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## 1. EXECUTIVE SUMMARY

See the DPP Protocol Section 1 for the executive summary of the randomized clinical trial including background, objective, study populations, interventions and outcomes, and the DPP statistical power and analysis plan. This document contains the protocol for the continued follow-up of the cohort of participants randomized to troglitazone prior to discontinuation of the troglitazone intervention in the DPP randomized clinical trial.

### Cohort Background

Randomization to the troglitazone pharmacological intervention was suspended on May 27, 1998, and discontinued by the NIDDK on June 3, 1998. The NIDDK, with input from the DPP Data Monitoring Board, discontinued use of troglitazone in the DPP based on liver toxicity with hepatic failure associated with troglitazone use. Participants randomized to troglitazone on or before May 27, 1998, were unmasked to their intervention assignment and monitored to ensure that no liver toxicity developed after discontinuing the troglitazone medication.

The investigators of the Diabetes Prevention Program (DPP) designed the following consensus protocol during June 1998. The protocol describes the continued follow-up of the cohort of participants originally randomized to the troglitazone intervention of the DPP.

### Cohort Objective

The objective of the prospective cohort study includes assessing differences over time in glucose, insulin, and cardiovascular and adverse events within the troglitazone treated participants and between the troglitazone treated participants and the concurrent control group of participants treated with double-placebo during the DPP.

### Cohort Population

DPP-eligible participants randomly assigned to troglitazone therapy between July 1996 and May 1998.

### Cohort Intervention

All participants randomly assigned to troglitazone therapy on or before May 27, 1998, were treated with active troglitazone and metformin-placebo until the participants were unmasked on June 5, 1998. At that time, all troglitazone treated participants discontinued the study medications. The troglitazone cohort will be offered lifestyle group sessions 4 time per year. The lifestyle group sessions will consist of lessons, supported by printed material, that address the principal components of the lifestyle intervention such as healthy eating, weight loss, and exercise.

### Cohort Outcomes

The troglitazone cohort will be followed with semi-annual visits for a duration of 4 years to determine the time to confirmed development of diabetes by ADA criteria. Fasting plasma glucose, weight, blood pressure and adverse events will be collected every 6 months. During annual visits, an OGTT will be conducted with determination of 30 and 120 minute glucose, fasting insulin and proinsulin, and 30 minute insulin. Also during the annual visit, a physical and interval history including an ECG will be performed, and specimens for HbA<sub>1c</sub> and fasting lipids will be collected.

### Cohort Design

The research design is a prospective observational cohort study of the 585 participants originally randomized to troglitazone in the DPP.

### Analysis of the Cohort

For the time to development of diabetes outcome, product-limit life-table distributions of the troglitazone cohort and the concurrent control group will be determined. In addition to comparing the two groups using the log-rank test statistic, the time to development of diabetes within the troglitazone cohort will be stratified by the duration of coded-troglitazone treatment prior to unmasking.