ACCORD TELEBRIEFING PREPARED REMARKS

WEDNESDAY, FEBRUARY 6, 2008

Diane Striar: Good morning. I am Diane Striar, acting communications director for the National Heart, Lung, and Blood Institute (NHLBI). Thank you for participating in this briefing. We will start with a statement from Dr. Elizabeth Nabel, Director of the National Heart, Lung, and Blood Institute. Following Dr. Nabel's remarks, several representatives from the leadership of the ACCORD clinical trial will make statements. ACCORD stands for Action to Control Cardiovascular Risk in Diabetes. After the remarks, we will field questions. The AT&T operator will provide instructions for asking questions. If you have not received the press release on ACCORD, it is now online at www.nhlbi.nih.gov. Dr. Nabel ....

Dr. Nabel: Thank you and good morning. Today we are sharing with you a major finding and decision regarding the ACCORD Trial. ACCORD is a large, important clinical trial designed to determine the best ways to decrease the high rate of cardiovascular disease among adults with type 2 diabetes who are at especially high risk for heart attack and stroke. Type 2 diabetes is a complex metabolic disease that results in elevated blood sugar levels. The ACCORD trial, which began in 2001, is testing three treatment approaches: intensive lowering of blood sugar levels compared to a standard blood sugar treatment; intensive lowering of blood pressure

compared to a standard blood pressure treatment; and treatment of blood lipids by a fibrate plus a statin compared to a statin alone.

This morning, we are announcing the outcome of one of the treatment strategies and a change in how the study will be conducted. After thoroughly reviewing the data collected to date, ACCORD investigators found that among these adults with type 2 diabetes who are at especially high risk of cardiovascular disease, a medical treatment strategy to intensively lower their blood sugar levels below the current guidelines increased the risk of death compared to standard blood sugar lowering treatment.

Because of this finding, and at the recommendation of the study's Data and Safety Monitoring Board, the NHLBI is stopping the intensive blood sugar lowering treatment part of the study 18 months early. Although we have stopped this treatment, we will continue to care for all study participants. Participants who were receiving the intensive blood sugar-lowering treatment will now receive the standard blood sugar lowering treatment, which aims for blood sugar control similar to that achieved in the general population of similar adults treated for type 2 diabetes, which is an A1C level of about 7.5 percent. As you know, A1C is a measure of blood sugar levels.

The treatment approaches for testing blood pressure and lipid control will continue until the study ends as planned in June 2009.

As always, our primary concern is to protect the safety of our study volunteers. We made the decision to stop the intensive treatment approach in the ACCORD study after a thorough review of the health risks to study participants. We will continue to monitor the health of all of the study participants, seek to understand the underlying causes for this finding, and carry on the other important research within ACCORD.

The findings from ACCORD will inform treatment decisions for the millions of individuals with type 2 diabetes who are at especially high risk of cardiovascular disease. It is important to note, however, that the results apply only to those individuals who are similar to the study participants. All 10,251 participants had type 2 diabetes on average for 10 years, when they enrolled in the study. In addition, ACCORD participants had blood sugar levels that were higher than most type 2 diabetes patients in the U.S. today, that is, on entry, their A1C levels were about 8.2 percent. To be eligible for the study, participants also had known heart disease or at least two risk factors, in addition to diabetes, including high blood pressure, high cholesterol levels, obesity, and smoking. In other words, they had diabetes plus other risk factors which place them at even higher risk for heart disease than if they just had diabetes alone. In this population of individuals with type 2 diabetes at especially high risk for heart disease, it has been observed that the risk of death is approximately 50 deaths per 1000 individuals per year (about 5 percent per year).

All ACCORD participants were randomly assigned to either an intensive medical treatment strategy, with a goal to lower A1C levels to less than 6 percent, or to a standard medical treatment strategy to lower A1C levels to 7 to 7.9 percent. A variety of FDA-approved medications were used to try to reach the assigned blood sugar goals.

Here is what the ACCORD researchers found:

- The median A1C level achieved in the intensive treatment group was 6.4 percent, while the median A1C level in the standard treatment group was 7.5 percent.
- In the standard treatment group, we observed 11 deaths per 1000 individuals per year, on average, over 4 years of follow-up. In the intensive treatment group, we observed 14 deaths per 1000 individuals per year. First and foremost, it is important to recognize that this death rate is lower than what has been previously observed in individuals with type 2 diabetes at especially high risk for heart disease.
- Nonetheless, in the intensive treatment group, there were 257 deaths and in the standard group, 203 deaths. This is a difference of 54 deaths, or 3 per 1,000 participants per year, over an average of 4 years of treatment. Because of this difference, the increased risk between the two groups outweighed potential benefits of the intensive treatment strategy on nonfatal events. Accordingly, the NHLBI has made the decision to stop this intensive treatment approach of the trial.

- This is an important finding which shows that if you have type 2 diabetes and are at especially high risk for heart disease, very intensive glucose lowering treatments aimed at normalizing blood glucose to an A1C of less than 6 percent may be detrimental.
- The findings of the ACCORD trial are consistent with recommendations from the American Diabetes Association in 3 aspects:

1. First and foremost, individuals with diabetes should not change their diabetes treatment without consulting with their healthcare provider.

2. Second, we concur with the general recommendation of the ADA that advises people with diabetes to aim for an A1C level of less than 7%.

3. However, for this special group of individuals with diabetes, as exemplified in the ACCORD population, which were average age of 62, had diabetes for an average of 10 years, and had know heart disease or were at high risk, less stringent A1C goals are likely appropriate, with an aim for around 7%.

ACCORD researchers have extensively analyzed the data available to date and have not identified any specific cause for the higher death rate among the intensive blood sugar treatment group. We know that the higher death rate is not due to episodes of low blood sugar, known as hypoglycemia, or due to any single drug, including rosiglitazone, or combination of drugs.

As I stated earlier, ACCORD researchers will continue to monitor participants and conduct additional analyses to try and explain the findings while continuing other important research studies which are a part of ACCORD.

Now, I'd like to take a minute to describe how the decision to change the blood sugar treatment part of the study was made. The ACCORD Data and Safety Monitoring Board, or DSMB, is an independent group of 10 experts who were appointed by the NHLBI to regularly examine study outcomes and safety data. The DSMB has expertise in diabetes, cardiovascular disease, statistics, ethics, epidemiology, and clinical trials. This group is responsible for providing recommendations to the NHLBI on starting, continuing, or stopping the study or portions of the study. The DSMB carefully considers the safety and efficacy of the study treatments and monitors the overall conduct of the study. The DSMB's recommendations are based on safeguarding the interests of study participants.

Since the study began in 2001, the DSMB has met regularly, generally every six months, to monitor study conduct and to review ACCORD data. In its regular review of the study data, the ACCORD DSMB noted an unexpected higher total death rate from any cause among participants who had been randomly assigned to the intensive blood sugar treatment group compared to those assigned to the standard blood sugar treatment group---the difference of 54 deaths which I described a moment ago.

Although there appeared to be some benefit of an overall lower death rate in both groups, the DSMB recommended stopping the intensive treatment because of the difference in deaths between the intensive and standard treatment groups; that is, the harm of the intensive treatment outweighed the potential benefit. NHLBI accepted the DSMB's recommendation to stop

the intensive treatment group and decided to continue treating all ACCORD participants at the standard treatment approach as well as to continue the blood pressure and lipid treatment parts of the study. We will continue to monitor all study participants for an additional 18 months as planned until the study ends in June 2009.

As I emphasized earlier, on the whole, the death rates in both blood sugar treatment groups were lower than those seen in similar populations. That is, although the death rate was higher in the intensive treatment group than the standard group, it was still lower than death rates reported in other studies of type 2 diabetes.

As people with diabetes learn the results of the ACCORD trial, we advise them to consult with their healthcare professional before making any changes to their treatment. This is an important message we will repeat several times today.

The NHLBI felt it was important to inform study participants and the diabetes community soon after reaching this decision. Accordingly, letters were sent to all study participants by their clinical site principal investigators on Monday with recommendations regarding further follow up care. Investigators have begun to prepare a report of these initial findings, which they will submit for publication in a peer-reviewed medical journal. We anticipate that these findings will be published shortly.

To summarize, ACCORD is the first major clinical trial to study whether lowering a raised blood sugar level to a level similar to that seen in people without diabetes reduces the risk of cardiovascular disease. We now have one part of the answer to this question. The study will continue to examine other ways to lower the risk of cardiovascular disease in high-risk adults with type 2 diabetes using blood pressure and lipid lowering approaches.

Our message to individuals with type 2 diabetes who are at especially high risk for heart disease is to target your A1C level to about 7 percent and not to more intensive levels. No one with diabetes should change their treatment without consulting with their healthcare professional first.

We have several experts with us today who have contributed to this research, and who will now provide additional detail about the ACCORD study and these important findings:

Dr. William Friedewald, Clinical Professor of Public Health and Medicine at Columbia University, and chairman of the ACCORD Steering Committee.

Dr. Hertzel Gerstein, professor at McMaster University and Hamilton Health Sciences in Ontario, where he holds the Population Health Institute Chair in Diabetes Research. Dr. Gerstein is principal investigator of one of the seven ACCORD clinical center networks and led the group that designed the blood sugar treatment approaches.

Dr. Judith Fradkin is the director of the Division of Diabetes, Endocrinology and Metabolic Diseases at the National Institute for Diabetes

and Digestive and Kidney Diseases here at the NIH and the key person from NIDDK involved in ACCORD over its duration.

Also with us to answer your questions will be **Dr. John Buse**, Professor of Medicine and Chief of Endocrinology at the University of North Carolina School of Medicine and vice chair of the ACCORD Steering Committee; Dr. Buse also serves as President of Medicine and Science of the American Diabetes Association. We also have **Dr. Robert Byington**, professor in the Department of Epidemiology and Prevention in the Division of Public Health Sciences at Wake Forest University School of Medicine, who leads the ACCORD Coordinating Center, and **Dr. Denise Simons-Morton,** project officer for ACCORD at the NHLBI and a member of the ACCORD steering committee.

Dr. Friedewald will start ---

Dr. William Friedewald: Thank you. As Dr. Nabel has just described, ACCORD first began recruiting participants in 2001. We have been treating and following our study participants for an average of about 4 years, ranging individually from 2 to 7 years.

At the same time that we began to observe the troubling mortality differences described by Dr. Nabel, we were also noticing a slight trend toward beneficial effects of the intensive blood-sugar lowering. The primary outcome for the study is a combination of heart attacks, stroke and cardiovascular death, and we were seeing about 10 percent fewer nonfatal cardiovascular events such as heart attacks in the intensive treatment group compared to the standard treatment group. However, it appeared that, if a heart attack did occur, it was more likely to be fatal. In addition, the intensive treatment group had more unexpected sudden deaths, even without a clear heart attack.

The ACCORD researchers undertook extensive analyses to try and understand potential causes of the mortality difference. Our analyses have not identified, to date, any specific cause for the increased deaths among the intensive treatment group. However, the magnitude of the difference in the death rate, with only a small improvement in nonfatal events, indicated that, in the interest of safety of the participants, the intensive blood-sugar treatment part of the ACCORD study should be changed and all participants treated according to the standard blood-sugar group.

As we examined the data, we sought to identify any drugs -- or combinations of drugs -- that might explain this higher mortality rate in our

intensively treated group. However, with our analyses so far we have not been able to find conclusive evidence that any medication or combination of medications is responsible for the increased risk.

Because of the recent concerns raised with regard to rosiglitazone, also known as Avandia, one of the drugs we use in ACCORD, we specifically analyzed the data to try and determine whether there was any link between this particular medication and the increased deaths we were seeing in the ACCORD intensive treatment group. At this time, we have found no link, and thus the use of rosiglitazone does not seem to explain the increased mortality.

Based on other studies, it is possible that the intensive blood-sugar lowering therapy benefits patients in other ways, such as by lowering the risk of other complications of diabetes, such as eye and kidney diseases. We will continue to analyze all of the effects of the intensive treatment group based on the data gathered to date and on future assessments of the participants in the intensive group, even though they will now be treated to standard blood-sugar lowering goals.

In addition to actively monitoring ACCORD participants, we will conduct additional analyses to try and explain the findings. Meanwhile, we are preparing a report of our current findings for publication in a peer-reviewed medical journal in the near future.

In a moment, Dr. Gerstein will provide more details on how the blood-sugar treatment part of the study was conducted and how ACCORD will continue over the next 18 months.

Before I close, I want to reiterate Dr. Nabel's comments and assure everyone, especially our study volunteers, that our first priority is to the safety of our participants. On Monday, our 77 clinical centers across the U.S. and Canada sent letters to each study participant explaining this important finding and describing the changes in the ACCORD study. For the participants in the standard treatment group, their care will continue without changes. Participants in the intensive treatment group will be transitioned to the standard treatment after consulting with their ACCORD clinician. They will be called by their study doctor in the next few days so they can discuss without delay any concerns or questions they might have.

Although the ACCORD findings are extremely important, most individuals with type 2 diabetes are not treated to blood sugar levels as low as those tested in the intensive treatment group in the study. In addition, these results only apply to patients like the ACCORD participants, who were selected to have cardiovascular disease or two additional risk factors for cardiovascular disease, in addition to diabetes. To reach the levels of blood sugar achieved by our intensive group required consistent hard work on the part of these participants, with frequent blood sugar monitoring, multiple medications, and frequent contact with our ACCORD clinical staff diabetes experts.

However, for this special group of individuals with diabetes, as exemplified in the ACCORD population, which were average age of 62, had diabetes for an average of 10 years, and had know heart disease or were at high risk, less stringent A1C goals are likely appropriate, with an aim for around 7%. No one with diabetes should change their treatment without consulting with their healthcare professional first.

Finally, I would like to reiterate that even with the higher death rate in our intensive group compared to our standard group, this death rate is still lower than that seen in similar populations in other studies, and it is lower among individuals with type 2 diabetes in the general community.

I would like to now turn to my colleague, **Dr. Hertzel Gerstein,** who leads the ACCORD clinical center network in Canada and the ACCORD blood-sugar working group. Hertzel will describe the blood-sugar treatments used in the ACCORD trial.

Dr. Gerstein: Thank you, Bill. Before we go into more detail regarding the blood-sugar treatment approach in ACCORD, I'd like to take a few minutes to describe why we tested an intensive blood-sugar lowering approach.

Adults with type 2 diabetes are two to four times more likely to have a heart attack, stroke or to die from cardiovascular disease than people without diabetes. This likelihood is even higher if an individual with type 2 diabetes is middle aged or older, has had a heart attack or stroke in the past, and has other risk factors for cardiovascular disease. Other risk factors include high blood pressure, high cholesterol, being overweight or obese, or being a smoker.

A large body of research has shown that higher glucose levels predict a higher likelihood of fatal and nonfatal cardiovascular events. Other studies have shown that lowering blood sugar levels can significantly lower the risk of certain complications of diabetes such as eye, nerve, and kidney diseases. In addition, a major study in people with type 1 diabetes – which is a different form of diabetes and used to be called "juvenile" diabetes – suggests that intensive blood-sugar lowering strategies reduce the risk of cardiovascular disease and death. Furthermore, a study in people with more recent onset of type 2 diabetes than ACCORD participants showed a trend toward fewer heart attacks. This body of research strongly suggests that lowering glucose levels to levels that are typically observed in people without diabetes could reduce the risk of cardiovascular disease in people with established type 2 diabetes.

But, until ACCORD, no major clinical trial had studied whether lowering a raised blood sugar level to a level similar to that seen in people without diabetes reduces the risk of cardiovascular disease in people with type 2 diabetes. In addition, no clinical trial has studied the effects of intensive blood sugar lowering in people with longstanding type 2 diabetes who already have cardiovascular disease or who have multiple risk factors for cardiovascular disease in addition to diabetes.

So, one of the key questions that ACCORD was designed to answer is whether intensively lowering blood sugar could reduce the risk of heart attack and stroke. Drs. Nabel and Friedewald have described the basic design of the study and the characteristics of the study participants.

The two blood-sugar lowering approaches studied by researchers in 77 centers in the United States and Canada used lifestyle approaches focused on modifying diet and physical activity, together with glucose-lowering drugs. All of the drugs were FDA-approved and are commonly used for glucose control in the general diabetes population. The choice of drugs was based on the doctor's medical judgment that took the clinical characteristics of the participant into consideration while maximizing safety and glucose-lowering effectiveness. Thus, the treatments used in ACCORD were similar to the way practicing physicians treat patients in the community.

Drugs representing all of the types of glucose-lowering therapies available when ACCORD began in 2001 were used, and a few more drugs were added as they became available. The same menu of medications were used in both treatment groups, although in different combinations and

doses. The medications included metformin; thiazolidinediones, or TZD's (such as rosiglitazone, pioglitazone); injectable insulins; sulfonylureas (such as glimepiride, glipizide, glyburide, and gliclazide); acarbose, and exenatide. Although the same drugs were used by both treatment strategy groups, more drug combinations and higher doses were prescribed to participants assigned to the intensive glucose lowering group than the standard group, in order to reach their assigned A1C goal.

Participants in the intensive treatment group were seen approximately every 2 months at an ACCORD clinical center, and participants in the standard group were seen about every 4 months. At each visit, clinical staff reviewed the participant's health status, discussed with the participant any side effects of drugs, adjusted medication dosages as needed, tested the participant's blood sugar, and performed other measures as appropriate.

Volunteer participants in both groups also received most drugs free. They received state-of-the-art medical care, with access to diet and physical activity counseling, experts in diabetes care, and the latest information related to diabetes. They were also provided with free glucose monitoring equipment so they could check their own blood sugar levels and make adjustments at home to achieve the goals to which they had been assigned. It is our view that the high standard of care received by all participants contributed to the lower death rates in both groups compared to the rates in the general community.

On average, the volunteer participants in both treatment strategy groups achieved a stable level of glucose within 6 to 9 months after being enrolled. The average blood sugar levels for both groups were lower than when they entered the study. The intensive treatment group achieved on average lower A1C values than the standard treatment group participants. Half of the participants in the intensive group achieved an A1C of less than 6.4 percent. In the standard treatment group, half of the participants achieved an A1C of less than 7.5 percent. Both groups have maintained stable glucose control throughout the study, which to date is an average of about 4 years.

Now, I'd like to turn to **Dr. Judy Fradkin** from the NIH's National Institute of Diabetes and Digestive and Kidney Diseases.

Dr. Fradkin: Thank you. I've been asked to address the implications of these new findings from the ACCORD study for diabetes patients. I will focus my remarks on type 2 diabetes, the form of diabetes being studied in ACCORD.

- Type 2 diabetes is by far the most common form of diabetes in the United States. It accounts for about 95 percent of the nearly 21 million diabetes cases in this country.

- Type 2 diabetes is most common in adults age 40 and older. It is strongly associated with obesity, inactivity, a family history of diabetes, and racial or ethnic background. Minority groups are at particularly high risk.

- As Dr. Nabel noted earlier, type 2 diabetes is a complex metabolic disease that results in elevated blood sugar levels. It usually begins as insulin resistance, a disorder in which cells in fat, liver, and muscle do not respond to or use insulin properly. As the need for insulin rises, the pancreas gradually loses its ability to secrete enough insulin to meet the body's needs. At diagnosis, many patients do not need medication, and most patients do well with oral medications such as metformin. Over time, however, they have a progressive loss in insulin production, and they need additional medications to control their diabetes.

- Eventually, especially if it is not well controlled, type 2 diabetes causes damage to the eyes, nerves, kidneys, heart and blood

vessels. Many people with diabetes also have high blood pressure and lipid or cholesterol problems—conditions that further add to their risk for cardiovascular disease. About 65 percent of people with diabetes die from heart disease or stroke. Diabetes is an increasingly important cause of cardiovascular disease in the U.S.

I would now like to briefly review how ACCORD is different from earlier studies. One crucial way in which ACCORD differed from earlier clinical studies is that it studied the effects of lowering glucose to a near-normal level, a lower level than that targeted in earlier studies.

ACCORD also differed in another critical way from earlier studies aimed at preventing complications through intensive glucose control. At enrollment, ACCORD participants were older – they were, on average, 62 years old; they had lived with diabetes for a longer time (an average of 10 years); and they were at especially high risk for cardiovascular disease. In contrast, participants in the earlier studies of intensive glucose control were younger, had recently been diagnosed with diabetes, and were not at a similar high risk for CVD. It is not yet known whether controlling glucose to near normal levels will prevent heart disease and extend life in other groups such as younger people with diabetes, those earlier in the course of disease and in whom glucose is easier to control, and those without established cardiovascular disease.

So what have we learned from ACCORD so far?

These new findings give us important information. They show that a medical strategy to intensively lower blood glucose to a goal of near normal, or non-diabetic levels, increases the risk of death and outweighs the potential benefits of such therapy for this specific group of patients—those with established or longstanding type 2 diabetes who have cardiovascular disease or are at especially high risk for it. In this group of patients, and with the treatments currently available to us, clinicians should be wary of striving for intensive glucose control to near-normal levels.

The ACCORD trial tells us that patients with diabetes and a high likelihood of established heart disease should not aim for near normal levels of blood glucose—levels that are rarely achieved with current medical care in comparable patients.

We've learned that a one-size approach does not fit all in treating diabetes, and the ACCORD findings reinforce this message. The National Diabetes Education Program, which is sponsored by the National Institutes of Health and the Centers for Disease Control and Prevention, promotes the American Diabetes Association's guidelines for diabetes care. Under these guidelines, the A1C goal for most people with diabetes is less than 7 percent. The guidelines also state that treatment should be tailored to individual needs. For example, a less stringent A1C goal should be considered for people with severe or frequent hypoglycemia or those with a limited life expectancy. In tailoring therapy to determine an individual patient's A1C goal, physicians should now consider whether the patient has established cardiovascular disease or additional CVD risk factors.

I want to stress that ACCORD is studying the effects of intensive glucose control in type 2 diabetes. We cannot extrapolate its results to patients with type 1 diabetes, which is a different form of diabetes.

Dr. Nabel: Thank you, Judy. And, thank you to all of our speakers this morning. In summary, we have discontinued the intensive blood-sugar treatment strategy in the ACCORD trial, and will now treat all the ACCORD participants according to the standard blood-sugar treatment strategy. The ACCORD blood pressure and lipid trials are continuing.

The findings we are reporting to you today are extremely important for the care of diabetic patients around the world. They indicate that in older patients with diabetes who also have existing cardiovascular disease or two or more CVD risk factors (like high blood pressure or elevated blood cholesterol), care should be taken to not intensively lower their blood sugar levels to a near-normal level using combinations of medications available today.

Now we will be pleased to take your questions. Please identify yourself and your organization.

[AFTER LAST QUESTION AND ANSWER -- AT APPROXIMATELY 11:30, DR. NABEL WILL MAKE A CONCLUDING STATEMENT:]

Dr. Nabel: I want to thank all of you who have called in today. You have a vital role in communicating this important health information to the public.

A recording of this press conference will be available at the following phone number within about 30 minutes.

(800) 475-6701, Access Code: 909685

The press release and Questions and Answers sheet have been posted to the NHLBI website, at www.nhlbi.nih.gov. A transcript of this teleconference will be posted in the next two days.

Thank you.