DEPARTMENT OF HEALTH & HUMAN SERVICES

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National Heart, Lung, and
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Bethesda, Maryland 20892

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Mr. Merrill Goozner
Director, Integrity in Science
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1875 Connecticut Avenue, NW, Suite 300
Washington, D.C. 20009-5728

Dear Mr. Goozner:

I am responding to the letter of September 23 addressed to Dr. Zerhouni, Director, National Institutes of Health, myself, and Dr. Cleeman, which was submitted by you for the signatories. The letter questions the validity of current Adult Treatment Panel III (ATP III) recommendations for cholesterol management developed by the National Cholesterol Education Program (NCEP) and requests that NCEP conduct a re-review of the data in the studies at issue. The NCEP is coordinated by the National Heart, Lung, and Blood Institute (NHLBI) on behalf of a national coalition of health-related non-profit organizations in the private and public sectors interested in reducing the toll from coronary heart disease (CHD) as well as other forms of atherosclerotic cardiovascular disease (CVD).

The letter raises two issues: whether the scientific basis for several recommendations is adequate, and concerns that the panel was influenced by conflict of interest arising from the interaction of panel members with industry. These two issues are addressed separately in this response.

I. The Scientific Basis for the Recommendations

The Institute does not agree with the letter's use of subgroup analysis, interpretation of the results of several of the clinical trials, and characterization of several recommendations of the ATP III update. Most importantly, the letter does not appear to appreciate the fundamental scientific rationale for the NCEP recommendations. We have incorporated our concerns in the responses addressing the letter's specific criticisms, which are shown in italics.

"We believe the evidence does not support extending these guidelines to women who are at moderately high risk of CVD (so-called "primary prevention")."

In describing the evidence for the benefits of lowering LDL cholesterol, the letter restricts its attention to subgroup analysis of the clinical trial results and conceptually separates primary and secondary prevention. By contrast, the approach of the NCEP is to review the entire body of scientific evidence in formulating recommendations, including animal, pathologic, genetic, and epidemiological studies and clinical trials. Studies utilizing gross pathology and histopathology have shown that atherosclerosis develops progressively beginning in late adolescence and early adulthood in both men and women, and the extent of atherosclerosis is correlated with the level of cholesterol and other risk factors.[1,2] Epidemiological studies such as the Framingham Heart Study have demonstrated that elevated cholesterol is a major risk factor for CHD in both

men and women**,** and women at moderately high risk experience cardiovascular events at the same rate as do men with that level of risk.[3,4]

There is abundant evidence from clinical trials in high-risk individuals that lowering LDL cholesterol with statins is significantly and similarly beneficial in both women and men.[5-7] There is also strong evidence from clinical trials demonstrating that lowering LDL cholesterol (by statins or other means) prevents heart attacks in men with or without prior heart disease.[8-11] In addition, a 1999 meta-analysis that combined the results of trials in primary prevention and high-risk individuals showed that LDL lowering produces similar reductions in CHD events in women and men and in older and younger patients.[12]

Since atherosclerosis is known to progress gradually over a lifetime, it is not consistent with the scientific evidence to maintain that the benefit of cholesterol lowering begins at the time a woman (or a man) has a clinical CHD event. What changes at the time of a heart attack is the absolute risk for future CHD events. The ATP III guidelines maintain, on the basis of all the evidence, that the relation of cholesterol to CHD risk is qualitatively similar in women (and men) with and without prior CHD, and the benefit of cholesterol lowering is present before the event as well.

It is a well-established principle in CVD prevention that, given similar relative risk reduction, the benefit of intervention is related to the absolute level of risk: the higher the risk, the greater is the benefit from risk reduction. A corollary of this principle is that the intensity of treatment should be matched to the level of risk. The level of absolute risk also determines whether the benefit of cholesterol lowering will be observable in the relatively short period of a clinical trial. If a woman's risk is high enough, as in the trials in which the participants had existing CHD, the benefit is seen within the trial period. The level of risk is what matters, not gender per se. It is true that the average woman has a lower risk for CHD events than the average man. That is why the NCEP guidelines set the threshold for cholesterol-lowering treatment according to future risk, and it takes more risk factors for a woman to reach the level of risk that would warrant the addition of drug therapy to the treatment regimen. But for the woman whose cholesterol level and other risk factors show that she is at moderately high risk, the fact that women as a group are at lower risk does not help her as an individual prevent a heart attack.

To be at moderately high risk, defined as having a 10-20 percent chance of a heart attack within 10 years, a woman has to have multiple major risk factors. For example, a woman who is 60 years old and has a high total cholesterol of 250 mg/dL and a below-average HDL cholesterol of 45 mg/dL, is a smoker, and has treated hypertension with a systolic blood pressure of 150 mmHg, would have a 10-year risk of 15 percent and be considered at moderately high risk. Such a woman with multiple risk factors and substantially elevated risk will require clinical management of her cholesterol level as well as her other risk factors to enable her to gain the benefits of treatment that have been demonstrated in the clinical trials**.**

The ATP III guidelines provide a practical tool, based on the Framingham Heart Study findings, for assessment of the 10-year risk for a heart attack in both men and women as part of evaluating the need for cholesterol-lowering therapy. In this way, the guidelines promote significantly improved treatment of women by enabling physician and patient to make a better match between the level of a woman's risk and the intensity of therapy than previously. According to ATP III, low-risk women are not generally candidates for intensive cholesterol-lowering drug therapy.

The overall results of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) demonstrated that moderately high risk individuals benefit from cholesterol-lowering drug treatment.[11] The letter cites the fact that, in ASCOT, the subgroup of women without heart disease did not show benefit in order to question whether women at moderately high risk should be treated. In reality, the women who participated in ASCOT had a 10-year risk of 5-6 percent, and were actually at low risk, not moderately high risk. Failure to show benefit in low-risk women in the short 3 years of the ASCOT study is thus not surprising.

In the absence of specific clinical trial evidence about moderately high risk women, guideline panels have two options: to exclude such women from treatment guidelines despite their having a 10-20 percent chance of suffering a heart attack in the next 10 years, or to rely on a combination of clinical trial and epidemiology data to make decisions. Considering the fact that as many women as men ultimately die from CVD, the ATP III panel chose the latter course. The alternative approach of insisting on waiting until clinical trial evidence becomes available specifically in moderately high risk women before regarding them as eligible for cholesterol lowering would mean that many women would have a potentially preventable heart attack before they are accorded the benefits of therapy. For many women, the first sign of heart disease is sudden death. Sound public health policy demands that the significant risk for illness and death in women be addressed with science-based prevention recommendations.

"We believe the evidence does not support extending these guidelines to older persons who are at risk of CVD (primary prevention)."

Clinical trials in high-risk individuals, such as the Heart Protection Study (HPS), provide strong evidence that cholesterol-lowering therapy is efficacious in older patients, for whom treatment confers significant benefit.[5-7,12-15] The sharp division between secondary and primary prevention that the letter authors would like to preserve is particularly untenable in older persons. Epidemiological data from the Framingham Heart Study show that individuals over 65 years of age are at significantly increased risk for heart attacks and death from CHD.[3] The average older man is at high risk (more than 1 in 5 will have a CHD event within 10 years) and the average older woman is at moderately high risk (more than 1 in 10 will have a CHD event within 10 years). This reflects the large burden of atherosclerotic plaque in the arteries of the average older person. Many older individuals with multiple risk factors, including elevated cholesterol, are at even higher risk than the average older person. As stated above with respect to women, a well-established principle in CVD prevention is that the benefit of intervention is related to the absolute level of risk: the higher the risk, the greater is the benefit from risk reduction. The combination of clinical trial and epidemiological evidence is especially applicable to cholesterol lowering in older persons, and provides the scientific basis for recommending therapy in this age group.

Excluding older individuals whose risk profile reveals that they are at moderately high risk from the cholesterol lowering recommendations would deny the benefits of therapy to the age group at greatest risk and would miss the opportunity to prevent or delay a large number of heart attacks. The ATP III update paper explicitly recognizes that "clinical judgment is required as to when to initiate intensive LDL-lowering therapy in older persons without CVD. Efficacy alone is not the key issue in this group. A host of factors must be weighed, including efficacy, safety, tolerability, and patient preference, in this age group." The application of clinical judgment is necessary, but excluding older individuals altogether from the recommendations is not supported by the scientific evidence.

The letter authors raise the specter of increased cancer risk from statin use in older individuals, citing a 25 percent increase in new cancers in the treatment group of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). As noted in the ATP III update paper, a meta-analysis of all trials with pravastatin, the agent used in PROSPER, and of all statin trials showed no increase in cancer incidence.[16] An analysis of each of the other statin trials individually also showed no increase in cancer risk. The letter criticizes the meta-analysis because it merges studies in younger populations with the patients in PROSPER, who were over 70. However, the HPS included as large a number of individuals who were over 70 and were treated with statin as did PROSPER, and more than half of the 20,000 participants in the HPS were over 65. The overall trial results showed no increase in cancer incidence.[5] Conducting a meta-analysis is the scientifically reasonable approach, rather than accepting a potentially chance result in a single study at face value.

"We believe the evidence in the five latest clinical trials for extending these guidelines to primary prevention of coronary heart disease in patients with diabetes is mixed."

The overall data from clinical trials document that patients with diabetes respond to cholesterol-lowering drug therapy with a significant reduction in risk for CVD. This has been shown conclusively in diabetics without known CVD both in the HPS[5] and in the Collaborative Atorvastatin Diabetes Study (CARDS),[17] which was published after the ATP III update paper. In addition, a 2004 meta-analysis showed that lipid-lowering drug therapy in primary prevention in patients with type 2 diabetes significantly reduced the risk for CVD events.[18]

Once persons with diabetes develop CVD, the rate of mortality from CVD is very high. Thus, in people with diabetes, even more than in other groups, the objective is to prevent the initial development of CVD. The trial evidence clearly shows that cholesterol-lowering therapy will help attain this objective. Failure to include diabetics in the recommendations would mean that many vascular events and subsequent deaths would not be prevented in this high-risk group.

The letter cites the non-significant risk reduction in subgroups of diabetics in three studies (ASCOT, PROSPER, and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [ALLHAT]) to question whether the evidence is adequate. It is not valid to use subgroup analysis of these studies in this way: ASCOT had a very small number of events; PROSPER comprised a relatively small number of participants with diabetes; and in the ALLHAT trial, there was only a small difference in mean cholesterol levels between the treated and the "usual care" group for reasons described below in the section on ALLHAT (pages 5-6).

In ASCOT, there were only 84 cardiovascular events in the participants with diabetes. In PROSPER, there were a total of about 600 individuals with diabetes in the treatment and placebo groups. By contrast, the HPS had 6,000 participants with diabetes, of whom approximately 2,900 had no history of vascular disease. CARDS had about 2,800 participants with diabetes, all without CVD. The findings from a small subgroup of a trial, in which random occurrences cannot be ruled out, should not be given equal weight with the significant results from much larger trials.

ALLHAT did not achieve its intended difference in cholesterol levels between the treatment and usual care groups and did not show an overall significant risk reduction. Therefore, the use of a subgroup analysis of diabetics from ALLHAT in order to argue that cholesterol lowering is not efficacious in people with diabetes is also not scientifically correct.

The letter states that "taking the HPS findings at face value, one death was prevented each year that 250 diabetic patients were treated with a statin," and it contrasts this clinical trial finding with an observational study that reported that "four times as many lives will be saved" by physical activity. The ATP III guidelines and update paper both emphasize the primacy of lifestyle changes in lowering cholesterol and reducing risk. Lifestyle and drug treatment are not competitive but complementary modalities. For diabetics, if lifestyle cannot produce sufficient risk reduction, the combination of drug therapy and lifestyle changes will produce significant benefit, as documented in the clinical trials.

The letter understates the benefit seen in the HPS trial. The HPS investigators estimated, on the basis of the trial findings, that cholesterol-lowering therapy with statin should prevent about 70 first and subsequent major vascular events (heart attacks, strokes, and revascularizations) in diabetics without CVD per 1,000 treated over 5 years, or more than 3 events prevented per year in 250 such treated diabetics. Therapy with this level of efficacy in preventing CVD events is worthwhile.

The science-based approach of the ATP III guidelines in including individuals with diabetes in treatment recommendations is echoed by the existing guidelines for cholesterol management from the American Diabetes Association[19] and the American College of Physicians.[20] The recommendations of the British Hypertension Society (BHS) for cholesterol management as part of blood pressure guidelines for patients with diabetes are more intensive than the ATP III recommendations. The BHS recommendations are: "In light of the high coronary event rates observed among many patients with type II diabetes, and the high long- and short-term fatality rates for such patients, it is recommended that patients with type II diabetes—diagnosed at least 10 years ago and/or aged 50 years or more—should be considered as CHD risk equivalents as far as lipid lowering is concerned, and hence should be treated as for secondary prevention. Other patients with type II diabetes could be considered as for primary prevention on the basis of an estimated risk threshold, but for simplicity regarding treatment threshold purposes, it is recommended to consider such patients as 'coronary equivalents.' Therapy should be titrated to lower total or LDL-cholesterol by 25% or 30%, respectively, or to <4.0 mmol/l (<155 mg/dL) or <2.0 mmol/l (<80 mg/dL), respectively, whichever is the greater reduction."[21]

Thus there is a broad agreement among expert groups that patients with diabetes should be offered cholesterol-lowering therapy, with cholesterol-lowering medication if necessary.

"We believe that the results of the ALLHAT study did not show a benefit from more than tripling the number of people taking statins (as recommended by the 2001 and 2004 NCEP updates)."

The letter does not reflect an adequate understanding of the design of the ALLHAT Lipid Lowering Trial.[22] ALLHAT was not a comparison of ATP III versus the ATP II guidelines released in 1993, and has no bearing on the new more aggressive regimens tested in PROVE-IT[23] and other ongoing trials. Patients in the active arm of ALLHAT received 20-40 mg/day of pravastatin -- a less aggressive regimen than the control group of PROVE-IT -- and the eligibility criteria (set in 1993) were consistent with the recommendations of ATP II (which were the guidelines at that time). Over the 8-year course of the trial, community standards changed, and many study participants developed indications for statin treatment (such as onset of CHD or rising LDL cholesterol), and the pattern of statin use in the usual care "control" group came increasingly to resemble that in the pravastatin group. Thus, the net cholesterol difference between the two groups was less than 10 percent, and the difference in CHD rates was too

small to be statistically significant. ALLHAT did not constitute a test of whether tripling the number of patients appropriately treated with drug therapy would be beneficial since it did not apply the ATP III recommendations for who should be treated and, for the reasons stated, it did not achieve the intended difference in LDL lowering between the treatment and usual care groups. In addition, however ALLHAT is interpreted, it did not test a high-dose regimen like 80 mg/day of atorvastatin. It is thus not valid to draw any inference from ALLHAT about whether such a regimen would be superior to "usual care."

"The vast majority of heart disease can be prevented by adopting healthy habits."

The NCEP and NHLBI have been advocates and champions of healthy lifestyle habits as the cornerstone of heart disease prevention for many years. ATP III devotes the first and largest section on therapy to lifestyle changes and establishes them as the primary cholesterol-lowering treatment. The scientific basis for such a lifestyle approach to cholesterol lowering and heart disease prevention is a combination of epidemiological and clinical trial evidence. NHLBI and NCEP accept this same combination as appropriate in support of drug therapy when risk is sufficiently elevated. The letter, however, is apparently prepared to use such a combination in support of lifestyle therapies such as diet and physical activity but requires randomized clinical trial evidence in a particular subgroup for drug therapy.

In a large number of Americans, lifestyles have not been altered sufficiently to achieve a low-risk status throughout life. A sizable number already manifest clinical CVD, type 2 diabetes, or multiple risk factors. In these persons, lifestyle alone has not been successful in spite of its potential. Consequently, clinical intervention is required to reduce cardiovascular morbidity and mortality. A minority of persons at elevated risk in the population will need drug therapy for primary or secondary prevention including anti-hypertensive agents, anti-platelet drugs, or cholesterol-lowering drugs. These drugs, when combined with lifestyle interventions, offer the prospect of further reducing the burden of CVD. It is not realistic to expect lifestyle intervention alone to be universally effective in lowering this large burden, particularly in individuals at substantially increased risk. NHLBI holds that NCEP guidelines convey a reasonable and balanced approach to use of cholesterol-lowering drugs as adjuncts to lifestyle therapies as part of an overall prevention strategy.

"The new NCEP report lowers the threshold for considering statin therapy. According to this report, people with moderately high risk of developing, but no previous history of heart disease ("primary prevention") and LDL-cholesterol levels between 100 and 129 mg/dL should now be offered the "therapeutic option" of cholesterol-lowering therapy with a statin. Similarly, statin therapy should now be offered to very high risk patients, those who already have heart disease ("secondary prevention"), when their LDL levels are between 70 and 100 mg/dL. Based on these new thresholds, millions more Americans now fall within the eligibility criteria for statin therapy."

With respect to moderately high risk people, the update paper informs physicians that, on the basis of recent clinical trial findings, they have a therapeutic option to employ a cholesterol-lowering drug in people with moderately high risk for CHD who have LDL cholesterol (LDL-C) levels in the range of 100-129 mg/dL. This option was introduced on the basis of the ASCOT trial, which documented that a cholesterol-lowering drug will significantly reduce risk for major coronary events in patients who fall into this category of risk.[11] The update paper does not

make this option available without qualification but states that the option may be appropriate on the basis of the physician's clinical judgment of the patient's absolute risk. The update cites several factors that might favor use of an LDL-lowering drug in this category, factors that would tend to raise absolute risk above the level typically seen in moderately high risk individuals. The update paper did not modify the basic treatment goal for LDL-C of <130 mg/dL for patients at moderately high risk, and did not translate the ASCOT findings into a firm recommendation to use cholesterol-lowering drugs in the very range where ASCOT found benefit. It did recognize that the ASCOT findings have implications for the treatment of moderately high risk patients, and conservatively translated the findings into a therapeutic option for the physician to consider.

With respect to very high risk patients: The ATP III update did not characterize all patients with CHD as being at very high risk, but only those with an acute coronary syndrome (e.g., a recent heart attack) or a combination of CHD together with other conditions, such as diabetes, that would exacerbate risk and place them at very high risk for a future heart attack and death from CHD. Moreover, the update report did not make a firm recommendation with regard to treatment of LDL-C levels between 70 and 100 mg/dL, but indicated that physicians have a therapeutic option to institute a cholesterol-lowering drug in patients who are at very high risk for CVD whose LDL-C is in this range. The identification of such an option is a restrained approach in relation to the evidence and in relation to the interpretation of the evidence by other experts in the cardiovascular community. The HPS demonstrated significant risk reduction for CVD events in high-risk patients with this LDL-C range who were treated with a statin.[5] The PROVE-IT trial further indicated that lowering LDL-C from near 100 mg/dL to <70 mg/dL with a high dose of statin provides significant additional risk reduction in patients following acute coronary syndromes.[23] Therefore, offering more intensive LDL-C lowering as a therapeutic option for very high risk patients is consistent with the data of recent clinical trials.

Since the release of ATP III in 2001, new clinical trial results have identified the benefit of cholesterol-lowering therapy in types of patients for whom trial evidence was not previously available. Because of these results, the ATP III update paper introduced new therapeutic options for more intensive therapy in the groups studied in the trials. Some authorities in the cardiovascular community who adhere strongly to basing recommendations solely on clinical trial results have been critical of the ATP III update for being too cautious. However, the update paper made it clear that there are a number of ongoing clinical trials that address in more detail the benefits of achieving LDL-C levels well below the ATP III goal for LDL-C in high-risk patients. For this reason, the ATP III update paper restricted itself to offering therapeutic options regarding the LDL-C goals of therapy, and did not introduce firm recommendations on this point. The update paper did make a firm recommendation to consider adding drug therapy to lifestyle changes for high-risk patients with LDL-C 100-129 mg/dL, whereas drug treatment in such patients was characterized as optional in ATP III, because the HPS yielded unequivocal evidence that this group obtained a significant benefit.[5] This change may increase the number of individuals treated with statins somewhat. Many of these high-risk patients may already have been treated with cholesterol-lowering drugs. Nevertheless, this increase is completely warranted by the scientific evidence showing that such treatment will reduce absolute risk.

II. The Integrity of NHLBI's Guideline Development Process

The letter questions the objectivity of the panel's recommendations for cholesterol-lowering medical therapies that it says "may not be scientifically justified" on the grounds that panel members have interactions with the pharmaceutical industry. As shown above, the scientific evidence supporting the panel's recommendations is strong.

NHLBI coordinates the development of clinical practice guidelines, such as ATP III, under the auspices of several national health education programs. The Institute seeks to ensure the scientific objectivity of these clinical guidelines and updates to guidelines through a variety of mechanisms. Expert panel members are carefully selected, and multiple levels of reviewers scrutinize the drafts of the guidelines.

The members of expert panels charged with developing guidelines are selected for their scientific and medical expertise, their stature and track record in the field, and their integrity. Individuals who are most expert in a subject area are the ones most suitable to serve on a guideline panel for assessing the science and developing clinical recommendations. They are also often the very people whose advice is sought by industry. Most guideline panels therefore include experts who interact with industry. Automatically eliminating all individuals who interact with industry from participating in guideline development could exclude important expertise and insights. To ensure that the guidelines are objective and science-based, NHLBI employs a careful development and review process.

In the case of the ATP III guidelines for cholesterol management released in 2001, the guideline panel conducted a thorough search of the scientific literature and critically evaluated the relevant studies. This examination provided the foundation for developing evidence statements, which summarized the main scientific conclusions, and evidence-based recommendations. Drafts of the ATP III report were reviewed by the NCEP Coordinating Committee (comprising representatives of over 35 leading medical, public health, voluntary, community, and citizen organizations and Federal agencies) and by prominent investigators acting as outside expert reviewers. Comments from the reviewers were incorporated into subsequent drafts in an iterative process until the report was judged to be ready for approval by the Coordinating Committee.

With respect to the recent update to the ATP III cholesterol guidelines, the task of the working group was to critically assess 5 recent trials in relation to the guidelines. For this relatively limited purpose, the Institute selected primarily members of the expert panel that developed the original ATP III guidelines. In addition, the working group included an expert representative of the American College of Cardiology and of the American Heart Association.

The update is a commentary on selected aspects of the ATP III recommendations, not a stand-alone guideline. When the update had been drafted, it was subjected to multiple layers of scientific review, first by the NCEP Coordinating Committee, and then by the scientific and steering committees of the American Heart Association and the American College of Cardiology. Approximately 90 reviewers were involved in the review of the draft. Their review was the basis for the endorsement of the update by the National Heart, Lung, and Blood Institute, American College of Cardiology, and American Heart Association.

The multiple levels of review for the ATP III guidelines and the update paper help ensure that the conclusions and recommendations are based on the scientific evidence.

Financial disclosure for guideline panels has been provided in accord with the publishing requirements of the peer-reviewed journal in which the guideline report was published. Financial disclosure for the working group members who served on ATP III was made in the Executive Summary of the ATP III report published in *JAMA* in 2001 (285:2486-2497). The NHLBI recognizes the desirability of having the financial disclosure information as publicly accessible as possible, and placed the financial disclosure for all 9 working group members on the NHLBI website where the update appears.

Many journals and organizations are currently reexamining their approaches to conflict of interest, and NHLBI is developing further policy to refine the management of potential conflict of interest. The Institute will routinely place financial disclosure information on the NHLBI website. The Institute will post future guidelines in draft form on the NHLBI website and provide opportunities for comment. This will increase the transparency of the process and invite comments that may not have been made during the formal review process.

III. Summary

The ATP III recommendations have a sound scientific basis, and NHLBI has used a careful development process, including multiple levels of review, to ensure the integrity and objectivity of the guidelines. Thus, the Institute does not believe a re-review of the data is warranted at this time. The ATP III update has taken a restrained approach to recent clinical trial results, for the most part providing therapeutic options rather than firm recommendations, and awaiting the publication of results from a number of ongoing clinical trials in high-risk individuals to determine whether revisions of the recommendations are scientifically warranted. When the results of the current ongoing trials are available, the Institute will consider the formation of a new panel to update the existing guidelines. The updated guidelines would be prepared with a view to their placement on a website in draft form for comment.

I hope this information is helpful to you and the letter's signatories. I am very willing to speak with you or with any of the signatories personally if you have any further questions or comments.

Sincerely,

/s/

Barbara Alving, M.D.
Acting Director

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