

## 1. EXECUTIVE SUMMARY

### 1.1. Background

Type 2 diabetes mellitus (Ty2DM) is rapidly becoming the most common chronic disease in the United States, with more than 7% of the adult population affected and 800,000 new cases per year. Ty2DM is even more common in the elderly and in minority populations including African Americans, Hispanic Americans, Asian and Pacific Island Americans, and Native Americans. In these populations, Ty2DM may be present in 10% to as much as 50% of the adult population. Diabetes is accompanied by a multitude of severe long-term complications that ultimately cause more adult cases of blindness, renal failure, and amputations than any other disease in the United States. In addition, persons with Ty2DM have a 2 to 4 fold increased risk for cardiovascular and peripheral vascular disease and stroke. Owing largely to the high costs of caring for Ty2DM and its attendant long-term complications, total health care costs for diabetes have been estimated at approximately 100 billion dollars per year, or 12% of total U.S. health care expenditures. The enormous human and financial costs that accompany Ty2DM, and the difficulty in treating it effectively once it has developed, make it an appropriate target for prevention.

The Diabetes Prevention Program (DPP) was a multicenter controlled clinical trial examining the efficacy of an intensive lifestyle intervention or metformin to prevent or delay the development of diabetes in a population selected to be at high risk due to the presence of impaired glucose tolerance (IGT). Development of diabetes, defined by 1997 ADA criteria, was the primary outcome while cardiovascular disease and its risk factors were important secondary outcomes. The DPP began recruitment in mid-1996 and completed recruitment approximately three years later with a study cohort composed of 68% women, 45% minorities, and 20%  $\geq$  age 60. All 3,234 volunteers received standard lifestyle recommendations and were randomly assigned to one of three interventions: intensive lifestyle with the aim of losing and maintaining 7% weight loss and achieving  $\geq$  150 minutes per week of moderate intensity physical activity, metformin therapy with 850 mg twice per day, or placebo. The troglitazone intervention in a fourth treatment arm (n=585) was discontinued in June 1998 because of the potential risk for severe liver toxicity that became apparent after the DPP was initiated.

The DPP had excellent retention, with >99% of the study cohort alive at study end and 93% of annual visits completed. In addition, the intensive lifestyle cohort achieved a mean weight loss of 7% (14.5 lb.) and 224 minutes per week of physical activity by the end of the 16-session core curriculum (at approximately 6 months) and maintained a 5% weight loss (10.3 lb.) and 189 minutes of activity per week after a mean study duration of 2.8 years. Seventy-two percent of participants assigned to metformin and 80% of those assigned to placebo took at least 80% of assigned medications during the study.

On the basis of a statistically significant and clinically compelling decrease in the development of diabetes in the lifestyle intervention and metformin-treated groups (58% and 31% reduction in hazards, respectively) compared with the placebo treated group, the DPP Data Monitoring Board and NIDDK ended the masked treatment phase of the study in August, 2001, one year earlier than originally planned.

At the end of the DPP all participants were offered a lifestyle modification program that incorporated the features of the original intensive lifestyle intervention, but was implemented in

group sessions during a 4-6 month period. The participants originally assigned to metformin continued open-label metformin therapy, and those assigned to placebo-treatment stopped the placebo.

The DPP addressed its primary objective, establishing the efficacy of lifestyle modification and metformin in decreasing the incidence of diabetes in an ethnically diverse population at high risk for an average of 2.8 years; however, many important issues remain unanswered. Specifically, whether the decrease in the development of diabetes can be sustained is unknown. Moreover, determining whether the delay or prevention of diabetes will translate into a decrease in retinopathy, nephropathy, neuropathy, and cardiovascular disease, all of which require more years to develop than the DPP period of study, is critical to establish the true impact of the DPP on public health.

The long-term follow-up study of the DPP, entitled the Diabetes Prevention Program Outcomes Study or DPPOS, is designed to take further advantage of the scientifically and clinically valuable cohort of DPP volunteers and the large volume of data collected during the study to address the issues above. The highly compliant DPP cohort, including 45% minorities, is the largest IGT population ever studied. Moreover, the large number of new onset Type 2 diabetic patients, carefully followed from near the time of their true onset, provides an unparalleled opportunity to study the clinical course of Type 2 diabetes.

## **1.2. Objectives**

The primary objective of the DPPOS is to evaluate the long-term effects of active DPP interventions on the development of a) diabetes during a further 5-10 years of follow-up and b) composite diabetes-related microangiopathic and cardiovascular disease outcomes. The hypotheses being tested are that both the continued lifestyle intervention and metformin will provide continued separation in the rates of diabetes development, compared with the former placebo group, and that the prevention or delay of diabetes during the DPP and DPPOS will translate into reduced rates of composite outcomes and improved health status.

The secondary objectives of the DPPOS are to evaluate the long-term effects of DPP interventions on selected individual health outcomes, the established and putative risk factors for those outcomes, and the costs and cost-utility associated with delay or prevention of diabetes.

Other research objectives include examining and comparing the incidence and determinants of these health outcomes in participants with new-onset diabetes and IGT, as well as assessing subgroups of participants in order to evaluate the effect of race/ethnicity and gender on health outcomes.

## **1.3. Study Population**

All DPP participants, including those previously assigned to intensive lifestyle, metformin, troglitazone, and placebo, whether or not they developed diabetes during the DPP, are eligible and will be invited to join DPPOS. At the time that DPPOS is initiated in September 2002, the mean age of the study population is 55 years, with 68 % being women. Fifty-five percent are Caucasian, 20% African-American, 16% Hispanic American, 4% Asian or Pacific Islander-American, and 5% American Indian. Approximately 840 participants have been diagnosed as having diabetes as of September, 2002.

## 1.4. Study Interventions

During DPPOS, quarterly group meetings will be held for all participants. These will focus on lifestyle lectures as well as other topics of interest to participants with IGT or diabetes. Additional group lifestyle booster sessions will be offered to the group originally assigned to intensive lifestyle intervention and open label metformin therapy (850 mg twice per day) will continue to be provided to the participants originally assigned to metformin.

## 1.5. Outcomes

The diabetes outcome is the same as the primary outcome during the DPP, i.e. development of diabetes according to American Diabetes Association criteria (fasting plasma glucose level  $\geq 126$  mg/dL [7.0 mmol/L] or 2-hour plasma glucose  $\geq 200$  mg/dL [11.1 mmol/L], after a 75 gram OGTT, and confirmed with a repeat test).

The Composite diabetes related outcomes are defined as:

Microvascular: Including having one or more of the following: a) a score  $> 2$  on the Michigan Neuropathy Screening Index (MNSI), b) the development of albuminuria ( $>30$  mg/gram creatinine) or renal dysfunction (end-stage renal disease or creatinine  $\geq 2$  mg/dL), or c) retinopathy by fundus photography, which will be measured in diabetic subjects and a subset of non-diabetic participants, will be evaluated for inclusion in this microangiopathic outcome.

Macrovascular: Including having one or more of the following: a) cardiovascular disease (CVD) events (fatal and non-fatal myocardial infarction and stroke), b) silent myocardial infarction on EKG, c) coronary artery stenosis  $> 50\%$  documented by angiography, d) coronary revascularization, e) absolute value of or change in carotid ultrasound measured intimal-medial thickness, either internal carotid artery or common carotid artery, that equals or exceeds a value known to be clinically relevant based on emerging research, or f) an ankle: brachial blood pressure ratio  $< 0.9$ .

**The secondary outcomes (see Chapter 4) include:**

- Diabetic retinopathy
- Loss of Vision
- Diabetic neuropathy
- Albuminuria
- Renal failure
- Cardiovascular disease events
- Subclinical atherosclerosis outcomes
- Risk factors for cardiovascular disease, including risk profiles
- Amputation
- Hospitalizations
- Quality of life indices
- Health care costs

## **1.6. Design and Power**

All participants will be followed for five years, with a total mean follow-up of approximately 9 years from the beginning of DPP. DPPOS is funded for 5 years, although some of the goals of the projects described will require a 10-year study.

Based on the high rate of adherence during DPP, we estimate that 90% of all participants will elect to continue in DPPOS. Assuming a placebo hazard rate of 0.08 in the former placebo group, the study has 83% power to detect a 30% difference in the hazard rate for conversion to diabetes between the former intensive lifestyle and placebo groups after 4 years of follow-up, and 94% power to detect a 35% difference. The study will have 80% power to detect a 30% difference for the comparison of metformin vs. former placebo group.

## **1.7. Analyses**

For the primary outcome, time to development of diabetes, product-limit life-table distributions of each intervention group and the control group will be compared using the modified log-rank test statistic. The primary analyses will include all participants in their originally assigned treatment group (intention-to-treat principle).