be kept separately from the data in locked files. All data collected will be coded by identification number only. Hard copies of data are kept in a locked office to which only research staff has access. Data for all participants will be kept strictly confidential, except as mandated by law. All research files are kept in locked file cabinets or in a locked file room. Statistical analyses will be performed on aggregate-level data; participants are never individually named.

Another issue related to confidentiality concerns the disclosure of health risk behaviors by minors or harmful behaviors to either the self or others. All participants will be informed during the consent process that their information will be kept strictly confidential unless information is revealed suggesting that the participant or someone else is in danger [e.g., abuse (see below), suicidality, homicidality]. Prior to eliciting this information, the participant will be fully informed that the interviewer may need to report such information. In the case of a minor, before parents are informed, the clinician first talks with the child and explains that the information will be disclosed to parents and to any other responsible parties (e.g., child protective services) as required by law.

In a multi-site study of this type, copies of some of the assessments will be sent to the data center for quality assurance (reliability) ratings. These audio-recordings and other data will be identified only by the non-meaningful research ID (001, 002, etc.) and will not have any identifying information in it. Only authorized research staff at the other sites will review these research audio-recordings or other data, and then only for the purposes of quality assurance and/or research training. Data sent to remote sites such as the coordinating center also will be kept locked and secure at those sites, using the same procedures identified here. All computerized data and digital recordings will be kept on secured computers or networks at each site. These data will be accessible only to research staff, using confidential usernames and passwords.

Reporting of child abuse and neglect. Because information relating to prior abuse and neglect will be assessed, participants will be informed of the need to report any current abuse prior to eliciting this information. All staff will follow federal and state child abuse reporting requirements. All study staff have access to Procedures for Managing Disclosure of Abuse, which provides instructions on reporting abuse. In our prior experience with these procedures in similar types of family-genetic studies, we found 15 cases, in nearly 2300 interviews, of unreported abuse that needed to be reported; in none of those families was the child removed, or the family lost to follow-up; nor were there any adverse mental health effects evident due to the reporting.

Procedures for minimizing risks related to participation in genetic studies. The genetic investigations within this study are strictly for research purposes. Genetic data are kept confidential within the research team. Genetic material is coded by ID number with no identifiers. Genetic material will be stored indefinitely by the investigators, but only for the purpose of looking at specific genes related to mood disorders and treatment response. In terms of predictive testing, any positive result pointing to a genetic test would have to be extensively replicated, validated, and standardized by relevant regulatory committees before it could be used in a clinical setting. Therefore, no individual test results will be given

to participants. If at any time a participant withdraws from the study, his/her DNA sample will be destroyed if s/he requests. Although the possibility of identifying non-paternity is explained to participants, evidence of non-paternity is never released to the participant or other family members under any circumstances.

Procedures for minimizing risks related to measurement of height, weight, and waist and hip circumference. Staff will remind subjects that their measurements are confidential and will ensure privacy during the measurement procedures. Measurements will be performed by same-sex interviewers, or participants can do the measurements themselves with the guidance of the interviewer. Participants will be offered a written report of their height and weight and blood pressure to provide to their primary care provider if they would like to do so.

Procedures for minimizing risks related to providing saliva samples for DNA. To minimize the risk of embarrassment, staff will ensure that the participant has privacy when delivering the specimen to the cup. Participants have the right to decline to answer any questions, participate in any measurement, or provide any saliva if they wish to do so.

Protection for emergent psychiatric crises or other problems. All participants will be assessed regarding severity of symptoms. All research clinicians are trained to assess severe psychopathology and suicidality and to take appropriate steps including more detailed assessment of intent, plan and possible method, discussion of findings with the participant, appropriate family member, senior clinician, or PI or co-PI. If, during any assessment, interviewers determine that a participant has a serious mental health problem (including but not limited to severe depression, suicidal behavior, etc.), we will provide referral information and the telephone numbers to appropriate services. If the detected problem is imminent and of crisis status, we will take appropriate action immediately including escorting and/or providing medical transportation for these individuals to an emergency room. The study assessments also provide extra monitoring for all respondents that permit the detection of disorders or conditions that might not be detected otherwise, but that merit referral and/or treatment.

5.2

What steps will be taken in the event that a clinically significant, unexpected disease or condition is identified during the conduct of the study?

* **Addressed below:**

All of the interviewers are trained clinicians with extensive experience in mental health. Therefore, they can pace the interview and interrupt it if the parent or child becomes too upset. If necessary, the interview can be interrupted or terminated. The patient and family are clearly informed that they are free to terminate participation at any time. All research clinicians are trained to assess suicidality and to take appropriate steps including more detailed assessment of intent, plan and possible method, discussion of findings with patient, project coordinator, and project psychiatrist, and appropriate referral for subject and family. If a subject is thought to be in imminent danger, then subject and family will be directed to closest emergency mental health facility. If parent or child manifests clinically serious psychopathology, the parent will be informed and information about referral sources will be provided.

5.3

All the risk questions (screening, intervention/interaction, follow-up) have been merged into one question (5.1).

[\[reviewer notes-\]](#)

5.4

Do any of the research procedures pose a physical or clinically significant psychological risk to women who are or may be pregnant or to a fetus?

* No

[\[reviewer notes-\]](#)

5.5 Do any of the research procedures pose a potential risk of causing genetic mutations that could lead to birth defects?

* No

[\[reviewer notes-\]](#)

5.6 Are there any alternative procedures or courses of treatment which may be of benefit to the subject if they choose not to participate in this study?

* Not applicable; the experimental intervention does not involve a diagnostic/treatment procedure

If Yes, describe in detail:

[\[reviewer notes-\]](#)

5.7 Describe the specific endpoints (e.g., adverse reactions/events, failure to demonstrate effectiveness, disease progression) or other circumstances (e.g., subject's failure to follow study procedures) that will result in discontinuing a subject's participation?

* Not applicable - There are no anticipated circumstances that would lead to discontinuing a subject's participation in this research study.

[\[reviewer notes-\]](#)

5.8 Will any individuals other than the investigators/research staff involved in the conduct of this research study and authorized representatives of the University Research Conduct and Compliance Office (RCCO) be permitted access to research data/documents (including medical record information) associated with the conduct of this research study?

* No

5.9 Has or will a Federal Certificate of Confidentiality be obtained for this research study?

* Yes

5.10 Question has been moved to 5.17

5.11 Question has been moved to 5.16

[reviewer notes→]

5.12 Does participation in this research study offer the potential for direct benefit to the research subjects?

Yes - Describe the direct benefit that subjects may receive as a result of study participation. Indicate if all, or only certain, of the subjects may derive this potential benefit.

Describe the benefit:

The benefits of participation in this study include having an extensive psychiatric assessment and a referral for treatment if clinically warranted. Participants are informed that they may not derive direct benefit from participation in this study other than the evaluation at no cost and the knowledge that the information gained in this study may help others in the future.

5.13 Describe the data and safety monitoring plan associated with this study. If the research study involves multiple sites, the plan must address both a local and central review process.

Central:

The preventive intervention study has been conducted at four sites (Nashville, TN; Pittsburgh, PA; Boston, MA; and Portland, OR) with adolescents at risk for developing depression. The proposed continuation study involves following these youth into young adulthood. The major risks of this study to the participants are the potential for a breach of confidentiality and the potential for emotional distress in discussing stressful life events and symptoms. The Principal Investigators (PIs) will be responsible for the data and safety monitoring, which will include monthly evaluation of the progress of the research study and oversight of assessments of data quality and timeliness, accrual and retention, and a review of study procedures designed to protect the privacy of the research subjects and the confidentiality of their research data. The general purpose of the data safety monitoring plan will be to maximize the safety and privacy of all study participants, and ensure the integrity, validity, and confidentiality of the data collection and analysis procedures.

Psychiatric, medical or other life crises that are high risk and imminent (e.g., suicidality) will be monitored (as is being done in the current phase of the study and described earlier) and acted upon immediately with staff linking participants to appropriate crisis or medical services. These objectives will be accomplished through regular monitoring and oversight by the PIs at each of the four study sites. The PIs will report to their institutional review boards (IRB) and NIMH any serious and unexpected adverse events and any unexpected problems that involve risk to the participants or others, or any breaches in confidentiality.

Annual reports to NIMH and the IRB will include a summary of data safety monitoring activities in the past year. These reports will include: (1) whether participants' safety, privacy, and confidentiality have been maintained during the time of the study; (2) a review of interim data analyses that bear on outcomes of the study and risk/benefit ratios to participants, including recommendations for new statistical analyses; (3) judgments as to whether research instruments have been administered in a uniform manner and in a way that maintains participants' privacy; (4) a review of the study's progress toward recruitment goals (broken down by site), quality of the data (e.g., appropriate completion of forms), and participant retention/attrition rates; (5) a review of new scientific literature pertinent to the safety of participants or ethics of research participation; and (6) monitoring any relevant information that may have an impact on the safety of study participants or the ethics of the research study; any conclusions regarding changes to the anticipated risk-to-benefit ratio will be reported to the IRB.

There will be regular, ongoing communication between the local PIs (Garber in Nashville, Beardslee in Boston, Brent in Pittsburgh, Clarke in Portland) and their local IRBs. Although no serious or unexpected adverse events are anticipated, such problems will be reported to the respective local IRBs. Adverse events at one site that are considered related to the study procedures also will be reported to the IRBs of the other sites. The study psychologists and psychiatrists will take all clinically appropriate actions to prevent and treat psychiatric emergencies in participants.

Local DSMP:

The PI, Co-investigators, project coordinator, research interviewers, and data team will meet monthly to review the progress of the research study including recruitment, completion of study procedures, and unanticipated problems, including any breaches of

confidentiality, subject complaints or adverse events. The procedures for ensuring subject privacy and confidentiality will also be reviewed. This results of these monthly DSM meetings will be submitted to the IRB at the time of annual renewal.

[\[reviewer notes-\]](#)

Section 5 - Potential Risks and Benefits of Study Participation

5.14

What precautions will be used to ensure subject privacy is respected? (e.g. the research intervention will be conducted in a private room; the collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected, drapes or other barriers will be used for subjects who are required to disrobe)

Prior to conducting the interview, research staff will ensure the privacy of the participant by making sure the interview is conducted in a private room away from family members. No unneeded sensitive information will be collected.

5.15

What precautions will be used to maintain the confidentiality of identifiable information? (e.g., paper-based records will be kept in a secure location and only be accessible to personnel involved in the study, computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords, prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information, whenever feasible, identifiers will be removed from study-related information, precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys, audio and/or video recordings of subjects will be transcribed and then destroyed to eliminate audible identification of subjects)

Paper records will be stored in a locked file cabinet in a locked office to which only the research staff will have access. Audiotapes will be destroyed after they are reviewed and scored. Electronic data will be coded by identification number and will be password protected. Precautions are in place to ensure data is secure by using passwords. Electronic data are protected by the institutional firewall.

5.16

If the subject withdraws from the study, describe what, if anything, will happen to the subject's research data or biological specimens.

Specimens will be destroyed at the subject's written request if they decide to withdraw from the study. Any identifiable information recorded for, or resulting from, the subject's participation in this research study prior to the date that the subject formally withdrew consent may continue to be used and disclosed by the investigators for the purposes previously described.

5.17

Following the required data retention period, describe the procedures utilized to protect subject confidentiality. (e.g., destruction of research records; removal of identifiers; destruction of linkage code information; secured long-term retention)

The four sites will collect data from a total of 316 probands, 282 target parents and approximately 600 other relatives over the proposed study period. The data will be archived within 3 years after completion of the study. The final datasets will include demographic data, psychiatric assessment data, and genetic data from saliva. Because the data are sensitive in nature, we will carefully ensure that appropriate privacy safeguards are in place. All data will be stripped of identifiers prior to release for sharing. Thus, we will make the data and associated documentation available to users under a data-sharing agreement that provides for: (a) a commitment to using the data only for research purposes and not to identify any individual participant; (b) a commitment to securing the data using appropriate computer technology; and (c) a commitment to destroying or returning the data after

analyses are completed

[\[reviewer notes→\]](#)

6.1

Will research subjects or their insurance providers be charged for any of the procedures (e.g., screening procedures, research procedures, follow-up procedures) performed for the purpose of this research study?

*

No

[\[reviewer notes→\]](#)

6.2

Will subjects be compensated in any way for their participation in this research study?

* Yes

6.2.1

Describe the amount of payment or other remuneration offered for complete participation in this research study.

Young adult probands each will receive \$150 total; index parents and the other 2 family members each will receive \$100 total.

6.2.2

Describe the amount and term of payment or other remuneration that will be provided for partial completion of this research study.

Young adult probands will receive \$75 for completing the research assessment, including interview, questionnaires and physical measurements. \$25 will be given for providing the saliva sample.

Index parents and the other 2 family members will each receive \$50 for completing the research assessment and \$25 for providing the saliva sample.

[\[reviewer notes-\]](#)

7.1

Summarize the qualifications and expertise of the principal investigator and listed co-investigators to perform the procedures outlined in this research study.

David Brent, M.D., is currently Endowed Chair in Suicide Studies, Professor of Psychiatry, Pediatrics and Epidemiology at the University of Pittsburgh. He is also the Academic Chief, Child and Adolescent Psychiatry, Western Psychiatric Institute and Clinic. His work in the area of suicide has focused on the epidemiology of adolescent suicide, and has helped to identify the role of firearms, substance abuse, and affective disorders as risk factors for youth suicide. Consequently, he and colleagues at Western Psychiatric Institute and Clinic have helped to establish the role of cognitive therapy as a treatment for depressed adolescents in an NIMH-funded clinical trial. Dr. Brent has also focused on the familial and genetic aspects of suicide; having found that suicidal behavior clusters in families and is currently, along with colleagues at New York State Psychiatric Institute, studying how suicidal behavior may be transmitted from parent to child.

Satish Iyengar, Ph.D., is Professor and Chair of the Department of Statistics, University of Pittsburgh. He shares his appointment with the Department of Psychiatry. Dr. Iyengar is very familiar with family study methodology, and longitudinal research, and has consulted to a number of child psychiatric projects at WPIC over the past decade, including this study during the initial project period.

Nadine Melhem, Ph.D., is currently an assistant professor of psychiatry at the University of Pittsburgh. Dr. Melhem has a K01 award (Genetic Linkage Study of Depression and Anxiety Disorders in an Arab Kindred; MH77930), with Dr. Devlin as her mentor and Dr. Brent as her co-mentor through June 30, 2012.

[\[reviewer notes-\]](#)

7.2

Indicate all sources of support for this research study.

*

Selections

Federal: Upload a copy of the entire grant application (**including the cover sheet**) if our site is the awardee institution; for federal contracts, upload a copy of the research plan.

If Federal support, provide the sponsor information:

Federal sponsor	Grant Title	Grant number	Awardee institution	Federal grant application
View NIH/NIMH	Prevention of Depression: Impact on the Transition to Early Adulthood	R01 MH064503	University of Pittsburgh	POD.2_FINAL.1_ALL_2-15-08.doc(0.01)

For projects not supported by a federal grant, upload the research plan that was submitted for funding:

Name Modified Date

If Industry support, provide the sponsor information and level of support:

If Foundation support, provide the sponsor information:

If Other support, provide the support information and level of support:

[\[reviewer notes→\]](#)

7.3

Is this study funded in part or whole by a PHS Agency?

* Yes

Does any investigator* involved in this study (select all that apply):

Name

- A.** Have a financial interest (aggregated value of equity and remuneration** during the past or next twelve months) in a **publicly-traded entity** that either sponsors*** this research or owns the technology being evaluated or developed that exceeds **\$5,000 but not \$10,000?**
- B.** Have a financial interest (aggregated value of equity and remuneration during the past or next twelve months) in a **publicly-traded entity** that either sponsors this research or owns the technology being evaluated or developed that exceeds **\$10,000?**
- C.** Receive remuneration (during the past or next twelve months) from a **non-publicly traded entity** that either sponsors this research or owns the technology being evaluated or developed that exceeds **\$5,000 but not \$10,000?**
- D.** Receive remuneration (during the past or next twelve months) from a **non-publicly traded entity** that either sponsors this research or owns the technology being evaluated or developed that exceeds **\$10,000?**
- E.** Have equity in a **non-publicly traded entity** that either sponsors this research or owns the technology being evaluated or developed?
- F.** Receive reimbursement or sponsorship of travel expenses (for one trip or a series of trips during the past or next twelve months) by an outside entity that either sponsors this research or owns the technology being evaluated or developed that exceeds **\$5,000?**
- G.** Have rights as either the author or inventor of **intellectual property** being evaluated or developed in this research that is the subject of an issued patent or has been optioned or licensed to an entity?
- H.** Have an officer or management position**** with a **Licensed Start-up Company** overseen by the COI Committee that either sponsors this research or owns the technology being evaluated or developed?
- I.** Receive compensation of any amount when the value of the compensation would be affected by the outcome of this research, such as compensation that is explicitly greater for a favorable outcome than for an unfavorable outcome or compensation in the form of an equity interest in the entity that either sponsors this research or owns the technology being evaluated or developed?
- None of the above options apply and there are no other financial conflicts of interest in the conduct of this research.**

* **Investigator** means the PI, co-investigators, and any other member of the study team, regardless of title, who participates in the design, conduct, or reporting of this research, as well as his/her spouse, registered domestic partner, dependents, or other members of his/her household. **The PI is responsible for ensuring that s/he and all other relevant members of the study team review the above questions describing Significant Financial Interests.**

	Section: Section 7 - Qualifications and Source(s) of Support
--	--

- **such as salary, consulting fees, honoraria, or paid authorship
- ***through the provision of funds, drugs, devices, or other support for this research
- ****Such as serving on the Board of Directors or Board of Managers or a position that carries a fiduciary responsibility to the company (e.g., CEO, CFO, CTO, or CMO).

[\[reviewer notes→\]](#)

Other Attachments (e.g., Reference List)

Additional documents:

<u>Name</u>	<u>Modified Date</u>	<u>Version</u>
POD2.Assessment Battery.doc	9/25/2008 10:41 PM	0.01
wpic research committee approval.pdf	9/5/2008 8:52 PM	0.01

Please use the Add button to the left to upload additional documents if needed.

5.4.b. Data Analysis Overview

Approach to Statistical Analysis: Various statistical methods will be used to address the primary and secondary aims of the study. We will emphasize sensitivity analysis: that is, the analysis of the data using various approaches that make different plausible assumptions. A finding is considered robust if it is qualitatively similar across the approaches. We will start with basic methods, such as the comparison of rates of outcomes of interest, and then move to examining the longitudinal course using random effects or survival analysis models. We also will check our models using residual plots and the associated quantitative methods, and will similarly check for site effects. Because this is a nested design, analyses will use random effects regression to test the effects of site and group. Intervention condition and site will serve as independent variables. If site differences or interactions are observed, we will estimate treatment effects separately within site and pool across settings, so as to minimize the risk of confounding site with treatment effects (Kraemer & Prunyn, 1990). This same procedure will be used to handle site differences in all subsequent analyses. Analyses of variance (ANOVA) and random effects regression will be used for continuous variables and non-parametric analyses (e.g., log-linear analyses) will be used for categorical variables. Any variable on which the intervention and control conditions differ initially (adopting a relaxed alpha level of .10) will be entered into a univariate linear regression (Cohen & Cohen, 1975) or proportional hazards linear regression (Cox, 1972) to determine its relation to the outcome. Any variable that both differentiates between intervention and control conditions and predicts subsequent outcome (after controlling for the effects of intervention and again adopting an alpha of .10) will be considered a potential confound and entered as a covariate in all subsequent analyses.

We recognize that measures from the different participants may be correlated because the intervention was given to groups of adolescents rather than individuals. We will model the groupings as random effects in the general linear model used. Advantages of this approach are: the random effect introduces correlations within groups, and the number of additional parameters introduced -- mean and variance of the random effects -- is small, so reduction in power is small enough to still allow us to detect main effects with probability greater than about 0.80. Also, we will test whether the within group correlation at the end of the acute phase is different from the correlation at follow-up using a likelihood ratio test of the equality of intra-class correlation coefficients.

Missing data. Despite our best efforts to retain participants, some dropout is expected. To address this potentially serious problem (Heyting et al., 1992; Lavori et al., 1995), we will (a) document the reason(s) for dropping out, which can help later in positing models for analysis; (b) follow-up all participants regardless of intervention adherence or dropout in order to do intent-to-treat analyses (Pocock, 1983); (c) use a sensitivity analysis: i.e., compare inferences that are based on different plausible assumptions to arrive at our conclusions. For example, we may compare the completer and last value analysis, and use more complex approaches that include multiple imputation procedures. We will use the Little and Rubin (1987) approach statistical analysis with missing data. Because of our careful data gathering and checking procedures, we expect few data to be missing completely at random (MCAR). More frequently, missingness will be due to known covariates (missing at random or MAR) or even intervention outcome (nonignorable missingness). The multiple imputation procedures are primarily for cases where such follow-up fails. We will apply the Multiple Imputation by Chained Equations (MICE) technique using STATA, which is based on each conditional distribution of a variable, given all other variables, and does not require that the multivariate joint normal distribution assumption be met. MICE allows the conjoint imputation of variables based on a set of predictor variables by an appropriate regression model (e.g., ordinary least square, logit). We will use the multiple imputation approach with an inclusive strategy as recommended by Collins, Schafer, and Kam (2001), which makes use of auxiliary variables that are correlates of missingness and/or correlates of the variable of interest, to improve the missing data imputation procedure. Using this approach, there is a reduced chance of inadvertently omitting an important cause of missingness, and with increased efficiency and a reduction in bias.

Data reduction. For outcomes with several domains (e.g., developmental competencies), we will use dimension reduction methods. We will compute a global score for these constructs, combining sub-measurements using (typically) a weighted sum that has been previously validated, or by a formal method such as principal components or factor analysis. For the latter, we will seek one or two interpretable components or factors to include in the model and will utilize our consultants in this process.

5.4.c. Analysis of Specific Hypotheses

Hypothesis 1. Compared to youth in the TAU control group, youth in CBP will show a lower rate of depression during early adulthood across several outcomes (e.g., more depression-free days; lower incidence of depressive episodes; longer time to onset of episodes; lower recurrence rates; fewer depressive symptoms). We will assess incidence rates of depression, which account for varying time periods of follow-up, and compare the groups on these rates. We will use Kaplan-Meier to test the equality of time to onset of an

episode between the two groups. Standard univariate tests will be used to compare the CBP and TAU groups on depression-free days, recurrence, and depressive symptoms. We will use chi-square for dichotomous outcomes (e.g., recurrence) and t-tests for continuous data (e.g., depression-free days, depressive symptoms). *Regression analyses will be used to compare the groups on various outcomes controlling for both fixed (e.g., baseline parental depression) and time-varying covariates (e.g., dose of participation in services over follow-up);* logistic regression for occurrence of depression in probands, linear regression for depression-free days, Cox regression for time to onset, and random effects models for depressive symptoms.

Power to test H1. We aim to test differences in time to recurrence/new-onset depression between CBP and TAU groups. We will assess hypotheses using two-sided tests with $\alpha=0.05$, requiring power=0.80. We will transform the scale appropriately (arcsine of square root of proportion for binomial) to stabilize variance and improve the normal approximation. We then use Gaussian distribution calculations to determine power or sample size. The basic analysis will compare the 80-month rates of incidence of depression for the two groups, first using a simple chi-square test followed by logistic regression. During that follow-up period, we have modeled a conservative 80% retention rate, leading to a mean person-years of approximately 603, which allows us to detect an effect size of $d=0.16$, or 0.18 after taking into account a conservative sib-sib correlation of $r=0.5$. Our significant 11% difference in 8-month incidence rates corresponds to an effect size of $d=0.24$. As these rates increase over time, so that rates in both groups are nearer to 50%, the roughly 10% difference corresponds to effect sizes range from 0.20 to 0.24, which are over the 0.16 detectable threshold.

Sib-Sib Correlation. We have incorporated sib-sib correlations into our power calculations. The sib-sib correlation has the effect of reducing the effective sample size, or increasing the minimum detectable effect size by a certain factor. Our sample has few sibships of size 2 and 3; thus, its impact is negligible: the factor is approximately $\sqrt{1 + 0.38r}$, where r is the sib-sib correlation, which we expect is in the range of 0-0.5. Thus, the factor ranges from 1.0-1.09 (e.g., for comparing incidence rates, the minimum d ranges from 0.17-0.185).

Hypothesis 2. Youth from this high-risk sample who are at relatively lower familial (e.g., genetic; familial loading) or environmental risk (e.g., life events) who received the CBP program will show less depression and better functioning across the transition to adulthood compared to those in the TAU group who were at the same level of risk. Genotyping errors will be evaluated using PedCheck (Rocha et al., 1998). Errors in the genealogy are of concern for any pedigree analyses. Potential errors will be investigated by comparing nominal and imputed relations among individuals by using RELPAIR (Boehnke & Cox, 1997) and PREST (McPeck & Sun, 2000). If errors are suspected in >1% of the genotyped samples, the genotyping will be re-examined for these samples. If the error rate cannot be improved, the locus will be dropped from the analysis.

Genetic and environmental moderators of a psychosocial intervention program. We will use family-based association analyses for analyses of candidate genes. FBAT/PBAT has tools for both binary (Yes/No) and survival outcomes (time to depression onset). A complementary family-based approach uses a conditional logit model (Cordell et al., 2004) (programmed by Melhem & Devlin in SAS statistical language), which will allow us to test for gene by gene or gene by environment interactions, as well as use other covariates (e.g., sex, age, characteristics of parents' depression) in the model. We recognize that interactions will have to be substantial to be detectable. Therefore, we will be cautious in interpreting any detected interaction.

Population stratification. We use here family-based analyses, which are robust to variation in ancestry and can draw greater power for variation in ancestry (Clarke & Whittemore, 2007; Ewens & Spielman, 1995).

Power to test H2: The CBP group has 159 subjects, including 18 sibling pairs and 1 sibling triplet. The multiplicity within families increases the power of family-based analysis. Thus, we can treat this family set conservatively as 159 trios. The TAU group has 157 subjects with 14 sibling pairs. We are interested in main effects of genetic variation on risk for depression, interaction effects of genetics and treatment to determine outcome, genetic and clinical characteristics as predictors of outcome, and genetic variants as predictors of clinical characteristics that themselves are associated with a less vigorous response to CBP (e.g., chronic or recurrent depression). Interactions will be challenging to detect unless the effect size is large. At this time, we see a 20% rate of depression in the CBP group and 30% in TAU. Assuming no interaction with treatment and these rates, we have power $\geq 80\%$ for a risk allele with relative frequency ranging from 0.2-0.4 when the allelic odds ratio is ≥ 2.3 . For smaller allele frequencies, the required odds for good power are greater, and exceed 6.0 for a risk allele with frequency close to .05. By the end of the study, we expect that 40% of the CBP group and 50% of the TAU group will become depressed. In this instance, we have power $\geq 80\%$ for a risk allele with relative frequency ranging from 0.2 -0.4 when the allelic odds ratio is ≥ 1.8 . All of these power calculations assume the risk allele has been genotyped, the prevalence of depression is 18%, and the significance level is .05. For interactions we must detect a significant difference in odds, or an odds ratio that significantly exceeds

one. By end of the study, we estimate a threefold difference in the odds (or an odds ratio of 3), indicative of an interaction at some level such as treatment, can be detected with 80% power.

Hypothesis 3. Compared to individuals in TAU, young adults who had been in the CBP program will show greater developmental competence, better mental and physical health, and fewer health-risk behaviors; this effect will be mediated by lower levels of inter-current depressive symptoms and episodes. We expect three domains of developmental competencies (educational, vocational, interpersonal), although we also will examine inter-correlations and apply data reduction methods (e.g., factor analysis) to create a single index. We will compare the groups on this index, and on individual domains using standard univariate tests and regression analysis. For developmental competencies that are unique to either adolescence or young adulthood, subgroup analyses will be restricted to the appropriate age group. For physical and other mental health outcomes, again the CBP and TAU groups will be compared using standard univariate tests and regression analyses to adjust for covariates. We also will include inter-current depressive symptoms or episodes in the models. Mediation would be indicated by an attenuation of the relation between treatment and a specific outcome variable after controlling for the level of inter-current depressive symptoms (or episodes).

We also will conduct exploratory path analyses to examine mediation; we summarize each outcome with one summary score. Summary scores are either standard global measures (e.g., functioning) or a dichotomous indicator (e.g., anxiety, Yes/No). When an outcome is measured with several domains (e.g., physical health includes global health, BMI, and sleep impairment), summary scores will be derived using standard dimension reduction methods such as factor analysis or principal components. We will use LISREL and M-Plus to estimate path coefficients and test the fit of the path model. We will use standard model selection criteria (e.g., AIC), along with substantive considerations to evaluate candidate models.

Power to test H3: For the mediation analyses, among the many algebraic formulations of mediation studied by MacKinnon et al. (2002) the one that is most appropriate for our purposes is the difference of coefficients method. In our case, we compare the unconditional correlation between treatment and a particular outcome, and the partial correlation between the same two attributes given inter-current levels of depressive symptoms or episodes. In particular, we expect to use the test of Olkin and Finn (1995), which compares an unconditional correlation with a partial correlation. We use MacKinnon's tables with interpolation. Table 5 of MacKinnon et al. shows that we have power of at least 0.9 to detect an effect size of $d=0.36$, which with a correction for sib-sib correlation, increases to approximately $d=0.39$.

Hypothesis 4.1: Long-term Cost-Effectiveness. The long-term cost per outcome (e.g., cost per depression-free day) achieved will be lower for youth in the CBP intervention than in TAU. We will now conduct cost-effectiveness analyses (CEA) of CBP vs. TAU for a median of 4 additional years of follow-up, after the last one of POD.1 (month 32). This enhanced CEA will allow us to better ascertain whether or not there are significant cost-offsets associated with providing the prevention program above usual care. Our original plan was to conduct an incremental CEA from the perspective of the health care organization (HCO). Following the methodology recommended by the Panel on Cost Effectiveness in Health and Medicine (Gold et al., 1996) for the estimation of the costs of the intervention and other health care costs, we will compare the intervention to usual mental health services available. The primary continuous measure of clinical outcome is depression-free days (DFD). For the CEA, we will convert the continuous depressive symptom ratings (DSR) into DFDs. This approach has been used in other CEA of depression interventions (Lave et al., 1998; Lynch et al., 2005; Schoenbaum et al., 2001). We will calculate the total intervention costs to the HCO. The intervention also may change the total amount of health care services used. We capture this by including the difference in total other health care costs (other than intervention costs). *Although our main analysis will focus on the perspective of the HCO, the intervention might shift costs to other stakeholders (e.g., schools). The CASA provides comprehensive data on service utilization across all major stakeholders (e.g., health care, schools, social welfare). We will analyze and present comprehensive profiles of service use. To the extent possible, we also will create unit costs for non-health services from secondary data sources, although no currently available data sources readily allow for the development of such costs. For example, there is no comprehensive source of data on the cost of social welfare services. Nevertheless, we will attempt to identify reasonable secondary sources for unit costs for non-health services.*

We will describe and compare the average cost per participant and average cost per unit change in depression scores. Both costs and outputs will be discounted at 5% (Lipscomb, 1989). A net cost-effectiveness ratio will be computed as follows (both costs and outcomes are discounted):

Incremental Cost-Effectiveness =

$$\frac{(\text{Direct Intervention Costs})_{Tx} + (\text{Total HCO Costs}_{Tx} - \text{Total HCO Costs}_{Control})}{[\Delta \text{Mean DFD}_{Tx} - \Delta \text{Mean DFD}_{Control}]}$$

This CEA will indicate the incremental cost per increase in effectiveness of the intervention program over usual care. This information can be used to motivate dissemination of the intervention in HCOs. In all other respects we will continue with our original analysis plan, collecting data on services used by youth with the CASA, Child Health Services Screen and creating unit cost coefficients using the MarketScan Research Database.

There are numerous empirical challenges to accurately estimating incremental cost-effectiveness ratios (Gold et al., 1996). Below we describe procedures for identifying and valuing resources consumed by participants. We will collect detailed data to minimize the need to estimate resource consumption. This will not alleviate all uncertainty in measurement of the CEA, however. To address the remaining uncertainty, we will conduct sensitivity analyses to ascertain the effects of variations in the key parameters—costs, outputs, and discount rate. If these analyses indicate considerable uncertainty, we will use simulation modeling such as bootstrapped estimates to reduce uncertainty, as we have done in previous studies (Lynch et al., 2005).

1. Measurement of the Components of the Cost Effectiveness Ratio. The effect of the CB program is assessed in terms of the clinical outcome (Δ Mean DFD). The other major component of the CE ratio, the costs, will be measured as follows: (a) calculate direct costs of preventive intervention inputs: labor, equipment, supplies, facilities, management, etc. (b) calculate the total other health care use and expense for each participant (including out of health plan use of services); and (c) evaluate the cost-effectiveness of CBP for producing improvements in depression from the perspective of the HCO (Udvarhelyi et al., 1992).

2. Measurement of Intervention Resources. The appropriate concept of costs for this analysis is opportunity costs; that is, those costs that could be avoided by foregoing the intervention program. An intervention input is any service provided to the CBP group that is not provided to the TAU group, not counting research inputs. Costs of CBP are salary and fringe benefits for labor inputs (e.g., therapists); medical office space to conduct the intervention meetings; books, educational materials, instructor's manuals, reference materials, supplies; and general administration and overhead. Inputs have been tracked via estimates by each staff person who has tracked hours worked on the various phases of the project. The financial management system for each research site will continue to gather these data on expenses for purchased goods and services. Purchased inputs will be valued at their invoiced cost. Professional labor inputs will be valued using unit cost estimates developed from a national database.

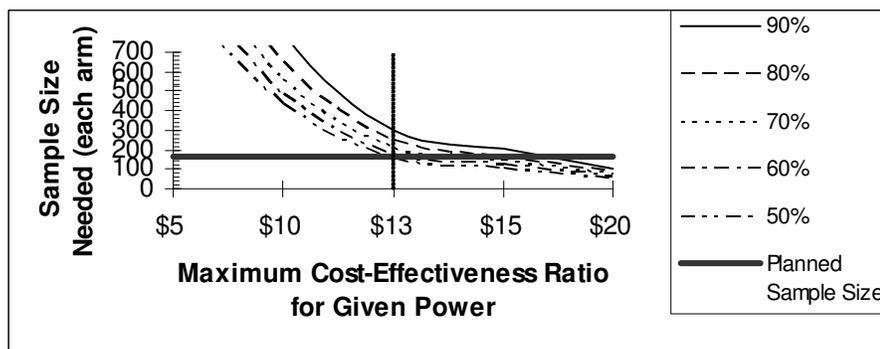
3. Measurement of Utilization of Health Care Services. Comprehensive medical care utilization profiles will be developed on every participant. Information about the 12 months prior to randomization was obtained at baseline and such data collection has continued throughout the intervention and follow-up periods. We have collected data on utilization with the CASA throughout POD.1 and use the same procedures in the proposed study (POD.2). The CASA collects comprehensive data on all types of health services received by the participant in any health care setting. For services received outside the intervention (e.g., from primary medical providers, schools, juvenile justice), we will complete the CASA, Child Health Services Screen followed by the Detailed Services Form, which we have used in other trials of youth mental health treatments (e.g., TORDIA).

4. Costing Algorithm. To value the utilization data and the mental health professional services used, we are developing a set of unit cost coefficients using the MarketScan Research Database. MarketScan is the largest multi-source database of privately insured claim and encounter data in the U.S. It contains approximately 4 million covered lives each year, representing persons enrolled in different types of health care organizations (e.g.; HMO, PPO, IPA) in multiple regions of the US. MarketScan captures clinical utilization, enrollment, prescription drug, and carve-out services; the database includes provider reimbursement, which we will use as a proxy for health care costs. We are working with economists at MEDSTAT to develop coefficients specific to the types of healthcare utilization reported by study participants. Working with MarketScan data for over 2 million youth, we will create unit costs for different types of mental health treatment services. These data will allow us to differentiate type of service (e.g., individual or group therapy), provider type (e.g., psychiatrist, psychologist), and setting (e.g., office based, hospital). For example, we will develop separate unit costs for individual therapy visits to a psychiatrist or a mental health therapist, and different unit costs for each specific medication, based on Red Book values available from MarketScan. Although our main analysis will use the overall unit costs from the pooled data, we also will conduct sensitivity analyses to examine potential regional differences in unit costs; i.e., we will calculate separate unit costs for the different US geographic regions: North East, North Central Data, South, and West. A similar approach recently has been used by other investigators conducting CEA of mental health interventions (Schoenbaum et al. 2001). MarketScan has been used in studies of mental health service utilization and cost (Crown et al., 2001; Croghan et al., 1999; Leslie & Rosenheck, 2000; Leslie et al., 2001). Health care costs will be converted to constant dollars by using the cost conversion coefficients for a year in the middle of the study period. This eliminates the effects of inflation on expenses and removes the burden of adjusting for inflation from the cost and cost-effectiveness models.

5. Discounting. A variety of experts in CEA methods suggest that costs and health outcomes should be discounted to present value if the study period extends beyond one year (Drummond, O'Brien, Stoddart, & Torrance, 1997; Gold et al., 1996). Following these recommendations, we will use a discount rate of 3% for both costs and health outcomes in our primary analysis. We also will perform sensitivity analyses to examine the impact of varying this rate and for using different rates for costs and outcomes.

Power to test H4.1. The outcome variable for the CEA is the ratio of incremental costs of CBP in relation to its incremental effectiveness compared to TAU. This outcome summarizes the joint behavior of cost and clinical outcomes. Calculating the power of a study is complicated by outcomes that are in a ratio with a numerator and denominator that are likely to be correlated (e.g., Briggs & Gray, 1998; O'Brien et al., 1994). Following the methods proposed by Briggs and Gray (1998), we will use the refined formulas of Laska et al. (1999; pp. 340-341), with an $\alpha = .05$ level of significance and varying levels of power in the analysis. Using these methods and preliminary cost-effectiveness data from our prior trial (Clarke et al., 2001; Lynch et al., 2005), we will measure effects as depression-free days and costs as total costs to the health plan for one year after intervention. These methods require that the analyst define a maximum cost-effectiveness ratio, or effect size, that would be acceptable to decision-makers. Two studies (Lave et al., 1998; Schoenbaum et al., 2001) have reported the cost-effectiveness of interventions to treat depression, with effects in depression-free-days (or depression burden days). We used these results to identify a maximum acceptable cost-effectiveness ratio for our power calculations. Lave et al. (1998) reported that one of their interventions would be considered cost-effective or efficient based on general standards and had an incremental cost-effectiveness of approximately \$13 per depression-free-day (DFD). Schoenbaum et al. (2001) reported that their two interventions also were reasonably efficient based on general standards. They did not directly report incremental cost per DFD, but extrapolating from their published data we estimated that their interventions were probably in a similar range to those of Lave et al. (1998). Figure 5 presents our power calculations, indicating the sample size (per arm) that would be needed to detect cost-effectiveness ratios below different maximum cost-effectiveness ratios (including \$13/DFD), for differing levels of power. The bold line, at sample size 160 (per arm), indicates the sample size already obtained. Our analyses indicate that our sample size of 160 (per arm) is likely to have between 50-60% power to detect a cost-effectiveness ratio as significantly below \$13/DFD. If the maximum acceptable cost effectiveness ratio is slightly higher, e.g., \$15/DFD, our proposed sample size is likely to have 80% power to detect a cost-effectiveness ratio below \$15/DFD.

Figure 5. Sample size needed for varying levels of power and maximum acceptable cost-effectiveness ratios



Although we may not be able to detect significant effects in the cost-effectiveness analysis if the maximum acceptable level is \$13/DFD or lower, we will be able to provide additional information about the likely effect size for CBP, which can be used to examine whether a larger sample size would have likely found a significant effect. This information could be used to refine the intervention in order to

increase its potential for implementation in HCO settings. Little is known about the cost of mental health services and interventions for youth (e.g., Hoagwood, Hibbs, Brent, & Jensen, 1995; Knapp, 1997), so these additional data could provide critical information to guide future intervention efforts. We also will employ sensitivity analyses to further explore the cost outcomes (Drummond et al., 1997; Gold et al., 1996).

Hypothesis 4.2: Labor Market Outcomes. Compared to participants in TAU, young adults who had received CBP will show better human capital accumulation (i.e., longer periods engaged in school; completing school) and workplace productivity (i.e., longer periods of employment, decreased absenteeism and presenteeism while employed). We will use a variety of measures of work place productivity used in previous studies of the labor supply effects of interventions for depression in adults (Timbie et al., 2006) although the current study focuses on individuals transitioning from adolescence to young adulthood. Given this context, we also plan to measure human capital accumulation because many of our participants likely will be in school or engaged in other training activities that would not be reflected in traditional measures of workplace productivity. Thus, we will examine outcomes for human capital accumulation (e.g., engaged in productive activity, number of hours engaged in school or other work training) and outcomes for workplace productivity (employed; absenteeism and/or presenteeism due to depression). *Similar to other studies of labor force outcomes related*

to depression (e.g., Fletcher & Wolf, 2007; Kessler et al. 2006; Schoenbaum et al. 2001; Simon et al. 2000), we will use regression analyses (logistic or linear) to analyze these outcomes controlling for key covariates.

Power to test H4.2. Power for Multiple Regression Analyses. According to Cohen (1988, p. 415), power for multiple regression analyses is established based on the noncentrality parameter, L , which is equal to

$\frac{R^2}{1 - R^2} \times (N - u - 1)$ where N is the sample size and u the number of independent variables in the equation.

Based on a recent meta-analysis of labor market outcomes related to depression interventions (Timbie et al., 2006), we expect effect sizes to be relatively small. Using the online software (Soper, 2007), we estimate that the minimum number of cases needed to detect small effects (using Cohen's convention of an effect size of 0.10 indicating a small effect) at 80% power with 10 covariates to be 172. This is larger than our sample size per arm of the trial for this study. However, if the effect size is slightly larger (.15; similar to larger effects observed in some adult depression trials) (e.g., Timbie et al., 2006), the number of cases needed to detect this effect at 80% power with 10 covariates would be 118, which is lower than the 158 per arm in the current study.