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This proposal is designed to address the need of the following statement in RFA: MH-02-003:

Development of an instrument or set of measures with one or more subscales based upon a theoretical model of depression substantiated by behavioral, psychophysiological, cognitive, self-report, and/or biological measures of the fundamental "core" components of the disorder.

1 Problem/Need

1.1 History

Depression has always been a difficult disorder to diagnose and treat because of the lack of visible physical evidence of its existence. For many years, it has been treated largely through observation of behavior, and subjective evaluation on the part of both physicians and patients.

The biochemical imbalance of severe, debilitating depression can cause a variety of symptoms, including:

- confusion and distortion of thinking and perception
- lack of ability to focus on a task
- indecisiveness
- behavioral inconsistency
- mood fluctuations
- extreme changes in appetite and sleep patterns

The problem is further complicated in that sufferers of depression may manifest their symptoms in very different ways, such as withdrawing, acting out anger toward self or others, or not being able perform simple daily tasks.

As a result, depression has commonly had a stigma associated with it that can affect depression sufferers adversely both in professional and social environments. Until recently, depression has not been thought of as a physical illness, but rather a "life style" illness and therefore, has been greatly misinterpreted. People suffering from depression were often thought of us as weak, wallowing in self-pity, lazy, and in some religious circles, giving into sin.

1.2 Statistics

According to the CDC National Center for Health, the final statistics regarding suicide in the year 2000 indicate that:

- Suicide was the 11th cause of death in the United States.
- The number of deaths due to suicide that year were 29,350.
- In Washington state, suicide resulted in 727 deaths (a rate of 12.5 per 100,000 people)

- For young people, ages 10 – 24 years, suicide was the third highest cause of death.¹
- The lifetime risk for depression is 7 to 12 percent for men and 20 to 25 percent for women.²
- Up to 15 percent of the population (or 35 million people) will suffer from MDD at some time in their life.³
- There is an increased incidence of depressive disorder in persons who are divorced or separated, who are from Western countries, and who were born after World War II.⁴

The National Foundation for Depressive Illness estimates that the cost of depression ranges from 15 to 35 billion dollars a year, including loss of time and productivity, personnel replacement, medical care, and loss of life.⁵ Yet, despite these and other staggering statistics, this potentially devastating illness does not receive nearly the public attention it deserves.

1.3 Major Depressive Disorder Defined

According to the criteria listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), Major Depressive Disorder (MDD) is characterized by an episode of two weeks or more where the subjects from the some of the following symptoms:

- A. At least one of the following three abnormal moods which significantly interferes with the person's life:
 1. Abnormal depressed mood most of the day, nearly every day, for at least 2 weeks.
 2. Abnormal loss of all interest and pleasure most of the day, nearly every day, for at least 2 weeks.
 3. If 18 or younger, abnormal irritable mood most of the day, nearly every day, for at least 2 weeks.

- B. At least five of the following symptoms have been present during the same 2 week depressed period.
 1. Abnormal depressed mood (or irritable mood if a child or adolescent) [as defined in criterion A].
 2. Abnormal loss of all interest and pleasure [as defined in criterion A2].
 3. Appetite or weight disturbance, either:
 - Abnormal weight loss (when not dieting) or decrease in appetite or,
 - Abnormal weight gain or increase in appetite.
 4. Sleep disturbance, either abnormal insomnia or abnormal hypersomnia.
 5. Activity disturbance, either abnormal agitation or abnormal slowing (observable by others).
 6. Abnormal fatigue or loss of energy.
 7. Abnormal self-reproach or inappropriate guilt.
 8. Abnormal poor concentration or indecisiveness.
 9. Abnormal morbid thoughts of death (not just fear of dying) or suicide.

- C. The symptoms are not due to a mood-incongruent psychosis.

- D. The individual has never had a Manic Episode, Mixed Episode, or Hypomanic Episode.

- E. The symptoms are not due to physical illness, alcohol, medication, or street drugs.
- F. The symptoms are not due to normal bereavement.

Although MDD is not determined by external factors such as post partum, stressful life events, and substance or alcohol abuse, these can definitely increase the risk factors of debilitating depression. Individuals also at risk include those with depressive illness in first-degree relatives, prior depressive episodes and/or suicide attempts, and women aged under 40 years.²

1.4 Selective Serotonin Reuptake Inhibitors

Since the advent of SSRIs in the early 1980's, growing scientific evidence supports the theory that ongoing, persistent depression is often induced by an imbalance in the brain involving two key neurotransmitters: serotonin and norepinephrine.

Neurotransmitters are carried throughout the brain by crossing over gaps, called synapses, between "sender" and "receiver" nerve cells. In the depressed person, serotonin does not make the jump over the synapse, but backs up on the side of the sender cell--a phenomenon known as "reuptake." This in turn, inhibits the release of norepinephrine within the central nervous system and possibly also in the areas of the brain that control emotion, sleep, appetite, and cognitive processing.

In recent years, a class of antidepressants known as SSRIs have revolutionized treatment of depression. Medications such as Prozac, Paxil, and Zolaft tend to have long-lasting results with relatively few side effects (mostly gastrointestinal, headache, and tremor). SSRIs relieve the build-up of serotonin and keep it flowing smoothly across the neural synapses in the brain. Similar medications, such as Effexor, blocks the reuptake of both serotonin and norepinephrine.⁶

While not all patients respond effectively to SSRIs, their overall success has gone a long way in increasing awareness within both the healthcare industry and the public in general that depression is often reflected by a biochemical imbalance in the brain rather than a sign of weakness or flaw in character.

Yet, the exact mechanism by which SSRI's work is still not completely understood and patients have different reactions to the medications or combinations of SSRIs and/or SSRIs combined with other antidepressants, such as the older tricyclics. Therefore physician and psychiatric treatment still largely have to use a trial and error method when treating their patients with different variations of these drugs.

As a result, recovery from severe episodes of depression can be lengthy and involve lost productivity, decreased social interaction, and coping with medication side-effects. It is not uncommon for patients to have to undergo a variety of medications and dosages to achieve the balance that works effectively for them.

2 Grant proposal

To provide an accurate instrumental method for measuring physical and fundamental core components of depression. Providing a physical, measurable means of diagnosing and treating depression will help decrease subjective diagnosis, increase accuracy and efficacy of treatment, and help remove social stigma associated with this illness.

Funds for this grant will be used to assess the reliability and accuracy of using Positron Emission Tomography (PET) scan instrumentation as a physical, measurable means for diagnosing and treating subjects suffering from a lifetime history of severe depression. These brain imaging scans use radioactive tracers attached to molecules of glucose to determine activity levels in specific brain areas. PET scans build computerized multi-colored images of the brain indicating levels of metabolic activity in various parts of the brain.

Studies using PET scan technology have already shown it to be extremely useful in the diagnosis and treatment of a wide-variety of diseases and disorders, including brain tumors, epilepsy, Parkinson's disease, Alzheimer's disease, bipolar disorder, and schizophrenia.

2.1 Previous Studies

Limited studies have also show PET scans to reveal areas of the brain where activity is unusually low in depressed patients. Several types of studies using PET scans have been conducted including:

- Comparison of subjects treated with Paxil for MDD vs. Obsessive Compulsive Disorder (OCD).³
- Comparing scans of elderly patients receiving drug treatment vs. no drug treatment⁷
- Study focusing on timing and sequence of changes that place during the brain during drug treatment (i.e. normalization of brain chemicals) in geriatric men⁸
- Comparing scans of patients receiving drug treatment vs. talk therapy⁹
- Comparing scans of depressed patients vs. control group (both men and women)¹⁰
- Comparison of PET scans and lower serotonergic activity in subjects more likely to attempt lethal suicide attempts (particularly in the ventral prefrontal cortex of the brain)¹¹

2.2 DRK Research Associates

DRK Research Associates located in Bothell, Washington is a non-profit organization dedicated to support research for the continued study of MDD, and specifically, to identify methods to determine physiological, measurable diagnosis and treatment for this illness. Our ultimate goal is to enable patients suffering from MDD to return to and maintain a functional and productive life with minimal risk of suicide ideations and attempts.

We will use grant monies received from the NIMH to conduct further research identifying PET scan imaging indicating depression in specific levels of the brain. Furthermore, we want to specifically investigate how the use of SSRIs work on different areas of the brain, based on previous studies that suggest “normalization” of brain chemicals between different areas of the brain.

In the follow-up studies with depressed patients treated with an SSRI, our researches hope to use PET scans identify critical abnormalities in the brain we can use as markers for diagnosis and treatment. This could also help discern where and when subjects are not responding to SSRIs and possibly provide ideas for alternative neurotransmitter treatments.

We specifically want to focus this study on adult women between the ages of 21 and 50 as statistics show that women suffer from a higher incidence of depression and yet, do not seem to receive as much focus as teens or the elderly for depression risk. (Statistically, women have a rate of higher suicide attempts, though men are more likely to actually succeed because they tend to choose more lethal methods.)⁴

3 Project Design/Plan of Action

3.1 Goals

The goal of this study are tri-fold:

3.1.1 Primary Goal

To provide additional evidence to support and expand on previous studies that MDD reflects a biochemical and physiological dysfunction in the brain by using PET scans as a physical, measurable means of diagnosing and treating depression, particularly in adult women.

3.1.2 Secondary Goal

To provide additional evidence to support and expand on previous studies suggesting that PET scans can be used to evaluate efficacy of treatment by SSRIs by determining specific areas of the brain affected. This would include being able to determine if the SSRI was “normalizing” brain activity by decreasing activity in certain parts of the brain and increasing activity in others.

3.1.3 Tertiary Goal

To see if PET scans can reveal other neurotransmitter treatment possibilities for patients who do not respond effectively to SSRIs.

3.2 Measurable Objectives

3.2.1 Positron Emission Tomography Defined

Positron emission tomography (PET) is a sophisticated imaging technique that can effectively and non-invasively measure brain metabolism and cerebral blood flow (CBF), which are indicators of brain function. These studies can be conducted at rest or after a task or drug administration to show which areas of the brain become more active. The picture it shows of brain function is created when a molecule, such as glucose, is synthesized using tiny amounts of radioactive carbon, for example (sugars are made out of carbon and other atoms). The PET camera detects this tiny amount of radiation. All of this information about brain activity is assembled into a composite picture by the computer system. However, at this time PET is still a research tool, rather than a diagnostic tool.¹²

Figure 1 shows how a PET scan is used to show the difference in brain level activities between a normal person and a depressed person.¹³

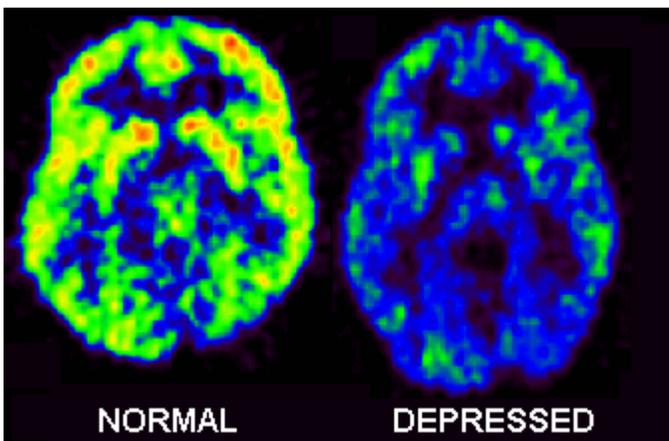


Figure 1. PET Scan demonstrating difference between normal and depressed brain activity.

In our study, we will use the PET scan specifically to identify areas of the brain affected by different levels of glucose metabolism, CBF, and serotonin levels for patients already diagnosed with MDD.

3.2.2 Objective 1

To **demonstrate** areas of brain that exhibit different levels of activity between the control group and the research (depressed) group, particularly in adult women.

3.2.3 Objectives 2a – 2d

Objectives 2a through 2d deal with **measuring** and **evaluating** activity in specific areas of the brain between adult women subjects treated with SSRI vs. placebo based upon results from previous studies, some of which are listed in Section 2.1.

3.2.3.1 Objective 2a

To **measure** changes in cerebral blood flow (CBF), glucose metabolism, and serotonin levels in the limbic system of the brain. This section of the brain is located in the temporal lobe of the brain and is generally associated with emotions: specifically the amygdala, cingulate gyrus, and thalamus. The hippocampus, also located in the limbic system, is associated with memory and modulating stress.⁸

3.2.3.2 Objective 2b

To **measure** changes cerebral blood flow (CBF), glucose metabolism, and serotonin levels in areas of the brain associated with cognition and reasoning, specifically, the dorsal cortical region of brain.⁸

3.2.3.3 Objective 2c

To **observe** if there are normalization patterns of activity between the brain areas mentioned in Objectives 2a and 2b. Specifically, to **identify** if there is a specific mechanism or marker path for the serotonin neurotransmitter as it attempts to normalize levels between the emotion and cognitive areas of the brain.

3.2.3.4 Objective 2d

To **measure** metabolism and levels of seroternegetic response in the ventral prefrontal cortex (PFC). (Previous studies have shown that localized hypofunction and impaired serotonergic responsivity are proportional to lethality of suicide attempts.¹¹)

3.2.4 Objective 3

To **categorize** subjects who respond to the SSRI in terms of mood and behavior and compare their scans with those who don't respond to the SSRI. To **analyze** brain scans for differences between the two groups in order to provide possible alternative neurotransmitter treatment.

Note:

A previous study of depressed men showed that those who responded well to Prozac showed decreased levels of brain activity in the cingulate (associated with emotional processing) and hippocampus (associated with memory and modulating stress) then those who did not respond to the drug. Our study will evaluate if similar patterns emerge for women treated with the SSRI.⁸

4 Project Implementation Strategy

The study will involve three phases:

- **Phase I** – Conducting PET scans of control group vs. research (depressed) group.
- **Phase II** – Conducting follow-up PET scans of research group after treatment with SSRIs or placebo.
- **Phase III** – Analyzing results of Phases I and II.

During each phase of the study, quality control checkpoints will be set up to make sure that subject selection and treatment, PET scan tests, and data collection are conducted in an accurate and consistent manner. (See attached *Guidelines for Internal Evaluation Plan* document for details.)

4.1 Study Methodology

4.1.1 Phase I – Initial study

The initial set of PET scans will be conducted on two groups in a relaxed, emotionally “safe” clinical environment (that is, individuals will not be judged in any way for their current mood or behavior, unless they threaten to harm themselves or someone else).

Comparisons will be made between areas of the brain that show low levels of activity in severely depressed patients (as determined by psychiatric evaluation beforehand) vs. those in the control group. The study will attempt to isolate specific portions of the brain affected by depression. Subjects will be limited to those whose history verifies that they have suffered from depression during a significant portion of their life, regardless of external circumstances. (See subject criteria discussed in Section 4.2.)

4.1.2 Phase II – Follow-up study

The study will then involve follow-up research to determine PET scan changes in the research (depressed) group while being treated with the selected SSRI. If possible, the neurotransmitter serotonin will be activated with a marker to determine the path it takes to different areas of the brain during treatment: neurologists and psychiatrists have already developed a means of gauging serotonin levels in living patients, by measuring levels of a breakdown product of serotonin called 5-HIAA in cerebrospinal fluid (CSF).¹⁴

1. The depressed group will be divided so that one-half of the subjects receiving the selected SSRI for a period of two-months. The other half of the depressed group will be given placebo. (A period of two months was selected because SSRIs typically do not start taking significant effect until at least six weeks.)

Note: This portion of the study will be partially blind in that both drug administrators and subjects will **not** know whether they are receiving an SSRI vs. placebo. However, the physicians performing the scan analysis will know which type of medication subjects are receiving to aid them in their assessment of the analysis of different brain areas from the PET scans.

2. At two week intervals for the next two months, a second set of PET scans will be conducted on all subjects in the research (depressed) group to evaluate preliminary changes in brain activity levels with particular focus on specified brain areas (limbic, PFC, dorsal cortex, etc.).
3. In addition, at two-week intervals, subjects will be interviewed by psychiatrists and psychotherapists to evaluate mood response to the medication.
4. At the end of two months, final brain scans and psychiatric/psychotherapy evaluations will be conducted to compare differences between the SSRI group and the placebo group.
5. Brain scans will also be compared and analyzed between subjects in the SSRI group that do and do not respond to the medication.

4.1.3 Phase III - Final Analysis

At the end of the two-month period, we will conduct a final PET scan on all subjects and analyze the results between those subjects treated with SSRI vs. placebo.

In addition, a psychiatric and psychotherapeutic evaluation will be given to assess which patients responded to the SSRI and which did not. The brain scans between these two types of subjects will be further analyzed for possible differences in the “path” that the serotonin transmitter took during treatment.

Finally, data analysis will be compared with previous studies such as those listed in Section 2.1.

4.2 Subject criteria

Adult women, between the ages of 21 and 50, who have a verified history of suffering from a chronic (lifetime) history of MDD episodes as defined by DSM-IV in Section 1.3. Subjects will be limited to those whose history verifies that they have suffered periods of episodic MDD during a significant portion of their life.

According to these criteria, subjects will not suffer depression from other causes such as bipolar disorder, normal bereavement, physical illness, substance abuse, or prescription medication. Subjects will **not** be suffering from post-partum depression or a short-term depression resulting from a specific traumatic or stressful event (such as rape, loss of a loved one, or a local or national disaster).

Note: The distinction needs to be made between a major traumatic circumstance, and certain types of relational or normal life situations that can trigger repetitive depressive episodes, (such as repeated perceptions of failure or rejection throughout their lives).

- Control group – 20 women who have never suffered a episodic period of MDD (as defined by DSM-IV in Section 1.3) for a period of two weeks or longer.
- Depressed group – 20 women who are currently suffering from severe episodic depression of two weeks or longer. These women will be assessed as having MDD based on psychiatric and psychotherapeutic evaluation, the subjects personal reports of mood, and behavioral observation. Reputable rating scales such as the Hamilton Depressed Rating Scale (HDRS) will be used to attach a score to the level of MDD that the subject is suffering. This score will be considered in the selection process but will not be used at the sole criteria.

Both control and research subjects will include a cross-cultural stratification of adult women residing with the United States, including all races, ethnic groups, religion, and socioeconomic backgrounds.

4.3 Timeline

Table 1 – Timeline For Using PET Scans to Diagnosis and Treat Depression

| Activity Task | 1st Qtr | 2nd Qtr | 3rd Qtr | 4th Qtr |
|---|---------------------------|---------------------------|---------------------------|---------------------------|
| Post award planning meeting | x | | | |
| Order equipment | x | | | |
| Interview and select staff team members | x | | | |
| Interview, evaluate and choose subjects for control and research groups | x | | | |
| Perform initial brain scan analysis between control group and research (depressed) group | | x | | |
| Perform brain scan analysis between two groups | | x | | |
| Perform statistical data analysis between two groups | | x | | |
| Randomly divide research (depressed) group into two groups | | x | | |
| Treat one-half of patients with placebo and other half with selected SSRI for two months | | x | | |
| Conduct preliminary analysis of brain scans every two weeks | | | x | |
| Conduct evaluation report with psychiatrists and psychotherapists every two weeks (to see which patients are responding to SSRI). | | | x | |
| At the end of two months, conduct final analysis of brain scans and psychiatric evaluations | | | x | |
| Perform statistical evaluation of study results | | | x | |
| Conduct quarterly evaluation meetings with team members and stakeholders | x | x | x | x |
| Conduct final evaluation plan to include: | | | | x |

| Activity Task | 1st Qtr | 2nd Qtr | 3rd Qtr | 4th Qtr |
|---|---------------------------|---------------------------|---------------------------|---------------------------|
| <ul style="list-style-type: none"> Impact on medical/psychiatric community Impact on public (adult women) | | | | |
| Conduct subject evaluation | | x | | x |

4.4 Impact Statement

- To provide measurable, instrumental data to support the validity of using PET scans as an accurate for the diagnosis and treatment of MDD.
- To use the information gathering to treat MDD patients, particularly adult women, more accurately, effectively, and rapidly, and reduce the need for “trial and error” medication treatment.

5 Management Plan

5.1 Staff Personnel

- 1 project administrator (existing staff member)
- 1 project director
- 1 technician to administer PET scan and medication.
- 2 psychiatrists to conduct patient interviews and evaluations for study qualification
- 1 psychotherapist to conduct patient interviews and evaluations for study qualification
- 1-2 psychopharmacologists to analyze PET scan results
- 1 expert in advanced psychometric techniques
- 1 statistician
- 1 psychiatric nurse or qualified therapist for comfort and support of patients. (This could be same psychotherapist mentioned above.)

See Figure 2 for proposed study team organizational chart.

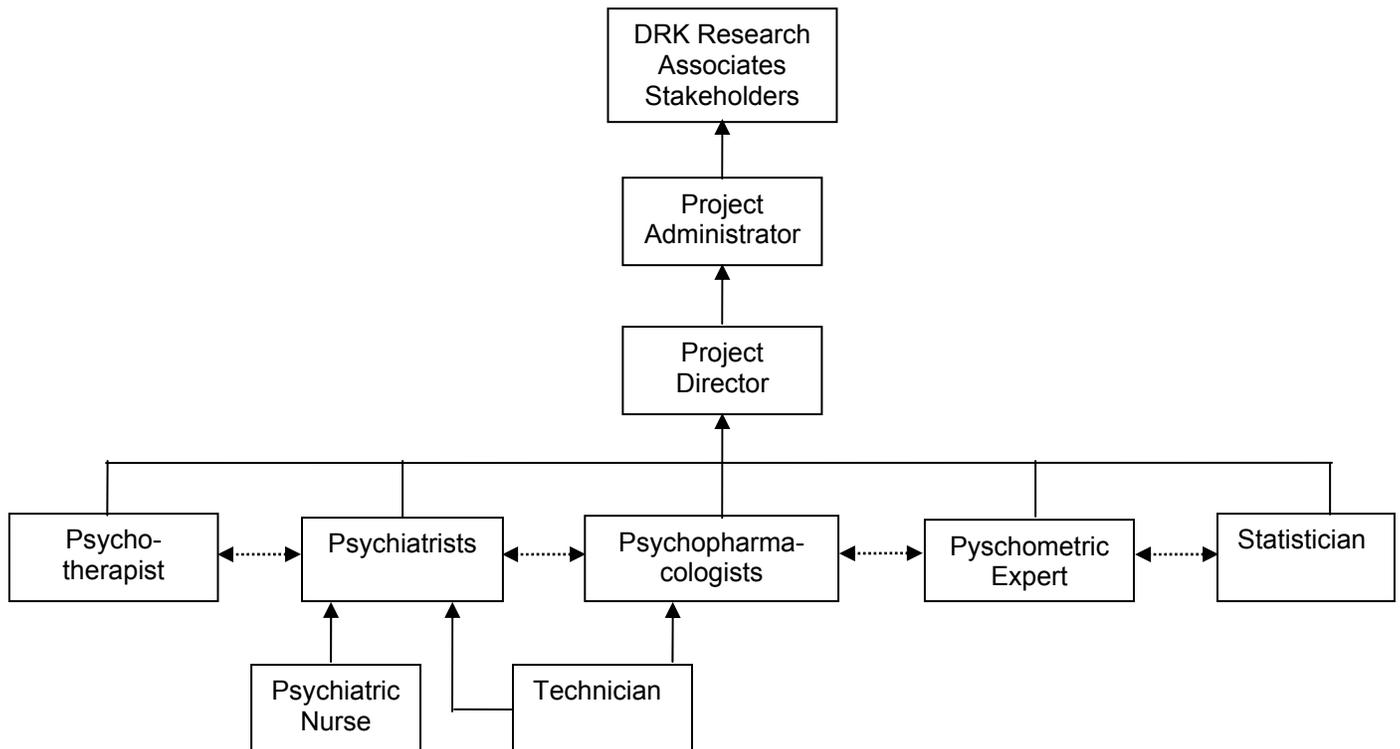


Figure 2. Proposed PET Scan Study Team Organizational Chart

5.2 Equipment Resources

- PET Scan machine (purchase or lease)
- Associated supplies (injection needles, radioactive tracer, etc.)
- Accessories needed to perform scans and analyses (light scanners, etc.)
- Two-month supply of SSRI and placebo

5.3 Environmental Resources

- Clinic area to perform scans
- Office area to analyze results
- Comfortable waiting area for subjects

5.4 Equity

Women from all walks of life and careers, race, national origin, economic and social status, and religious preference will be considered.

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