Should Veterans with a Diagnosis of Post-Traumatic Stress Disorder Be Considered a Vulnerable Population for the Purpose of Applying Guidelines for the Protection of Human Subjects in Research?

Report of a Work Group Convened by
the National Center for Ethics in Health Care of
the Veterans Health Administration on Behalf of
the Secretary of Veterans Affairs

October 2008

Executive Summary

The Secretary of the Department of Veterans Affairs charged the Work Group on Post Traumatic Stress Disorder (PTSD) and Vulnerable Populations in Research to examine the tension between the need to study veterans with PTSD to help improve their condition and the need to protect veterans with PTSD from further risk, given their potential vulnerability as research participants. Specifically, the Secretary of Veterans Affairs charged the Work Group to provide consensus recommendations to the Under Secretary for Health (USH) for the following questions:

1. Is it ever ethically permissible for the Veteran's Health Administration (VHA) to support the conduct of research on veterans with PTSD?

2. Are veterans with a diagnosis of PTSD considered "vulnerable" for the purpose of applying guidelines for the protection of human subjects in research?

3. Should veterans with a diagnosis of PTSD be afforded special consideration and/or extra protections under VHA guidance to protect human subjects in research?
    a. If yes, what criteria would trigger the application of special consideration and/or extra protections?
    b. If yes, what special consideration and/or extra protections should be afforded, and what mechanism would be used to implement them?

The Work Group, consisting of nine Federal employees from six different agencies, met three times over the course of sixty days to discuss the charge, receive testimony and comments from national experts inside and outside of VHA, and deliberate on recommendations for VHA leadership. The Work Group answered the charge questions as follows:

QUESTION 1: Is it ever ethically permissible for VHA to support the conduct of research on veterans with PTSD?

CONSENSUS RECOMMENDATION 1: The Work Group concludes that it is not only ethically permissible for VHA to support the conduct of research involving veterans with PTSD but VHA has an ethical obligation to do so.

QUESTION 2: Are veterans with a diagnosis of PTSD considered “vulnerable” for the purpose of applying guidelines for the protection of human subjects in research?

CONSENSUS RECOMMENDATION 2: The Work Group concludes that, as a group, veterans with PTSD are not categorically vulnerable and, therefore, do not require special protections in the form of new regulations, policy or guidance. Under current Federal regulations and VA policy, Institutional Review Boards (IRB) are directed to scrutinize individual protocols to determine whether potential participants may have impaired decision-making capacity, an increased susceptibility to undue influence or coercion, or an increased susceptibility to the risks associated with a particular research study. None of these factors applies categorically to veterans with PTSD; however, one or more of these factors might apply to certain veterans with PTSD who are involved in a particular research study. If an IRB determines that this is the case with respect to a particular research study, the IRB should give special consideration to protecting the welfare of those veterans with PTSD who are involved, and consider whether special safeguards are needed to protect them, just as they would for any other study population.

QUESTION 3: Should veterans with a diagnosis of PTSD be afforded special consideration and/or extra protections under VHA guidance to protect human subjects in research?

a. If yes, what criteria would trigger the application of special consideration and/or extra protections?

b. If yes, what specific consideration and/or extra protections should be afforded, and what mechanism would be used to implement them?

CONSENSUS RECOMMENDATION 3: The Work Group concludes that veterans with a diagnosis of PTSD should be afforded special consideration consistent with current regulation and policy if and when an IRB determines that these veterans have impaired decision-making capacity, an increased susceptibility to undue influence or coercion, or an increased susceptibility to the risks associated with a particular research study. Because veterans with a diagnosis of PTSD are not categorically vulnerable, no extra protections in the form of additional regulation or policy are needed for this group beyond what is already specified for all participants in research.

As a society, we owe a special obligation to all veterans for the sacrifices they have made for our country including veterans who have developed PTSD and other disorders as a direct result of their military service. VHA, as part of its mission to advance the health and well-being of veterans, must adhere to the highest ethical standards in all of its research practices. Investigators, IRBs, and research teams should apply existing regulations and guidance regarding protecting human subjects with sensitivity to the needs and interests of veterans with PTSD within the context of the study under review.

In addition, the Work Group made the following general recommendations:

1. The Work Group recommends that this report be disseminated to the VA and affiliate IRBs and the interested public.

2. The Work Group recommends that VHA's Office of Research and Development conduct an educational needs assessment to determine what further information and resources, if any, researchers and IRBs need to implement the considerations and protections for vulnerable populations specified in regulation and policy. Such information may relate to PTSD specifically or to the assessment of vulnerability among subject populations more generally. The assessment should have input from veterans who have participated in or been recruited for research.

3. IRBs should continue to review protocols involving veterans with PTSD with the same care and attention with which they review other protocols, consistent with current regulation and policy pertaining to the protection of human research subjects, including ensuring that the review process is informed, as appropriate by both scientific/clinical expertise and experiential/advocacy expertise relating to veterans with PTSD.

4. If an IRB determines that veterans with a diagnosis of PTSD have an increased susceptibility to the risks associated with a particular research study, as described under answer Charge Question 2 and Consensus Recommendation 2 above, the IRB should add safeguards particular to the study to protect veterans with PTSD in that study.

INTRODUCTION

Post Traumatic Stress Disorder (PTSD) is a potentially disabling mental disorder that can develop after exposure to traumatic events, such as those encountered in military service. Among veterans who serve in a combat zone, it is estimated that 13 to 20 percent will eventually develop PTSD. Among veterans with a mental disorder who seek health care from the Veterans Health Administration (VHA), it is estimated that more than half have PTSD.

PTSD in veterans is associated with significant societal costs, in terms of both health care resources and human suffering. Suffering can result both directly from the symptoms and indirectly from the toll these symptoms can take on family, career, and lifestyle. When PTSD results from military combat, it holds special significance in American society: the diagnosis symbolizes to the public what veterans have sacrificed on behalf of the nation. At an earlier time in US history, before PTSD was well established as a mental disorder, veterans with PTSD were often misunderstood and even ostracized. Today it is recognized that the nation has a special obligation to veterans with PTSD – to understand their needs and assist in their recovery.

As part of its mission to improve the health and well-being of veterans, VHA conducts research into injuries and illnesses that are associated with military service in an effort to better understand these conditions, develop effective treatments, and improve the delivery of care. VHA's research portfolio currently includes over 500 studies involving veterans with PTSD.

Recent media coverage of the plight of veterans with PTSD has led to questions about whether veterans with a diagnosis of PTSD should be considered “vulnerable” for the purpose of applying the various guidelines that have been developed to protect human subjects in research. Some have even questioned whether, given the potential vulnerability of veterans with PTSD, it is ever ethical to perform research involving this population.

Work Group Charge

The Secretary of the Department of Veterans Affairs (VA) charged the Work Group on PTSD and Vulnerable Populations in Research to examine the tension between the need to study veterans with PTSD to help improve their condition and the need to protect veterans with PTSD from further risk, given their potential vulnerability as research participants (Appendix A). Specifically, the Secretary of Veterans Affairs charged the Work Group to provide consensus recommendations to the Under Secretary for Health (USH) for the following questions:

1. Is it ever ethically permissible for VHA to support the conduct of research on veterans with PTSD?

2. Are veterans with a diagnosis of PTSD considered “vulnerable” for the purpose of applying guidelines for the protection of human subjects in research?

3. Should veterans with a diagnosis of PTSD be afforded special consideration and/or extra protections under VHA guidance to protect human subjects in research?
    a. If yes, what criteria would trigger the application of special consideration and/or extra protections?
    b. If yes, what special consideration and/or extra protections should be afforded, and what mechanism would be used to implement them?

The Work Group, consisting of nine Federal employees from six different agencies, met three times over the course of sixty days to discuss the charge, receive testimony and comments from national experts inside and outside of VHA, and deliberate on recommendations for VHA leadership. The findings and recommendations of this report represent the consensus opinion of these Federal experts and are not intended to represent the position of their respective agencies or to constitute approval of the report by those agencies. This document outlines the findings of the Work Group and its recommendations.

QUESTION 1: ***Is it ever ethically permissible for VHA to support the conduct of research on veterans with PTSD?***

CONSENSUS RECOMMENDATION 1: The Work Group concludes that it is not only ethically permissible for VHA to support the conduct of research involving veterans with PTSD, but VHA has an ethical obligation to do so.

Rationale

In responding to this question, the Work Group addressed six related questions:

A. Is there a need for more research on PTSD?

B. Could this research be conducted without the participation of PTSD patients?

C. Does research on PTSD patients expose them to undue risk?

D. Is it an appropriate role for VHA to conduct this research?

E. Has prior VHA research been effective in advancing the understanding of PTSD?

F. Would denying veterans with PTSD access to research participation be unfair?

A. Is There a Need for More Research on PTSD?

Yes. Additional research on PTSD is needed to fully understand the disorder and to develop effective treatments. In a 2008 report commissioned by VA, the National Academy of Science Institute of Medicine (IOM) concluded that, for the majority of available treatments for PTSD, scientific evidence to support the effectiveness of these treatments is still lacking. The IOM summarized its findings by stating, "The committee could only conclude that well-designed research is needed to answer the key questions regarding the efficacy of treatment modalities in veterans." (pg. x). Similarly, in testimony provided to the Work Group, Dr. Freidman concluded that many gaps still exist in the current understanding of PTSD and in knowledge of effective treatments. Dr. Friedman and his colleagues highlighted a need for more research into the efficacy of pharmacologic interventions and psychotherapies, mechanism of memory, the biology of the disorder, and the differences in the manifestation of the disorder in particular populations such as women, minorities, and the elderly (Friedman, Resick, and Keane, 2007). In his testimony to the Work Group, Dr. Paul Appelbaum also noted that very little is known about factors that contribute to or detract from valid informed consent among veterans with PTSD, as compared to other patient populations. Work Group members further noted that little research has been undertaken to examine how veterans with PTSD experience the research process.

B. Could this research be conducted without the participation of PTSD patients?

No. While some aspects of the basic biology of PTSD can be studied in animals or healthy volunteers, other aspects of the disorder and its treatment can only be studied in PTSD patients. Examples of research topics that require work with PTSD patients

include epidemiological investigations, the effects of PTSD on an individual's life experiences, the impact of PTSD on family members, the effectiveness of specific treatments for PTSD in particular patient populations, the effectiveness of psychosocial interventions, and the best service delivery approaches for PTSD care.

C. Does research on PTSD patients expose them to undue risk?

No. There is no evidence to suggest either that the research currently being done on PTSD patients is riskier than research on other populations of patients, or that PTSD patients are inherently at higher risk from research participation.

VHA has multiple mechanisms in place to ensure that veterans participating in research are not exposed to undue risk. Two national program offices within VHA, the Office of Research and Development (ORD) and the Office of Research Oversight (ORO), have specific responsibilities for ensuring the welfare of research participants. ORD created the Program for Research Integrity, Development, and Education (PRIDE), whose mission is to protect participants in VA human research. PRIDE is responsible for developing national VHA policy on human research protections and for providing education and training to investigators, Institutional Review Board (IRB) members, local research and development staff, and facility leadership. VHA requires that all VA human research protection programs be formally accredited. VHA is the only Federal agency that mandates such accreditation. (See Appendix B for additional information on PRIDE).

ORO is the primary VHA office responsible for compliance and assurance related to human subjects protections. In this role, ORO is responsible for managing Federal Wide Assurances for VHA, monitoring external accreditation of VHA research programs, educating Research Compliance Officers in VHA facilities, and providing technical assistance and information to VHA research facilities to enhance and promote research compliance. Together, ORD and ORO spent an estimated $12.8 million in fiscal year (FY) 2008 on human research protection activities in VHA.

In response to an incident involving a veteran with PTSD in which VHA received unfavorable press attention, ORO directed IRBs in the field on July 1, 2008, to conduct focused reviews of PTSD research at VHA. As a result of this intensive scrutiny, 7.6 percent of the 537 protocols reviewed were in some way modified, while the remaining 92.4 percent were continued without modification. After reviewing reports from these IRBs, ORO concluded that that the current research at VHA facilities displayed "appropriate sensitivity" to the PTSD population. While they noted several ways in which research oversight in VHA could be strengthened overall, which are currently being addressed by VHA, they made no recommendations that were unique to research on PTSD (ORO, Special IRB Reviews of PTSD Research, 2008).

Almost all research exposes research subjects to some level of risk. In order to be ethically justifiable, any risks to research subjects must be outweighed by the expected benefits of the research. The Work Group is not aware of any evidence that research involving PTSD patients is inherently riskier than research on other populations of

patients. On the other hand, given the shortage of effective treatments for PTSD, the potential benefits of research involving PTSD patients are substantial.

D. Is it an appropriate role for VHA to conduct this research?

Yes. VHA has an explicit mission to carry out research on medical conditions related to military service, including research to understand and treat PTSD. As stated in the authorizing statute for VA, Title 38, United States Code (U.S.C.) 7303:

> In order to carry out more effectively the primary function of the Administration and in order to contribute to the Nation's knowledge about disease and disability, the Secretary shall carry out a program of medical research in connection with the provision of medical care and treatment to veterans.

The statute further states that VA should conduct "research into injuries and illnesses particularly related to service" (38 U.S.C. 7303(a)(1)(B)). In an update to the authorizing statute, Public Law 102-405 directed VA to focus specifically on PTSD, stating that "the Secretary shall assign a high priority to the conduct of research on mental illness, including research regarding (1) post-traumatic stress disorder, (2) post-traumatic stress disorder in association with substance abuse, and (3) the treatment of those disorders." This direction from Congress is captured in VHA's current strategic plan under Strategic Goal #6, to "focus research and development on clinical and system improvements designed to enhance the health and well being of veterans," and Strategic Initiative 6.1, to "identify and assess opportunities for extensive VA involvement in research related to service connected injuries (e.g., Traumatic Brain Injury, polytrauma, Spinal Cord Injury, and PTSD)."

Both Congress and VHA recognize that as a responsible steward of public dollars, VHA must continue to pursue research on conditions that affect veterans, but for which highly effective and efficient treatments are unavailable. As agents of President Lincoln's charge to "care for those who have borne the battle," VHA has an obligation to carry out research that will improve the health and well-being of veterans with PTSD.

E. Has prior VHA research been effective in advancing the understanding of PTSD?

Yes. As described by Dr. Marmar in his testimony to the Work Group, VHA research is internationally recognized as leading the world in understanding PTSD including the "prevalence, course, risk and resilience factors, complications, biology, and treatment of PTSD." Veterans, including the 80 percent not treated at VA facilities, and the general population have benefited considerably from PTSD research at VHA. (See Appendix C for a summary of Dr. Marmar's testimony on PTSD research conducted in VHA.)

F. Would denying veterans with PTSD access to research participation be unfair?

Yes. Subjects enter into research projects for many reasons including altruism (Kass, Sugarman, Faden, and Schoch-Spana, 1996). The ability to contribute to society may be a significant psychological benefit, especially for people whose options to serve others may be limited by illness. There is evidence that for many veterans, altruism is a substantive factor in their decisions to participate in research (Scott, 2008). Participation in research may also directly benefit the research subjects (Braunholtz, Edwards, and Lilford, 2001).

The principle of justice requires that participation in research be made available to all eligible subjects equally (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). Limiting the participation of veterans with PTSD in research without the justification that the research is unsafe or that the population could not give adequate consent would violate this principle.

QUESTION 2: ***Are veterans with a diagnosis of PTSD considered "vulnerable" for the purpose of applying guidelines for the protection of human subjects in research?***

CONSENSUS RECOMMENDATION 2: The Work Group concludes that, as a group, veterans with PTSD are not categorically vulnerable and, therefore, do not require special protections in the form of new regulations, policy or guidance. Under current Federal regulations and VA policy, IRBs are directed to scrutinize individual protocols to determine whether potential participants may have impaired decision-making capacity, an increased susceptibility to undue influence or coercion, or an increased susceptibility to the risks associated with a particular research study. None of these factors applies categorically to veterans with PTSD; however, one or more of these factors might apply to certain veterans with PTSD who are involved in a particular research study. If an IRB determines that this is the case with respect to a particular research study, the IRB should give special consideration to protecting the welfare of those veterans with PTSD who are involved, and consider whether special safeguards are needed to protect them, just as they would for any other study population.

Rationale

In responding to this question, the Work Group addressed the following related questions:

A. What is meant by “vulnerable” in the context of human subject research?

B. How is the term “vulnerable” used in guidelines for the protection of human research subjects?

C. What are the general characteristics of PTSD in veterans?

D. Do veterans with a diagnosis of PTSD have impaired decision-making capacity?

E. Do veterans with a diagnosis of PTSD have an increased susceptibility to undue influence or coercion?

F. Do veterans with a diagnosis of PTSD have an increased susceptibility to research risks?

G. Should veterans with a diagnosis of PTSD be considered categorically “vulnerable” for the purpose of applying guidelines for the protection of human subjects in research?

A. What is meant by “vulnerable” in the context of human subject research?

The term “vulnerable” is used in a number of different ways in the research ethics context, and there is no single definition of vulnerability that is universally accepted. As noted by the National Bioethics Advisory Commission (1988), vulnerability can originate in either an individual’s clinical condition (e.g., Alzheimer’s disease that impairs decision making) or an individual’s social context (e.g., economic disadvantage), both of which can fluctuate over a lifetime. Kipnis (2001) has described a taxonomy of seven ways in which a person can be vulnerable. Indeed, Kottow (2003) suggests that we are all

vulnerable in one way or another. There has been a trend in the research ethics literature to broadly apply "vulnerability" to many populations, for example to those with a terminal illness, employees, the elderly, healthy volunteers, minorities, the unemployed, the medically disadvantaged, people in emergency rooms, and homeless persons. Levine and colleagues argue that applying the term "vulnerability" in such a broad way to so many groups has diluted the impact of the term and the protection it is supposed to bring to research subjects (Levine et. al., 2004). Therefore, in this analysis, the Work Group has applied term vulnerability cautiously, adhering to the definitions of vulnerability embodied in Federal regulation, policy and guidance.

B. How is the term "vulnerable" used in guidelines for the protection of human research subjects?

The need for concern and protection of vulnerable populations was described in the 1979 report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, commonly known as *The Belmont Report*. The principles defined in that report were subsequently codified in the "Common Rule," a set of Federal regulations for the protection of human research subjects subscribed to by 17 Federal agencies and set forth in Title 45 Code of Federal Regulations (CFR), Part 46. The Common Rule, in turn, forms the basis for VHA Handbook 1200.05, *Requirements for the Protection of Human Subjects in Research.*

In Federal regulations and VHA policy, the term "vulnerable" applies in the context of the protection of research subjects in three ways. First, "vulnerable" is used to refer to certain populations that have been singled out as categorically vulnerable and,

therefore, in need of special protections that do not apply to other research subjects. Under federal regulations three groups are considered categorically vulnerable: fetuses and pregnant women (45 CFR Part 46, Subpart B); prisoners (45 CFR Part 46, Subpart C); and children (45 CFR Part 46, Subpart D). Under VHA policy, a fourth group is also considered categorically vulnerable: mentally disabled persons or those persons with impaired decision-making capacity. For each group, regulations and policy set forth specific requirements for IRBs.

The term “vulnerable” is also used in a broader sense to include individuals who, while not categorically vulnerable, may be considered more susceptible to coercion or undue influence than other individuals, at least in the context of a particular research study. In this sense a wide range of individuals are considered potentially vulnerable including, for example, individuals who are economically or educationally disadvantaged (45 CFR 46.107(a)), elderly, severely ill, homosexual or bisexual, women, or minorities (IRB Guidebook, 1993). For these and other potentially vulnerable groups, federal regulations do not set forth any explicit requirements for IRBs, but do set forth a general requirement for IRBs to give special consideration to protecting the welfare of such individuals.

Finally, “vulnerable” is sometimes used in a third sense to refer to increased susceptibility to the risks associated with a particular research study. For example, when determining whether the risks of a particular vaccine trial are reasonable in relation to its benefits, IRBs should consider “any special vulnerability of the subject population to the potential adverse effects of the vaccine” (Office of Human Research

Protections (OHRP) IRB Guidebook Chap. V, Sec. 6). IRBs have an obligation to minimize risks and ensure that risks are reasonable, taking into account any increased susceptibilities of the research subjects.

C. What are the general characteristics of PTSD in veterans?

The American Psychiatric Association (APA) defines specific symptoms and criteria for the diagnosis of PSTD in its Diagnostic and Statistic Manual of Mental Disorders (DSM), which is widely regarded as the gold standard for psychiatric diagnosis (DSM-IV-TR, 2000). To be diagnosed with PTSD, a person must have experienced, witnessed, or been confronted with a traumatic event, that involved actual or threatened death or serious injury of self or others, to which his or her response involved intense fear, helplessness, or horror (DSM-IV-TR, 2000). To be diagnosed with PTSD, a person must have symptoms that persist for at least one month from each of the three categories, and that cause clinically significant distress or impairment in functioning. (See Appendix D for the full DSM-IV description of PTSD Criteria.)

PTSD is a common disorder, especially among combat veterans. In the general United States population, the lifetime prevalence of PTSD is approximately 5 to 6 percent for men and 10 to 14 percent for women (Yehuda, 2002). In a recent analysis of data on Vietnam theater veterans found that 18.7 percent of these veterans had PTSD at some time in their lives, and that that 9.1 percent continued to have PTSD at 11- and 12-year follow-up (Dohrenwend et al., 2006). A recent survey of soldiers who served in Iraq and Afghanistan found that about 14 percent had probable PTSD (Tanielian and Jaycox, 2008). It is also notable that a substantial number of individuals exposed to traumatic

stress develop sub-threshold or partial PTSD associated with increased risk of suicide and functional impairment (Marshall et al., 2001; Stein et al., 1997; Wiess et al., 1992).

Individuals correctly diagnosed with PTSD can vary widely in their actual symptom pattern and intensity, and in their ability to function. Among Vietnam veterans with PTSD persisting 11-12 years, considerable variability was displayed in functional impairment related to PTSD (Dohrenwend et al., 2006). (See Appendix E for a chart of functional level variation in Vietnam veterans with PTSD persisting 11-12 years.)

PTSD often occurs concurrently with other disorders, most frequently depression and substance abuse. There is also a high prevalence of traumatic brain injury (TBI) among recently returning combat veterans with PTSD. Such comorbidities can complicate the clinical care of veterans with PTSD, as well as the question of whether patients with PTSD are vulnerable in research. (See Appendix F for a chart of comorbid conditions in veterans returning from Iraq and Afghanistan.)

D. Do veterans with a diagnosis of PTSD have impaired decision-making capacity?

No, not in general. As a mental disorder, PTSD can affect several aspects of mental function that in some cases could influence decision making, including thinking (e.g., decreased concentration and foreshortened sense of future), mood (e.g., depression and irritability), experience (e.g., dissociation), and relational functioning (e.g., lack of social supports and divorce). However, these effects are generally not severe enough to render individuals with PTSD incapable of giving voluntary informed consent. Expert testimony before the Work Group from Drs. Strauss, Marmar, Freidman, and

Appelbaum concluded that most individuals with PTSD will be able to give adequate informed consent most of the time, although there may be times when an individual with PTSD will not be able to give adequate informed consent because of unusually severe symptoms or complicating factors. Examples of such problems include severe dissociative events, psychotic-like states, uncontrolled emotions, or complicating comorbid conditions like traumatic brain injury.

E. Do veterans with a diagnosis of PTSD have an increased susceptibility to undue influence or coercion?

No, not in general. It is possible that some veterans who rely on VA for health care or other benefits may feel pressured to participate in research out of fear that if they refuse to participate, their benefits might be somehow affected. However, this is the case for all veterans who seek VA health care, not just those with PTSD. In addition, in all VA protocols, potential research subjects are specifically assured that declining to participate in research will not result in any penalty or loss of benefits to which the subject is otherwise entitled. Further some veterans, including those with PTSD, are homeless, unemployed and poor, which may make them susceptible to coercion or undue influence.

F. Do veterans with a diagnosis of PTSD have an increased susceptibility to research risks?

No, not in general. However, as with other populations of potential research subjects, veterans with PTSD may have an increased susceptibility to the research risks involved in a particular study. For example, it is possible that veterans with PTSD might be

particularly susceptible to the adverse effects of a particular drug. IRBs and researchers also need to be sensitive to the fact that individuals with PTSD might experience emotional discomfort related to participation in research about their trauma. In research conducted following mass urban disasters, Boscarino et al. (2004) found that “respondents who met study criteria for posttraumatic stress disorder, depression, or anxiety were more likely to find questions stressful, with people having posttraumatic stress disorder or depression the most likely to be upset and to consent to psychiatric consultation at completion” (pg.515). However, less than 2% of participants reported being upset at survey completion.

On the other hand, Newman et al. (2006) summarized the literature on research with trauma survivors as follows: “Clearly the majority of studies suggest that when trauma survivors are appropriately recruited, informed about the study and make choices, the majority do not regret the experience or feel harmed by participation.” (pg. 42). Additionally, Newman and Kaloupek (2004) reported on research indicating that participation by psychiatric inpatients showed 35.6 percent reporting that participation led to new insights, 16.4 percent finding it generally helpful to be able to talk about their experiences, and 12 percent reporting that it clarified past memories. The authors go on to report that “the issue of emotional distress is often mischaracterized in terms of the potential for a protocol to ‘retraumatize’ research subjects. Use of this term is unwarranted in the research context because it equates recounting a traumatic experience with the actual occurrence of traumatic exposure” (pg. 390).

It remains unclear whether negative emotions experienced by some individuals during participation in trauma-related studies exceed in any meaningful way the magnitude of distress these individuals confront during their daily lives life or during the performance of routine physical or psychological examinations and tests. It is also uncertain whether any upset reflects acute intensification of their typical symptoms or involves emotional responses that are uncharacteristic for them.

G. Should veterans with a diagnosis of PTSD be considered categorically "vulnerable" for the purpose of applying guidelines for the protection of human subjects in research?

No. As a group, veterans with PTSD are not categorically vulnerable and, therefore, do not require special protections in the form of new regulations, policy, or guidance. Under current Federal regulations and VA policy, IRBs are directed to scrutinize each protocol to determine whether potential participants may have impaired decision-making capacity, an increased susceptibility to undue influence or coercion, or an increased susceptibility to the risks associated with a particular research study. None of these factors applies categorically to veterans with PTSD; however, one or more of these factors might apply to certain veterans with PTSD who are involved in a particular research study. As with all human subjects research, if an IRB determines that this is the case with respect to a particular research study, the IRB should give special consideration to protecting the welfare of those veterans who are involved, and consider whether special safeguards are needed to protect them, just as would be done for any other study population.

QUESTION 3: ***Should veterans with a diagnosis of PTSD be afforded special consideration and/or extra protections under VHA guidance to protect human subjects in research?***

a. ***If yes, what criteria would trigger the application of special consideration and/or extra protections?***

b. ***If yes, what specific consideration and/or extra protections should be afforded, and what mechanism would be used to implement them?***

CONSENSUS RECOMMENDATION 3:: The Work Group concludes that veterans with a diagnosis of PTSD should be afforded special consideration consistent with current regulation and policy if and when an IRB determines that these veterans have impaired decision-making capacity, an increased susceptibility to undue influence or coercion, or an increased susceptibility to the risks associated with a particular research study. Because veterans with a diagnosis of PTSD are not categorically vulnerable, no extra protections in the form of additional regulation or policy are needed for this group beyond what is already specified for all participants in research.

As a society, we owe a special obligation to all veterans for the sacrifices they have made for our country including veterans who have developed PTSD and other disorders as a direct result of their military service. VHA, as part of its mission to advance the health and well-being of veterans, must adhere to the highest ethical standards in all of its research practices. Investigators, IRBs, and research teams should apply existing regulations and guidance regarding protecting human subjects with sensitivity to the needs and interests of veterans with PTSD within the context of the study under review.

Rationale

In answering these questions, the Work Group addressed the following related questions:

A. Do veterans with PTSD require special consideration?

B. Do veterans with PTSD require extra protections?

C. When there is a need for special consideration, what safeguards might be applied?

A. Do veterans with PTSD require special consideration?

Sometimes. As discussed above, special consideration is warranted if and when an IRB determines, within the context of a particular research study, that the veterans with PTSD involved in the study have either impaired decision-making capacity, an increased susceptibility to undue influence or coercion, or an increased susceptibility to the risks associated with a particular research study.

B. Do veterans with PTSD require extra protections?

No. Because veterans with a diagnosis PTSD are not categorically vulnerable, no extra protections are needed for this group beyond what is already specified in regulation and policy for all participants in research.

C. When there is a need for special consideration, what safeguards might be applied?

When an IRB determines that a study population is vulnerable within the context of a particular research study, "[t]he IRB must ensure that additional safeguards have been included in each study to protect the welfare of vulnerable subjects" (VHA Handbook

1200.05, 7.a.(4)(b)(8)). The appropriate safeguard(s) will vary depending on the factors potentially contributing to vulnerability.

Safeguards for impaired decision-making capacity

Veterans with PTSD should be assumed to have the capacity to give informed consent unless a clinical assessment determines otherwise. However, in the context of a particular study, an IRB might determine that it is appropriate to screen a certain subpopulation of veterans with PTSD to ensure that they have decision-making capacity (e.g., individuals with severe PTSD and recent symptoms of dissociation). If incapacity is identified, the provisions regarding research with the decisionally incapacitated of Appendix D, section 6 of VHA Handbook 1200.05 apply.

Some physical or mental impairments may cause study participants to have difficulty understanding a proposed research study and its implications, even though the participants have the legal capacity to give informed consent. (Advisory Committee on Human Radiation Experiments, 1996; Appelbaum et al., 1987; Appelbaum, Lidz, and Grisso, 2004; Misra et al., 2008). Such individuals can often benefit from the use of different educational modalities, tools, or decision aids (Appelbaum, 2006). For example, Palmer and colleagues (2008) found that educational intervention improved understanding of information presented in the consent process across a range of study populations, including persons with PTSD.

Safeguards for increased susceptibility to undue influence or coercion

As mentioned above, veterans may be susceptible to coercion or undue influence if they believe that their VA benefits might somehow be affected if they fail to participate in research. In VA, veterans often rely on the Department not only for health care but also for other benefits such as disability payments. Poverty, unemployment, and homelessness can increase dependency on VA benefits and, therefore, susceptibility to undue influence or coercion in the context of research participation.

This kind of susceptibility can be partially mitigated by including clear and definitive statements during recruitment and informed consent to assure potential subjects that they are free to participate or not participate without fear of any penalty or loss of benefits to which they are otherwise entitled, as is required for all research involving human subjects in VHA. An IRB might also determine that someone other than the patient's own health care provider (such as a research assistant) should obtain informed consent, or that an independent consent monitor should be engaged to oversee the consent process and advocate for the research subjects.

In addition, IRBs can raise their sensitivity to coercion or influence in recruitment methods or informed consent documents by involving individuals who have experiential expertise (i.e., direct knowledge of the personal and social experiences of the population under study). This can be achieved, for example, by including a PTSD patient or advocate on the IRB or by consulting with experiential experts on protocols involving PTSD patients.

Safeguards for increased susceptibility to research risks

The IRB is charged with ensuring that the protocol is safe enough and that the risk-to -benefit ratio is low enough to ethically justify moving forward with the research. If a study is approved, two methods for overseeing the safety of subjects are built into current regulations: data and safety monitoring. These methods can be accomplished through Data Safety Monitoring Boards (DSMB) and adverse event reporting. DSMBs provide ongoing independent monitoring of research data to make sure that there are no unanticipated risks. Researchers are also required to report all adverse events to the IRB, which is responsible for assessing the nature of the adverse event and for requiring changes to the study when indicated by the updated risk and benefit assessment.

Another protection mentioned in the Common Rule, VHA Handbook 1200.05, and other guidance documents is the inclusion of relevant expertise in IRB deliberations either through membership or consultation. The inclusion of scientific or clinical expert advice is especially pertinent for understanding the clinical condition under study and accurately assessing study risks.

Another way to ensure that potential subjects will not be harmed in the research process due to a specific clinical circumstance of the patient is to consult with the patient's health care providers. A patient's therapist, psychiatrist, or primary care provider can be consulted about whether a patient's participation in a particular study is likely to have a negative impact upon the patient's condition or treatment, including a disorder like PTSD. This mechanism to ensure clinical safety can limit the autonomy

and privacy of potential subject and so should be used with specific justification and be part of the voluntary consent process and materials.

ADDITIONAL RECOMMENDATIONS

The Work Group was unable to assess whether there is a need for further information or resources to enable VA researchers and IRBs to fully implement the considerations and protections for vulnerable populations specified in regulation and policy. Therefore, in addition to the recommendations above, the Work Group also recommends that VHA disseminate this report and conduct a needs assessment of researchers and IRBs, informed by veterans, to discern what information and resources are required, and in what form they should be delivered.

Specifically, the Work Group makes the following general recommendations:

1. The Work Group recommends that this report be disseminated to the VA and affiliate IRBs and the interested public.

2. The Work Group recommends that VHA's Office of Research and Development conduct an educational needs assessment to determine what further information and resources, if any, researchers and IRBs need to implement the considerations and protections for vulnerable populations specified in regulation and policy. Such information may relate to PTSD specifically or to the assessment of vulnerability among subject populations more generally. The

assessment should have input from veterans who have participated in or been recruited for research.

3. IRBs should continue to review protocols involving veterans with PTSD with the same care and attention with which they review other protocols, consistent with current regulation and policy pertaining to the protection of human research subjects, including ensuring that the review process is informed, as appropriate, by both scientific/clinical expertise and experiential/advocacy expertise relating to veterans with PTSD.

4. If an IRB determines that veterans with a diagnosis of PTSD have an increased susceptibility to the risks associated with a particular research study, as described under Charge Question 2 and Consensus Recommendation 2 above, the IRB should add safeguards particular to the study to protect veterans with PTSD in that study.

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APPENDIX A

National Center for Ethics in Health Care Work Group on PTSD and Vulnerable Populations in Research July 2008

OFFICIAL DESIGNATION: National Center for Ethics in Health Care Work Group on Defining Whether Veterans with a Diagnosis of Post Traumatic Stress Disorder are a Vulnerable Population for the Purpose of the Protection of Human Subjects in Research (hereinafter, "Work Group on PTSD and Vulnerable Populations in Research").

OBJECTIVES AND SCOPE OF ACTIVITY: On behalf of the Under Secretary for Health (USH), the National Center for Ethics in Health Care (Ethics Center) will convene a Federal work group to examine the participation of veterans with PTSD in research at VHA. The work group will consist of Federal experts in research ethics (in particular, the ethics of research with vulnerable populations), the protection of human subjects, clinical treatment and management of PTSD in veterans, and research on PTSD. The work group will receive formal testimony, input, and feedback on these same topics from non-federal experts individually. The work group will take this input into consideration in the development and refinement of recommendations made to the USH. Only the work group members may be involved in the active deliberation over and approval of recommendations.

BACKGROUND AND RATIONALE: The Veterans Health Administration (VHA) is authorized by law (38 USC 7303) to support research that advances health care for veterans and the Nation. Exposure to combat leads to specific conditions and health concerns for which veterans seek care from VHA. Research focused on understanding these conditions and developing effective treatments to improve the health and functioning of our veteran patients is a prime focus of research in VHA.

In carrying out its research obligations, VHA abides by the Federal Policy for Protection of Human Subjects of Research (the Common Rule) and the principles outlined in the Belmont Report and the Nuremberg Code. The rights and welfare of all persons participating in research at VHA are vigorously protected. All research involving human subjects complies with all federal regulations and VA requirements that address the protection of human subjects (38 CFR 16 and 45 CFR 46, Subpart A and implementing policies included in VHA Handbook 1200.5).

About one third of all VA patients have a mental health diagnosis. Of those patients, almost one quarter have a diagnosis of PTSD, and many patients with PTSD suffer from concomitant conditions such as alcohol, drug and tobacco abuse. PTSD is associated with exposure to traumatic events such as those experienced in combat and therefore is a common diagnosis among our veteran population. Therefore, conducting research in this patient population in an effort to develop effective treatments and programs to improve their functioning is a high priority for VHA and it is consistent with Congressional intent for our research portfolio.

However, some have raised concerns about whether veterans with a diagnosis of PTSD should be considered a "vulnerable population" for the purpose of applying guidelines for the protection of human subjects in research. Others have suggested that veterans with a diagnosis of PTSD should be afforded specific consideration and/or extra protections under VHA guidance to protect human subjects in research. Some have even questioned whether, given the potential vulnerability of patients with PTSD, it is ever ethical to perform research on VA patients with PTSD.

This Work Group will examine this tension between the need to study veterans with PTSD to help improve their condition and the need to protect veterans with PTSD from risk given their potential vulnerability as research participants.

TIME FRAME AND WORK PROCESS: The work group will first be convened 45 days after the approval of this charge. The work group will conclude its efforts 105 days after the approval of this charge. The work group will meet three times. Every effort will be made to convene the work group in person but LiveMeeting or video conference and teleconference capability will be used to ensure full participation by all work group members under the time frame described.

During the first meeting, work group members will receive testimony and individual comments from experts and consider these opinions in light of the specific charge and questions to the work group. During the second meeting, the work group will deliberate and develop draft recommendations for the USH. During the third meeting, the work group will receive input and feedback from experts on an individual basis with respect to the draft recommendations under consideration. The work group will consider this individual input from expert witnesses in the final deliberations and agreement on recommendations. The Ethics Center will submit a final report to the USH on October 31, 2008, summarizing the findings and recommendations of the Work Group on PTSD and Vulnerable Populations in Research.

APPROVAL: Any changes in objectives, scope, or membership of work group members must be approved by the Under Secretary for Health.

WORK GROUP MEMBERS: The Federal employees listed below will be invited to serve as members of the Work Group on PTSD and Vulnerable Populations in Research.

Department of Veterans Affairs

Ellen Fox, MD (Chair)
Chief Ethics in Health Care Officer
National Center for Ethics in Health Care
VA Central Office
Washington, DC

Joel Kupersmith, MD
Chief Research and Development Officer
VA Central Office
Washington, DC

Charles Marmar, MD
Director for PTSD Activities
Sierra Nevada MIRECC
Vice Chair and Professor of Psychiatry
University of California, San Francisco
San Francisco, CA

Other Federal Agencies:

H. Westley Clark, MD, JD, MPH
Director, Center for Substance Abuse Treatment
SAMHSA
Rockville, MD

Sara F. Goldkind, MD, MA
Senior Bioethicist
Food and Drug Administration
Rockville, MD

Christine Grady, MSN, PhD
Head, Section on Human Subjects Research
Department of Bioethics
National Institutes of Health
Bethesda, MD

Robert Ireland, MD, DMin, MA, COL MC USAF
Director, Mental Health Policy
Department of Defense
Arlington, VA

Farris Tuma, ScD
Chief, Traumatic Stress Research Program
National Institutes of Mental Health
Rockville, MD

Capt. Paul Andreason, MD
Compliance Oversight Coordinator
Office of Human Research Protections
Rockville, MD

Staff:

Sherrie Hans, PhD
Deputy Chief Ethics in Health Care Officer
National Center for Ethics in Health Care
VA Central Office
Washington, DC

Douglas P. Olsen, RN, PhD
Nurse Ethicist
National Center for Ethics in Health Care
VA Central Office
Washington, DC

OUTSIDE EXPERTS: The following outside experts will be invited to provide testimony to the work group and/or feedback on the draft recommendations put forward by the work group. The Ethics Center may also hire outside experts on a temporary basis to conduct work and produce draft documents on behalf of the workgroup and otherwise act as staff to the Committee.

Paul S. Appelbaum, MD
Professor of Psychiatry
Director, Division of Psychiatry, Law and Ethics
Department of Psychiatry
Columbia University College of Physicians and Surgeons
New York, NY

Arthur Caplan, PhD
Director, Center for Bioethics
University of Pennsylvania
Philadelphia, PA

Thomas A. Mellman, MD
Professor and Vice Chair for Research
Department of Psychiatry
Howard University
Washington, DC

David Matcher, MD
Director and Professor of Medicine
Center for Clinical Health Policy Research
Duke University
Durham, NC

John H. Mather, MD, CIP, FACPE
President, Uni-CORN LLC
233 B Constitution Ave., NE
Washington, DC 20002

David H Strauss, MD
Chairman, IRB at NY State Psychiatric Institute
Co-Chair, OHRP's Subcommittee on Inclusion of Individuals with Impaired Decision-Making in Research (SIIIDR)
New York, NY

Thomas H. Murray, PhD
President, The Hastings Center
Garrison, NY

VHA EXPERTS: The following internal experts will be invited to provide testimony to the work group and/or feedback on the draft recommendations put forward by the work group.

Alfonso R. Batres, PhD, MSSW
Chief Readjustment Counseling Officer
VA Central Office
Washington, DC

Matthew Friedman, MD, PhD
Executive Director
National Center for PTSD
White River Junction, VT

Ira Katz, MD, PhD
Deputy Chief Patient Care Services Officer for Mental Health
VA Central Office
Washington, DC

Joan P. Porter, MSC, DPA, MPH, CIP, CIPP/G
Deputy Chief Officer, Office of Research Oversight
VA Central Office
Washington, DC

MEMBERS RESPONSIBILITY: Work group members will deliberate together and provide consensus recommendations to the USH on the following questions:

1. Is it ethically permissible for VHA to support the conduct of research on veterans with PTSD?
2. Are veterans with a diagnosis of PTSD considered "vulnerable" for the purpose of applying guidelines for the protection of human subjects in research?

3. Should veterans with a diagnosis of PTSD be afforded specific considerations and/or extra protections under VHA guidance to protect human subjects in research?

c. If yes, what criteria would trigger the application of these special considerations and extra protections?
d. If yes, what specific considerations and extra protections should be afforded, and what mechanism would be used to implement them?

ADMINISTRATIVE SUPPORT RESPONSIBILITY: VA members of the work group will be provided administrative support from the Ethics Center. Other federal employees will depend on administrative support from his/her parent agency. Non-federal participants (experts) will be responsible for providing their own administrative support but will be reimbursed for approved travel costs and paid a modest honorarium for their participation.

CONCUR / NON-CONCUR:

_____ _____
Michael J. Kussman, MD, MS, MACP Date
Under Secretary for Health
Veterans Health Administration

APPROVED / DISAPPROVED:

_____ _____
James B. Peake, M.D. Date
Secretary
Department of Veterans Affairs

APPENDIX B

Human Research Protection in VA

The Department of Veterans Affairs has long been at the forefront of human research protection. Decades ago, VA created Human Rights Committees to protect the rights and welfare of individuals volunteering to participate in VA studies. In 2003 the VA Office of Research Compliance and Assurance became the Office of Research Oversight (ORO), and the VA Office of Research and Development (ORD) created the Program for Research Integrity Development and Education (PRIDE) to enhance protections for VA human research subjects.

VA has increased funding for human research protection activities performed by ORO and ORD from approximately $7.8 million in FY 2003, $10.5 million in FY 2007, and a projected $12.8 million in FY 2008. In addition, VA currently spends an estimated $14 million per year for local VA facilities' human research protection activities.

Program for Research Integrity Development and Education (PRIDE)

PRIDE is responsible for:

1) Developing policy on human research protection, and providing guidance on the ethical principles of human research to employees at all VA facilities that perform human research

PRIDE has provided guidance in many forms as listed under guidance, training and education below. PRIDE staff are continuously available to answer phone and email questions from the field and, when appropriate, perform site visits. It also posts relevant resources on its web site at http://www.research.va.gov/programs/pride/default.cfm.

In July 2003, PRIDE published VHA Handbook 1200.5, *Requirements for the Protection of Human Subjects in Research*. This handbook is currently being revised.

Other policies from ORD include the following Directives:

2003-031, *Establishment of a Facility Human Protections Program.* This directive requires that VA facilities cannot accept industry grants, including grants funded through nonprofit corporations (NPCs), that are not sufficiently funded to support the Facility Human Protections Program.

2007-040, *Appointment of Facility Information Security Officer (ISO) and Privacy Officer to the Institutional Review Board (IRB or the Research and Development (R&D) Committee.*

2008-064 *Research Compliance Officers and the Auditing of VHA Human Subjects Research to Determine Compliance with Applicable Laws, Regulations, and Policies*

2008-014, *Auditing of VHA Human Subjects Research to Determine Compliance with Applicable Laws, Regulations, and Policies*. (In concurrence as of October 31, 2008, WebCIMS #410135).

2008-072 *Notification of Research Personnel about VA Pharmacy Benefits Management (PBM) Safety Issues and Adverse Events Related to Interventional Human Subjects Research Studies*

2008-079 *Research Participant Outreach Program* (In concurrence as of October 31, 2008, WebCIMS # 410654 as of 10/31/2008).

2) Providing guidance, training and education in human research protection throughout VA

ORD requires annual training in both human subjects protection and Good Clinical Practices (GCP) for all VA staff (e.g., investigators, research office staff, IRB members and staff, Research and Development Committee members and staff, etc.) who are involved in human research, with the exception of secretarial support. PRIDE's Center On Advice and Compliance Help (COACH) is responsible for creating the courses to fulfill this annual requirement. The following is a list of COACH guidance, training and educational programs on human research protection, research ethics and standards for protecting human subjects since its inception in 2003:

In-person Courses

- **2009 ORD Local Accountability for Research Meeting.** January 13-14, 2009, meeting for all Medical Center Directors, Chiefs of Staff, ACOS/R&D, AO/R&D, and Research Compliance Officers of the 117 VA facilities that perform research. Estimate over 600 attendees.

- **Local Accountability for Research Meetings.** Fall and Winter 2007-08. ORD presented six 2-day meetings. There were 611 attendees.

- **Local Accountability for Human Research Protection at VA Facilities Meetings.** Fall and Winter 2006-07, PRIDE held four regional 2-day meetings. There were 336 attendees.

- **Human Research Protection Program (HRPP) 101 Course.** COACH presented eight 2-day courses on the basics of human research protection regulations, guidance, and implementation for individuals new to their human research protection responsibilities from Oct 2004 to June 2008. There were a total of 493 attendees. This course will be offered two times each year.

- **Human Research Protection Program (HRPP) 201 Course.** COACH presented one 2-day course on more advanced human research protection regulations, guidance, and implementation for individuals with experience in human research protection on September 8-9, 2008. There were at total of 31 attendees. This course will be offered two times each year.

- **VA IRB Chair Meetings.** COACH held a one-day training meeting for VA IRB Chairs in November 2006 for 68 VA IRB Chairs, and a 2-day training meeting for IRB Chairs in April 2004 for 85 VA IRB Chairs.

- **Association for the Accreditation of Human Research Protection Programs (AAHRPP) Getting Started Meetings.** AAHRPP presented four one-day workshops to prepare VA facilities in 2006 and 2007 for the AAHRPP accreditation process. There were 294 attendees.

- **Research Compliance Officer (RCO) Training.** COACH presented a 2-day conference on human research protection for RCOs in Las Vegas, Sept 2005. There were 102 attendees.

- **Associate Chief of Staff for Research and Development (ACOS/R&D) Training.** COACH presented sessions on human research protection at the ACOS/R&D meeting in January 2004. There were 120 attendees.

- **Administrative Officer for Research and Development (AO/R&D), Research Compliance Officer and Research Pharmacist Training.** COACH presented sessions on human research protection at AO/R&D meetings in 2003 and February 2004. There were 346 attendees.

- **VA Day at Public Responsibility in Medicine and Research (PRIM&R).** COACH presented a one-day conference on human research protection at the annual PRIM&R meeting in October 2004. There were 87 attendees.

- **ACE! (Accreditation Consulting Experts!) Human Research Protection Training.** COACH's ACE! Team presented four 2-day courses on human research protection using the National Committee for Quality Assurance (NCQA) standards as teaching tools in 2003 and 2004. There were 330 attendees.

- **Leadership Training.** COACH presented two VA Secretary-mandated Human Research Protection courses for VHA leadership in 2003. Attendees were VISN Directors, Medical Center Directors, Associate Medical Center Directors and Chiefs of Staff. There were 580 attendees.

- **Train-the-Trainer Course.** NCQA presented a 1.5-day course in September 2003 for PRIDE, the VHA Office of Research Oversight (ORO), and the field. There were 35 attendees.

Online Courses

- **Good Clinical Practices (GCP) and Ethical Principles of Human Research Protection.** In 2003, COACH developed its first online course for annual training for VA staff involved in human research. It focused on GCP and the ethical principles of human research protection. At total of over 15,600 individuals completed the course within 90 days after it became available. Subsequently, COACH incorporated its GCP module into the national Collaborative IRB Training Initiatives (CITI) course. All GCP and Human Subjects Protection online training moved to CITI in January 2007. This has allowed co-registration with participating academic affiliates so that both sets of requirements can be fulfilled simultaneously. Each year since 2003, over 15,000 individuals have received course credits for online GCP and human research protection training.

- **VA Research Data Security and Privacy Course.** In February 2007, PRIDE developed a course in VA Research Data Security and Privacy. All VHA research personnel were mandated to take this course by June 12, 2007. It was offered via Webinar, in-person, and on-line through the Employee Education System (EES). There were 29,929 individuals completing this course.

Site Visits

- Each year from 2004 through 2007, COACH conducted an average of 14 site visits to provide help for local human research protection programs.

3) Ensuring that all VHA Human Research Protection Programs become accredited

In 1999, Dr. Kenneth Kizer, VA's Under Secretary for Health, announced at a Congressional hearing that VA would "establish an external accreditation program for VA research involving human subjects." Currently, VA leads all federal agencies in obtaining accreditation of its HRPPs and is the only Federal agency that mandates accreditation.

From 2000 to 2005, VA had a contract with the National Committee for Quality Assurance (NCQA) to provide accreditation. From 2003 until the contract ended in 2005, 58 VA facilities' HRPPs providing services to 71 VA facilities with FWAs were accredited by NCQA.

After an open competitive contracting process, on December 1, 2005, the VA awarded the HRPP accreditation contract to the Association for the Accreditation of Human Research Protection Programs (AAHRPP). As of May 31, 2008, 112 of 117 VA facilities with FWAs were either accredited by AAHRPP or had submitted an application to AAHRPP. The five that have not submitted applications have new IRB arrangements and will undergo the AAHRPP process after the new arrangements have been in place for several months.

As of September 12, 2008, AAHRPP has awarded accreditation to 58 VA facilities that provide HRPP services for a total of 72 VA facilities with FWAs. The VA is the only federal agency that mandates accreditation. In total, including VA facilities, AAHRPP has accredited 138 organizations covering over 600 entities.

4) Creating a VA Central IRB

VA has created a Central IRB that reviewed its first project in August 2008. Its purpose is to improve the lives of veterans by enhancing the quality of human research protection in VA multi-site research projects. The VA Central IRB will provide expert ethical and scientific review of VA multi-site projects while ensuring local issues are addressed. By enhancing the efficiency of IRB review for these projects, it also has the potential to facilitate faster translation of research results to advancements in clinical care.

Other advantages of the VA Central IRB include:

- More efficient IRB approval of notices to be sent to research subjects (e.g., new information about the project, changes in the protocol or informed consent, etc.)
- Earlier identification of trends in adverse events
- Centralized investigator accountability

Currently, the VA Central IRB has 20 voting members, including 2 co-chairs, and 6 nonvoting members with expertise in privacy, the law, ethics, regulatory affairs, information security, and information systems. Four of the 20 VA Central IRB members are veterans.

PRIDE staff have conducted a series of Webinars to provide guidance to 58 local VA facilities on how they can use the VA Central IRB as one of their IRBs of record. To date, 26 facilities have completed the process of signing up to use the VA Central IRB as an IRB of record. PRIDE staff have conducted another series of Webinars designed to guide VA investigators on the VA Central IRB application process.

APPENDIX C

VA Research at the Forefront of Understanding PTSD

(Excerpted from Dr. Marmar's Written Testimony to the Work Group)

- VA investigators have played a major role in determining the course and complications and need for services for veterans with PTSD beginning with the landmark National Vietnam Veterans Readjustment Study, studies of PTSD and related problems in Persian Gulf War veterans, and more recently the rates of PTSD in returning Iraq and Afghanistan veterans.
- VA funded research has led to advancements in cognitive behavioral therapy, cognitive processing therapy, and group psychotherapy for PTSD.
- VA research has informed VA decision making in the allocation of clinical resources for the care of traumatized war veterans.
- VA research has established the impact of PTSD on the families of veterans.
- VA research experts were key members of the DSM-III, III-R and IV committees that established the diagnostic criteria for PTSD.
- VA supported research has led to advances in destigmatizing PTSD and related mental disorders in veterans, improving access to care, integration of mental health care into primary care, using technology including telemental health to bring care to underserved veterans in rural areas, and improving diagnostic screening and training of primary care and specialty care staff in VA to better co-manage PTSD.
- VA research has defined the evidence-based measures used to diagnose PTSD.
- VA research has advanced the understanding of the pathophysiology of PTSD, including the neurocircuitry of resilience and vulnerability to PTSD.
- VA research has helped to establish the importance of selective serotonin reuptake inhibitors, mood stabilizing agents, sedative hypnotics, and adrenaline blocking agents in the treatment of PTSD.

APPENDIX D

PTSD Diagnostic Criteria from DSM-IV-TR

Diagnostic Criteria for 309.81 Post Traumatic Stress Disorder

A. The person has been exposed to a traumatic event in which both of the following were present:

(1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others.
(2) the person's response involved intense fear, helplessness, or horror. **Note:** In children, this may be expressed instead by disorganized or agitated behavior.

B. The traumatic event is persistently reexperienced in one (or more) of the following ways:

(1) recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. **Note:** In young children, repetitive play may occur in which themes or aspects of the trauma are expressed.
(2) recurrent distressing dreams of the event. **Note:** In children, there may be frightening dreams without recognizable content.
(3) acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated). **Note:** In young children, trauma-specific reenactment may occur.
(4) intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.
(5) physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:

(1) efforts to avoid thoughts, feelings, or conversations associated with the trauma.
(2) efforts to avoid activities, places, or people that arouse recollections of the trauma.
(3) inability to recall an important aspect of the trauma.
(4) markedly diminished interest or participation in significant activities.
(5) feeling of detachment or estrangement from others.
(6) restricted range of affect (e.g., unable to have loving feelings).
(7) sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span).

D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:

(1) difficulty falling or staying asleep.
(2) irritability or outbursts of anger.
(3) difficulty concentrating.
(4) hypervigilance.
(5) exaggerated startle response.

E. Duration of the disturbance (symptoms in Criteria B, C, and D) is more than 1 month.

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

Acute: if duration of symptoms is less than 3 months

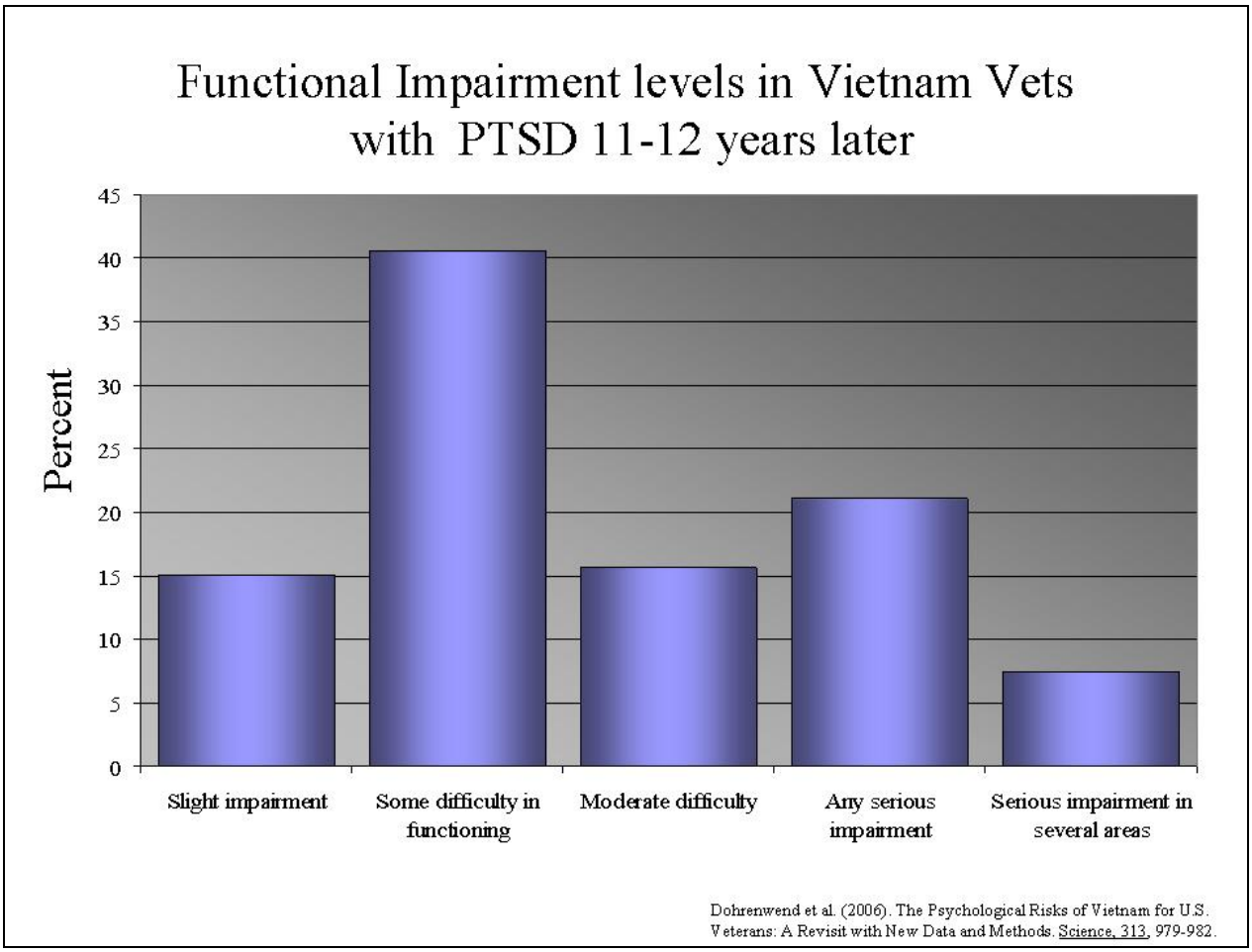
Chronic: if duration of symptoms is 3 months or more

Specify if:

With Delayed Onset: if onset of symptoms is at least 6 months after the stressor

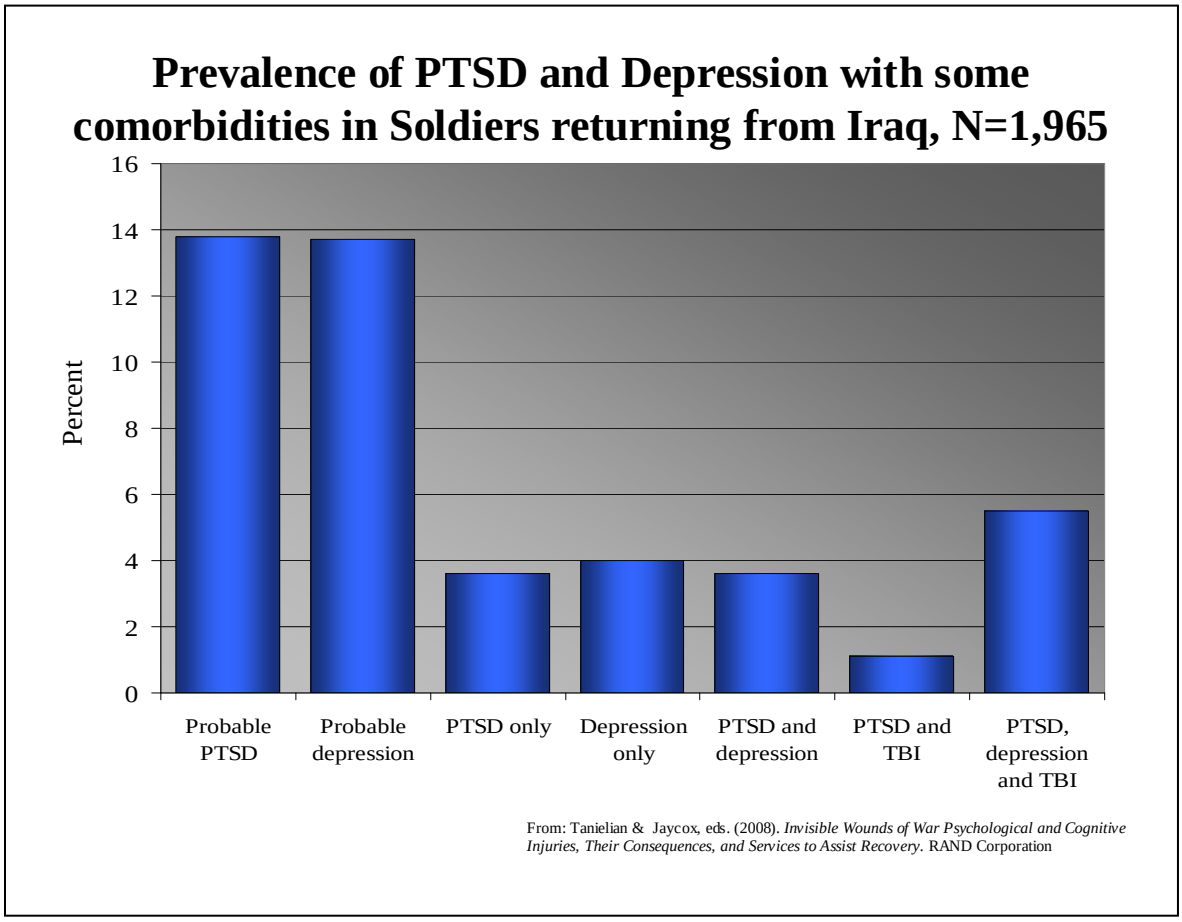
APPENDIX E

Variations in Functional Impairment in Vietnam Veterans with PTSD



APPENDIX F

PTSD Comorbidities in Troops Returning from Iraq



Department of Veterans Affairs

CONCURRENCE AND SUMMARY SHEET

SUBJECT: Report and recommentdations of the Work Group on PTSD and Vulnerable Populations in Research

NAME OF ADDRESSEE (For Correspondence Only)

TO BE COMPLETED BY EXECUTIVE SECRETARIAT (001B)

REMARKS	CONTROL NO.	NAME OF REVIEWER

CONCURRENCES - TO BE DETERMINED BY THE ORIGINATING OFFICE

CONCURRENCE REQUIRED	TITLE OR ORGANIZATIONAL ELEMENT	MAIL ROUTING SYMBOL	DATE IN	SIGNATURES		DATE OUT
				CONCURRENCE	NONCONCURRENCE	
X	VETERANS HEALTH ADMINISTRATION	10				
	VETERANS BENEFITS ADMINISTRATION	20				
	NATIONAL CEMETERY ADMINISTRATION	40				
	INSPECTOR GENERAL	50				
	ASSISTANT SECRETARY FOR PUBLIC AND INTERGOVERNMENTAL AFFAIRS	002				
	ASSISTANT SECRETARY FOR MANAGEMENT	004				
	ASSISTANT SECRETARY FOR INFORMATION AND TECHNOLOGY	005				
	ASSISTANT SECRETARY FOR HUMAN RESOURCES AND ADMINISTRATION	006				
	ASSISTANT SECRETARY FOR POLICY, PLANNING, AND PREPAREDNESS	008				
	ASSISTANT SECRETARY FOR CONGRESSIONAL & LEGISLATIVE AFFAIRS	009				
	BOARD OF VETERANS' APPEALS	01				
	GENERAL COUNSEL	02				
	BOARD OF CONTRACT APPEALS	09				
	VETERANS SERVICE ORGANIZATION LIAISON	00C				
	WHITE HOUSE LIAISON	WHL				
X	OFFICE OF RESEARCH AND DEVELOPMENT	12		O'Leary		11/13/08
X	OFFICE OF RESEARCH OVERSIGHT	10R		Tom Puglisi		11/05/08
X	READJUSTMENT COUNSELING	15		Charles Flora		11/17/08
X	PATIENT CARE SERVICES, MENTAL HEALTH	11		Stanlie Daniels		11/14/08
		10A		/s/ Gerald Cross		12/5/08

ACTION BY OFFICE OF THE SECRETARY (*Do NOT use for Correspondence*)

ACTION TAKEN	SIGNATURE	DATE
☐ APPROVED ☐ DISAPPROVED		

VA FORM
May 2003 (RS) **4265**

Department of Veterans Affairs

Memorandum

Date: February 5, 2009

From: Chief Ethics in Health Care Officer (10E)

Subj: Work Group on PTSD and Vulnerable Populations in Research

To: Under Secretary for Health (10)

1. I am pleased to submit for your information and review, the report and recommendations of the work group on Post Traumatic Stress Disorder (PTSD) and Vulnerable Populations in Research. VHA's response plan to the recommendations of the work group is attached to this memo.

2. The work group, initiated at the request of the Secretary of Veterans Affairs, met three times from September 2008 to October 2008 to examine the ethical concerns regarding the inclusion of veterans with PTSD in research at the Veterans Health Administration (VHA). The work group consisted of nine federal employees from within VHA and other federal agencies, including the Food and Drug Administration, the National Institutes of Health, and the Department of Defense.

3. The work group concluded that it is essential to do research in VHA on PTSD and that it is ethical to include veterans with PTSD in research. Suggestions are offered for ways to ensure VA applies protections for these veterans when it is appropriate to trigger such protections.

4. The report and its recommendations were approved by the full work group on October 31, 2008. The report and VHA response plan was approved in concurrence on November 21, 2008, by the Office of Research and Development, the Office of Research Oversight, Patient Care Services (Mental Health), and the Office of Readjustment Counseling.

5. The National Center for Ethics in Health Care requests that the Under Secretary for Health accept the report of the work group and approve the response plan, summarized in the attachment to this memo.

/s/ Ellen Fox

Ellen Fox, MD

VA FORM MAR 1989 **2105**

Work Group on PTSD and Vulnerable Populations in Research (417608)

Request approval of VHA's response plan to the recommendations of the Work Group on PTSD and Vulnerable Populations in Research.

Approve/Disapprove:

/s/ Michael J. Kussman
Michael Kussman, MD, MS, MACP
Under Secretary for Health

2/19/09
Date

Attachment(s)

VHA Response plan to the recommendations of the Work Group on PTSD and Vulnerable Populations in Research