ATTACHMENT 6

ATTACHMENT 6.1

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ATTACHMENT 6.2

NATIONAL HEART, LUNG, AND BLOOD INSITUTE

STRATEGIC PLAN FY 2002-2006

Contents *and* Executive Summary
Introduction
Development & Progression of Disease
Diagnosis of Disease
Treatment of Disease
Maintenance of Health / Prevention of Disease
Translation of Research Results Into Practice
Reduction of Health Disparities
Research Workforce and Research Resources
Appendix

Maintenance of Health/Prevention of Disease

Goal 1: Increase understanding of how individual and organizational behavior affects the development and progression of risk factors for cardiovascular, lung, blood, and sleep disorders.
Morbidity and mortality from cardiovascular, lung, blood, and sleep disorders would decrease significantly if known risk factors could be controlled or prevented. A better understanding of how some lifestyles contribute to risk factor development would allow more effective interventions to be designed. The effects of years of poor diet, physical inactivity, or smoking are obvious. But other questions remain unanswered, such as what causes blood pressure and weight to increase with age; how genes, environment, and behavior interact to affect development of risk factors; and how diet, weight, sleep, and stress early in life affect risk development later on. Much is known about behaviors that are healthful and those that are not, but more effective methods are needed to help people replace unhealthful behaviors with healthful ones in the long-term.

Action:

Potential FY 2002 initiative:

- **Develop and test worksite and community-based interventions to promote weight loss and maintenance of weight loss.** Since about half the adult population in the U.S. is overweight, interventions are needed that will reach large numbers of individuals. Interventions at worksites and interventions involving community organizations, local governments, and the business community are able to reach a wide population. Innovative approaches are needed to promote population-wide improvement in long-term weight loss and increased physical activity. Interventions designed for minority individuals and low socioeconomic status (SES) populations are especially needed.

Additional action:

- Form a working group to evaluate research in organizational and workplace systems that could be applied to reduce behavioral risk factors, such as occupational stress and other health habits that contribute to heart, lung, and blood diseases.
- Hold a workshop to identify potential uses for improved environmental and behavioral measures in population-based epidemiologic studies.
- Analyze the relationship between behavioral and environmental factors early in life and cardiovascular disease risk factors later in life.
- Test interventions for maintaining long-term healthful behaviors.

- Test interventions for preventing the age-related rise in cardiovascular disease risk factors (e.g., rise in blood pressure during adulthood) and the increase in risk factor levels that occurs at key transitional times in life (e.g., reduction of physical activity during adolescence).
- Determine whether high intake of sodium during infancy is associated with higher levels of blood pressure later in life.

Goal 2: Determine how to combine lifestyle changes and medical management to prevent or reduce risk factors for cardiovascular, lung, blood and sleep disorders.
Improved methods are needed to combine medical intervention and lifestyle changes to treat patients. For example, antihypertensive medications are highly effective in controlling blood pressure, but increased physical activity, weight loss, and a diet high in fruits, vegetables, and low-fat dairy products can also contribute to lower blood pressure. Similarly, asthma medications are effective in preventing and treating asthma attacks, but avoidance of environmental triggers, development of coping skills, and learning techniques for proper use of asthma medications are also critical. Researchers need to study how best to combine these two approaches.

Action:
- Test whether transdermal (i.e., entering through the skin) estrogen therapy mitigates the thromboembolic events (i.e., events related to the obstruction of a blood vessel with thrombotic material) that occur during the first year of initiating oral estrogen hormone replacement therapy for women with coronary artery disease.
- Investigate the influence of declining cognitive functioning that occurs with age, especially observed among individuals with high blood pressure, on effectiveness of behavioral risk factor management.
- Test whether combined medical and lifestyle management of cholesterol levels is more effective than medical management alone, and whether the effects can be sustained over time.
- Test whether combined medical and lifestyle management of sleep disturbances is more effective than medical management alone, and whether the effects can be sustained over time.

Goal 3: Continue to improve the safety and supply of blood for transfusion.
An estimated 3.8 million Americans receive blood transfusions annually. Yet, improvements in transfusion medicine are still needed. Adverse immune responses in patients happen too frequently; crises due to severe reductions in the nation's blood supply occur periodically; and the presence of pathogens in the blood supply remains a problem. Although rigorous scrutiny of blood donors and the screening of donated blood has significantly reduced morbidity and mortality due to transfusion-associated infectious agents, transfusion practices still carry a small, but unacceptable, risk of infection from transfusion-transmitted viruses. Procedures are currently available, such as the use of photochemicals, that destroy virus infectivity with minimal adverse effects on the blood components. Cost-efficient technological advances are needed to permit the use of photochemicals, as well as other inactivation procedures, in large-scale blood centers.
Action:

Potential FY 2002 initiative:
- **Enhance understanding of blood donor motivations to improve donor recruitment and retention and increase blood donations.** Blood donations in the U.S. have gradually declined over the past 10 years. Potential projects to study blood donor recruitment and retention and ways to increase blood donations include:
    - intervention to increase the frequency of blood donations by making an appointment for a donor's next donation at the time of donation and sending reminder postcards before the appointment

- study of the use of double red blood cell collection by apheresis, a procedure that can effectively double the units of blood derived from a donor in a single procedure. (In apheresis, blood is drawn through a needle in the arm, much like donating whole blood. The blood is processed through a machine that separates the different components so that the required platelets or white cells can be removed. The rest of the blood is returned to the donor, usually through a needle in the other arm.)

Additional action:

- Determine reasons why "at-risk" blood donors continue to donate.
- Investigate how to motivate "low-risk" populations to start (or to continue) donating blood or marrow.
- Continue research to inactivate viruses and other transfusion-transmitted pathogens in blood components while maintaining the therapeutic effectiveness of these components.

Goal 4: Develop knowledge leading to more comprehensive dietary recommendations for prevention of cardiovascular, lung, and blood diseases.

Advice about what to eat is everywhere—from health messages in newspapers to food labels in grocery stores. Yet a number of important nutritional issues with implications for cardiovascular health remain unresolved. For example, it is not clear which dietary components should replace saturated fats so that optimal cholesterol levels will result. Also unknown are the proportions of proteins, fats, and carbohydrates in the diet that lead to healthy blood pressure levels. It has been speculated that antioxidants slow the development of atherosclerosis, but how diets should be modified to increase antioxidant levels remains to be determined. In addition, research is needed on the effects of dietary components on subclinical disease (disease in its early stages, even before symptoms are detectable) and how the diets of special populations affect their disease risk. Nutritional factors also affect the lungs; they appear to have an effect on the immune system and may have a direct role in the development of a variety of lung diseases. For example, vitamin deficiencies have long been thought to contribute to the development of bronchial dysplasia (a chronic lung disease) in pre-term infants. More research in needed to clarify the role of dietary factors in lung diseases.

Action:

Potential FY 2002 initiative:

- **Determine an optimal diet to prevent heart disease.** Intervention studies are needed to compare the long-term (at least 3 years) effects of diets that vary in proportions of proteins, fats, and carbohydrates. The effects of the diets on a number of risk factors assessed as a group, rather than individually, should be evaluated; the risk factors of interest include blood lipids, blood pressure, glucose tolerance, weight, homocysteine (an amino acid), Lp(a) (a lipoprotein correlated with increased risk of heart disease at very high levels), and immune function. The effect of the diets on some measure of subclinical atherosclerosis should also be evaluated. Dietary effects on specific population subgroups, defined by race, sex, age, and risk factor levels, need to be assessed.

Additional action:

- Improve methodology currently used in dietary research, including self-reporting methods (e.g., use of new technologies, like bar code scanners and disposable cameras, to improve dietary data collection) and biomarkers of dietary components (e.g., reduction of variability between labs and improved standardization of assays for nutrient biomarkers).
- Improve methodology for estimating nutrient intake from dietary supplements.
- Study dietary effects on development of subclinical disease in animal models.
- Study gene-diet interactions in animal models and in humans.

- Determine the efficacy of dietary components, at various points in the life cycle, in reducing development of subclinical disease and cardiovascular disease risk factors.

Goal 5: Determine how to prevent cardiovascular, lung, and blood diseases that occur during pregnancy.

It is estimated that up to five percent of pregnant women experience serious complications. The rates tend to be higher in older women and in women with pre-existing conditions such as diabetes or multi-fetal pregnancies. Some of the complications are related to cardiovascular, lung, and blood conditions and risk factors. For example, preeclampsia is a complication characterized by hypertension, edema, and/or excess serum proteins in the urine. Also, complications involving obstruction of a blood vessel, known as thromboembolic complications, occur in 1 to 2 of every 2,000 deliveries and are a major cause of death among women during and immediately after pregnancy. Research is needed to find ways to prevent these complications.

Action:
Potential FY 2002 initiative:

- **Study how to prevent the formation of blood clots (thrombosis) and fetal loss during pregnancy.** During pregnancy, changes occur in plasma concentrations and in the activities of several proteins (coagulation proteins) that tend to promote thrombosis. A number of genetic mutations that predispose an individual to thromboembolic disease have been identified. Recent investigations using genetic tools have shown that some coagulation proteins have functions related to embryonic development. These findings suggest an opportunity for researchers to improve maternal and fetal health by studying the role of coagulation proteins in embryonic development.

Additional action:

- Conduct clinical studies of therapies for controlling high blood pressure in women with hypertension who become pregnant.

ATTACHMENT 6.3

IRON QUESTIONNAIRE: DESCRIPTION OF EACH QUESTION OTEM, SOURCE AND GOAL

1. First time ever donated blood? Number of donations ever? Source: *REDS* Survey. This data is important to confirm the donor status: first time, reactivated or repeat.

2. Date of last donation? Source: *REDS* Survey. This data is collected to evaluate the association of the time between last donation and the current donor iron status.

3. Number of donations in the last 2 years? Source: *REDS* Survey. This data will help confirm the donor status and also relate the frequency of donation to the donor iron depletion.

4. Any apheresis donations? Source: *REDS* Survey. This data is useful to assess the red blood cell volume based on the type of donation: platelets, plasma, red cells, or a combination of these

5. Smoked at least 100 cigarettes in entire life? Any cigarettes smoked in the last 90 days? Number of days smoked in the last 30 days? How many cigarettes smoked per day? Source: *California Smoking Survey.* This data will provide basis for relationship between smoking behavior and donor iron status.

6. Food frequency questions, Any vitamins, supplements and aspirin taken in last 12 months and the frequency of intake? Source: NIH Diet History Questionnaire. This is a very important information to determine the iron status of the donor based on his dietary iron intake and also if the donor routinely consumes any vitamin supplements.

7. Menstrual history questions: Source: *NHANES,* Menstrual flow question: Mansfield-Voda-Jorgensen Menstrual Bleeding Scale.

8. Ever been pregnant? Source: *NHANES.* This question is designed to identify female donors who have ever been pregnant. This is important as pregnancy is related to the iron status and results in an iron loss of 700-1000 mg, equivalent to the donation of 3-4 units of blood.

9. Number of pregnancies? Source: *NHANES.* Female donors are asked the number of times they have been pregnant to assess the iron loss related to number of pregnancy.

10. Number of pregnancies resulting in live birth? Source: *NHANES.* Female donors are asked to give the number of pregnancies ending in live births. This data is important to differentiate these women with the ones who had miscarriages or abortions. This data is crucial as the iron loss varies for pregnancy resulting in

live birth to those resulting in miscarriages. Miscarriage or other earlier termination of pregnancy will have a lesser, but meaningful impact on body iron stores.

11. Date of birth of last baby born? Source: *NHANES.* Female donors are asked this question to relate their iron status to the time period between current donation and last pregnancy resulting in live birth.

ATTACHMENT 6.4

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Heart, Lung, and
Blood Institute
Bethesda, Maryland 20892

August 29, 2006

MEMORANDUM

TO: George Schreiber, Sc.D.
REDS-II DCC Principal Investigator

FROM: Traci Heath Mondoro, Ph.D.
REDS-II OSMB Executive Secretary

SUBJECT: SUMMARY OF PROTOCOL REVIEW

The Observational Study Monitoring Board (OSMB) for the Retrovirus Epidemiology Donor Study II (REDS II) met by conference call August 24, 2006 to review the REDS II protocol titled "Predicting Hemoglobin Deferral and Development of Iron Depletion in Blood Donors".

The REDS-II OSMB recommended that the study proceed and made the following recommendations.

- Consider adding text to Section E. 3 "Final Study Size" to acknowledge that measurement errors and the multiplicity of hypotheses to be examined decrease the power of the study relative to the values stated in the protocol, although not necessarily providing details about the extent of the degradation since this is an exploratory study.
- If there are substantial margins built into the sample size calculations then consider adding text to indicate why these concerns are unlikely to seriously compromise the most important features of the study.
- To increase the comfort level of the donors, add language to the informed consent document stating that no additional genetic testing will be performed on the sample.
- Consider eliminating the concept of using financial compensation to motivate donors who do not come in for the last follow-up visit. This gives the appearance of treating subjects within the same cohort differently.

The Institute accepted the OSMB recommendations.

If you have any questions regarding this approval, please contact the Project Officer, George J. Nemo, Ph.D. at nemog@nhlbi.nih.gov or 301-435-0065.