PROTOCOL

for the

DIABETES PREVENTION PROGRAM OUTCOMES STUDY

(DPPOS)

IND # 49,782
ClinicalTrials.gov # NCT00038727

Diabetes Prevention Program Outcomes Study Research Group

Date: February 2, 2009

Version 3.0

Version 1.0 May 30, 2002
Version 1.1 October 8, 2002
Version 2.0 November 18, 2004
Version 2.1 July 5, 2006

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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 1,600,000 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 176 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.

More than 87% of the original surviving DPP cohort has joined DPPOS as of December, 2007 and, to date, after 5 years of DPPOS and 10 years of combined DPP/DPPOS, 93% of the DPPOS cohort continue to attend annual follow-up visits. Interim analyses performed after 5 years of DPPOS have demonstrated a durable effect of diabetes prevention associated with the lifestyle and metformin interventions with 34 and 19% reductions in diabetes incidence, respectively, compared with the placebo group. Interim analyses also reveal significant reductions from baseline in CVD risk factors in the lifestyle intervention group, but with decreased utilization of glucose-lowering and lipid-lowering medications. Analyses of the participants in the placebo group who have developed diabetes during DPP/DPPOS, compared with those who have remained non-diabetic, reveal an increased frequency of retinopathy and microalbuminuria. The current, updated protocol describes the DPPOS including the revisions incorporated to complete the second five-years of the study.

1.2. Objectives

The primary objective of the DPPOS is to evaluate the long-term effects of active DPP interventions on the further development of diabetes (during the first phase of DPPOS), and on macrovascular composite events and composite diabetes-related microvascular complications. During the second phase of DPPOS, the hypothesis being tested is that, compared to the former placebo group, both the continued lifestyle intervention and metformin groups, will experience a reduced rate of microvascular and neuropathic complications.

The secondary objectives of the DPPOS are to evaluate the long-term effects of DPP interventions on the further development of diabetes and 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, age, and gender on health outcomes.

1.3. Study Population

All DPP participants, assigned to the original intensive lifestyle, metformin, troglitazone, and placebo groups, whether or not they developed diabetes during the DPP, were eligible and were invited to join DPPOS. The former troglitazone participants were followed during Phase 1 of DPPOS, but will no longer participate as research volunteers in the study. At the time that DPPOS was initiated in September 2002, the mean age of the study population (including the former troglitazone participants) was 55 years, with 68% being women. Fifty-five percent were Caucasian, 20% African-American, 16% Hispanic American, 4% Asian or Pacific Islander-American, and 5% American Indian. Among intensive lifestyle, metformin, and placebo participants, 849 had been diagnosed as having diabetes as of September, 2002, and another 503 participants developed diabetes during the first phase of DPPOS.

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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 boost 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 (see Chapter 4)

Microvascular and neuropathic: Having one or more of the following at year 11:

a. Nephropathy: development of albuminuria (≥30 mg/gram creatinine) or renal dysfunction (end-stage renal disease or GFR < 30 ml per min based on serum creatinine and using the MDRD equation), or
b. Retinopathy: retinopathy by fundus photography (ETDRS grade of 20 or greater) or history of documented laser surgery for retinopathy or
c. Neuropathy: reduction or absence of monofilament light touch in either foot (10 gram Semmes-Weinstein Monofilament < 8 applications detected).

The secondary outcomes include:

- Further development of diabetes (defined below)
- Diabetic retinopathy
- Diabetic neuropathy
- Albuminuria
- Renal failure
- Macrovascular disease (defined below)
- Cardiovascular disease events
- Subclinical atherosclerosis outcomes
- Risk factors for cardiovascular disease

- Amputation in a lower extremity not resulting from major trauma
- Hospitalizations
- Physical activity, nutrition, body mass and obesity
- Dietary and exercise behaviors
- Physical functioning
- Quality of life indices
- Health care costs
- Cognitive performance
- Urinary incontinence

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 ≥ 126 mg/dL [7.0 mmol/L] or 2-hour plasma glucose ≥ 200 mg/dL [11.1 mmol/L], after a 75 gram OGTT, and confirmed with a repeat test).

The DPPOS *macrovascular* outcome is the time to first occurrence of any one or more of the individual events as listed below:

a. cardiovascular disease (CVD) events (CVD death, 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. hospitalized CHF
f. hospitalized unstable angina/acute coronary syndrome
g. revascularization or amputation in lower extremity not resulting from major trauma

CVD events are determined at the time of their report and classified and adjudicated by an outcomes committee whose members are blinded to treatment assignment.

1.6. Design and Power

All participants will be followed for a minimum of eleven years, with a total mean follow-up of approximately 15 years from the beginning of DPP.

Based on the high rate of adherence during DPP and enrollment in DPPOS, we estimate that 85% of all participants will elect to continue in DPPOS. The global test will provide 91% power for detecting a 25% reduction in microvascular complications due to intervention, from a projected placebo group average prevalence of 12.1% (each of 2 pair-wise comparisons, 2-sided, α=0.025), and 74% power for a 20% reduction (1).

1.7. Analyses

The primary outcome analysis will compare the three intervention groups with respect to the DPPOS year 11 assessment of the components of the microangiopathy outcome using the global test (1). The global test, which gives the component outcomes equal weight, is interpreted as testing for a consistent difference between groups across the component outcomes.

The primary and secondary outcome analyses will follow the "intention to treat" principle and will include all participants in the original DPP placebo, lifestyle and metformin intervention groups who have enrolled in DPPOS. Since the participants originally assigned to troglitazone only had a limited exposure to that intervention, owing to the premature termination of the troglitazone arm, and were not included in the primary DPP outcome analyses, they will not be included in the DPPOS primary and secondary outcome analyses.

2. OBJECTIVES

2.1. Primary Research Question

The primary objective of the DPPOS is to evaluate the long-term effects of the DPP interventions (Intensive Lifestyle and Metformin, currently Boost Lifestyle, and Metformin) on the prevalence of the composite diabetes-related microangiopathic and neuropathic outcome.

2.2. Secondary Research Question

The secondary objective of the DPPOS is to evaluate the long-term effects of DPP interventions on selected health outcomes including:

- Further development of diabetes
- Diabetic retinopathy
- Diabetic neuropathy
- Albuminuria
- Renal Failure
- Macrovascular disease
- Cardiovascular disease events
- Subclinical atherosclerosis outcomes
- Risk factors for cardiovascular disease
- Amputation in a lower extremity not resulting from major trauma
- Hospitalizations
- Physical activity, nutrition, body mass and obesity
- Dietary and exercise behaviors
- Physical functioning
- Quality of life indices
- Health care costs
- Cognitive performance
- Urinary incontinence

2.3. Other Research Questions

Other research questions of the DPPOS 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 age, race/ethnicity, and gender on health outcomes.

3. BACKGROUND AND RATIONALE

3.1. The Diabetes Prevention Program

3.1.1. Study Rationale and Design

The Diabetes Prevention Program (DPP) was a multicenter controlled clinical trial examining the efficacy of an intensive lifestyle intervention or metformin vs. placebo 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) (2-4). Development of diabetes, defined by 1997 ADA criteria (5), was the primary outcome while cardiovascular disease (CVD) and its risk factors were important secondary outcomes. The original study design included four treatment arms: intensive lifestyle (ILS) intervention, troglitazone (TRO) treatment (400 mg/day), metformin (MET) treatment (850 mg twice per day), or placebo (PLB). All medication-treated subjects received identical appearing coded medications, and treatment was double blind. Troglitazone treatment was stopped in June 1998, owing to the accumulating evidence that troglitazone was responsible for rare, but potentially severe idiosyncratic liver toxicity. The volunteers assigned to troglitazone therapy were offered a modified lifestyle intervention and continue to be followed as a separate group in the DPP.

The original rationale for a study to prevent or delay diabetes was the following: 1. Diabetes mellitus, and in particular Type 2 diabetes (Ty2DM), had become epidemic in the US, affecting 7% of the adult population and with almost 800,000 new cases per year (6); 2. The consequences of TY2DM including diabetes-specific complications, such as retinopathy, nephropathy, and neuropathy, and cardiovascular disease were causing severe morbidity and mortality with enormous human and financial costs (7); 3. Although therapies to treat diabetes once it develops were available, the complex medical regimens required were difficult and costly to apply and many patients failed to achieve the glycemic levels and other treatment goals required to prevent or delay the long-term complications; 4. A pre-diabetic state was well recognized, and could be identified with relatively simple screening methods, providing the opportunity of identifying persons at high risk for diabetes (8); and, finally, 5. Potentially modifiable environmental factors, such as overweight and a sedentary lifestyle, that were known to increase risk for diabetes (9-11), and medications that ameliorate hyperglycemia had been identified. In concert, these factors suggested that interventions with the potential to prevent or delay the development of diabetes could be applied in persons identified at high risk to develop diabetes mellitus, a common chronic disease with grave long-term consequences.

The DPP was designed with the expectation that prevention or delay of diabetes would ultimately prevent or delay the development of long-term, duration dependent diabetes-specific complications. In addition, prevention or amelioration of CVD and/or CVD risk factors would provide a major benefit to those with IGT or diabetes. Accomplishing either of these aims would provide a major benefit with regard to long-term health by virtue of decreasing morbidity and mortality. However, the duration of the DPP, planned as a 3-6 year study, did not allow an examination of whether "prevention" or delay of diabetes would translate into a reduction of clinical outcomes that usually require a longer period of time to develop. Thus, the DPP was designed on the basis of power calculations directed at diabetes prevention (2). The ability to demonstrate a reduction in microvascular complications or "hard" CVD endpoints was

acknowledged from the outset to be limited. Instead, changes in CVD risk factors and measures of atherosclerosis, such as ankle/brachial index and carotid ultrasonography, were analyzed.

3.1.2. Study Cohort

The DPP recruited its study cohort between June 1996 and 1999, screening more than 150,000 self-referred individuals. Oral glucose tolerance testing (75 grams) was performed in approximately 20,000 persons to select high-risk individuals with impaired glucose tolerance (IGT) with two-hour plasma glucose values 140-199 mg/dL. The eligibility criteria also required a fasting glucose level of 95-125 mg/dL, representing approximately the upper half of the IGT population. Based on previous epidemiological studies (8), this population was projected to have a conversion rate to diabetes of 7.5% per year. (2,8) The baseline characteristics of the study population have been described in detail. (3) (Table 1)

At the time of the analysis of study end data (visits completed as of April 1, 2001), total study exposure was a mean of 2.8 years (range 1.8 to 4.6) with a total of ≈10,000 patient years in the 3,234 volunteers in the 3-arm study. (See Table 1 for Baseline Characteristics of DPP Cohort, 3) An additional ≈2,000 years of follow-up data had been collected in the approximately 550 volunteers in the ex-troglitazone treated group. Finally, 623 members of the DPP cohort developed diabetes during the course of the study, with the expectation that more will develop diabetes over time. (8) The date of diabetes onset is known within 6 months of its actual occurrence, due to repeat glucose testing throughout the trial.

Table 1: Baseline Characteristics of DPP Cohort

	Overall	Lifestyle	Metformin	Placebo
N	3234	1079	1073	1082
Age (yr)	51±11	51±11	51±10	51±10
Sex:				
Male	1043(32%)	345(32%)	363(34%)	335(31%)
Female	2191(68%)	734(68%)	710(66%)	747(69%)
Race/ethnicity:				
Caucasian	1768(55%)	580(54%)	602(56%)	586(54%)
African-American	645(20%)	204(19%)	221(21%)	221(20%)
Hispanic	508(16%)	178(17%)	162(15%)	168(16%)
American-Indian	171(5%)	60 (6%)	52 (5%)	59 (6%)
Asian-American	42(4%)	57 (5%)	36 (3%)	49 (5%)
Fasting glucose (mmo1/L)	5.9±. 5	5.9±. 5	5.9±. 5	5.9±. 5
BMI (kg/m²)	34±7	34±7	34±7	34±7
Blood pressure (mmHg)				
Systolic	124±15	124±15	124±15	124±14
Diastolic	78±9	79±9	78±10	78±9

From Diabetes Care 2000; 23:1619-29 (3)
Data are means + SD or n(%) unless otherwise stated. Percentages may not add up to 100 because of rounding.

All in all, the DPP population represents the largest cohort of IGT subjects, including a large representation from minority populations in the US, followed over time. (Table 1)

3.1.3. Outcome Data from DPP

Study data included: measurements of glycemia, including mid-year or annual fasting and OGTT glucose values and HbA1c levels; measurements of insulin and proinsulin (to help determine underlying causes of decline in glucose tolerance and as putative risk factors for CVD); demographic and clinical variables that reflect risk for diabetes and/or CVD such as body mass index, weight distribution, direct measures of fat mass/distribution (CT scans on a sample), blood pressure, and lipids; biochemical measures that are established or putative risk factors for the development of CVD including hemorheological factors; clinical CVD events categorized and adjudicated in a similar fashion to other interventional and epidemiological studies; and measures of atherosclerosis such as ankle/brachial index measured by Doppler and carotid intimal-medial thickness (IMT) measured by B-mode ultrasonography. Finally, the DPP has stored samples that are suitable for analysis of other putative risk factors or mediators of diabetes or CVD that could not be afforded during the study. Samples suitable for genetic analysis have also been collected, and are being analyzed. In addition, samples have been kept in storage for participants who consented. The data collected include standardized measurements using uniform methods and central analysis/reading/grading with easily accessible stored data.

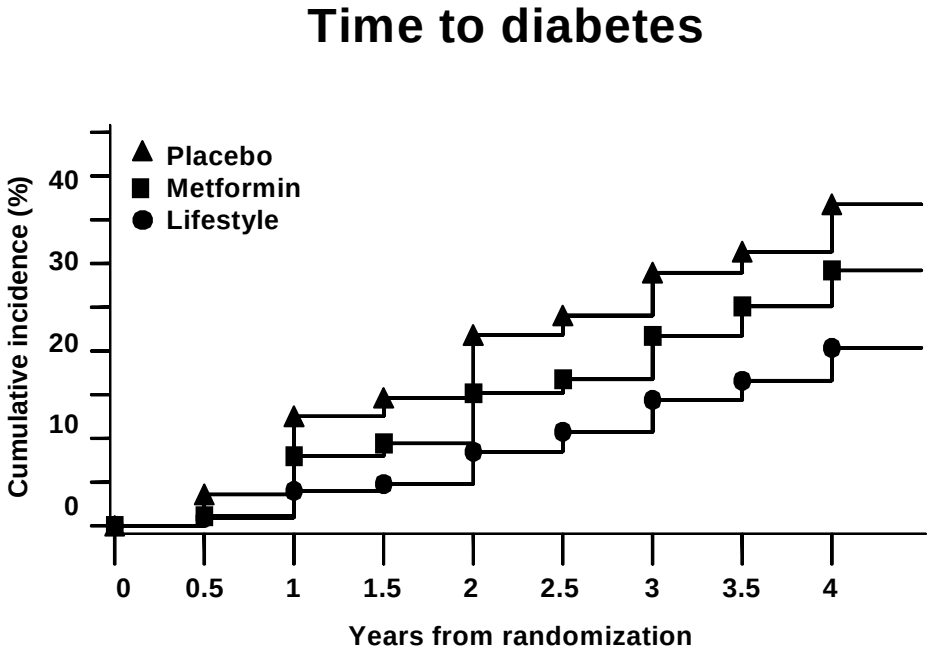

Figure 1: Life-table Analysis of Cumulative Incidence of Diabetes Development During DPP

3.1.4. Study Results

After approximately 2.8 years of mean study time, the external Data Monitoring Board and sponsoring institute, the NIDDK, concluded that the DPP had convincingly demonstrated that the intensive lifestyle intervention and metformin therapy decreased the development of diabetes. Compared with placebo, intensive lifestyle and metformin reduced the development of diabetes by 58% and 31% risk reduction, respectively. (Fig 1) Both results were significant and lifestyle was significantly more effective than metformin. (4) The therapies were effective across all ethnic and racial groups and in men and women. The intensive lifestyle intervention cohort achieved the target goal of 7% mean weight loss and at least 150 min of activity per week at year 1. (Table 2) The entire cohort proved to be remarkably compliant, with 94% retention of volunteers over time, and completion of $\geq$ 90% of study requirements. Adherence (>80% of assigned medication) to metformin was 72%.

Table 2: Summary of Outcomes During DPP

	Placebo	Metformin	Lifestyle
Development of diabetes (percent per year)	11	7.8	4.8
Reduction of diabetes compared with placebo (%)		31	58
Number needed to treat to prevent 1 case in 3 y		13.9	6.9
Weight loss kg (%)			
Year 1	.43(0.5)	2.72(2.9)	6.7(7.2)
Year 2	.06(0.1)	2.07(2.2)	5.4(5.7)
Year 3	-.37(-0.4)	1.18(1.3)	4.7(5.0)
Leisure Activity (Met hours /wk)			
1 year	4.46	4.92	5.57
2 year	4.61	4.37	5.27
3 year	4.95	4.29	5.08

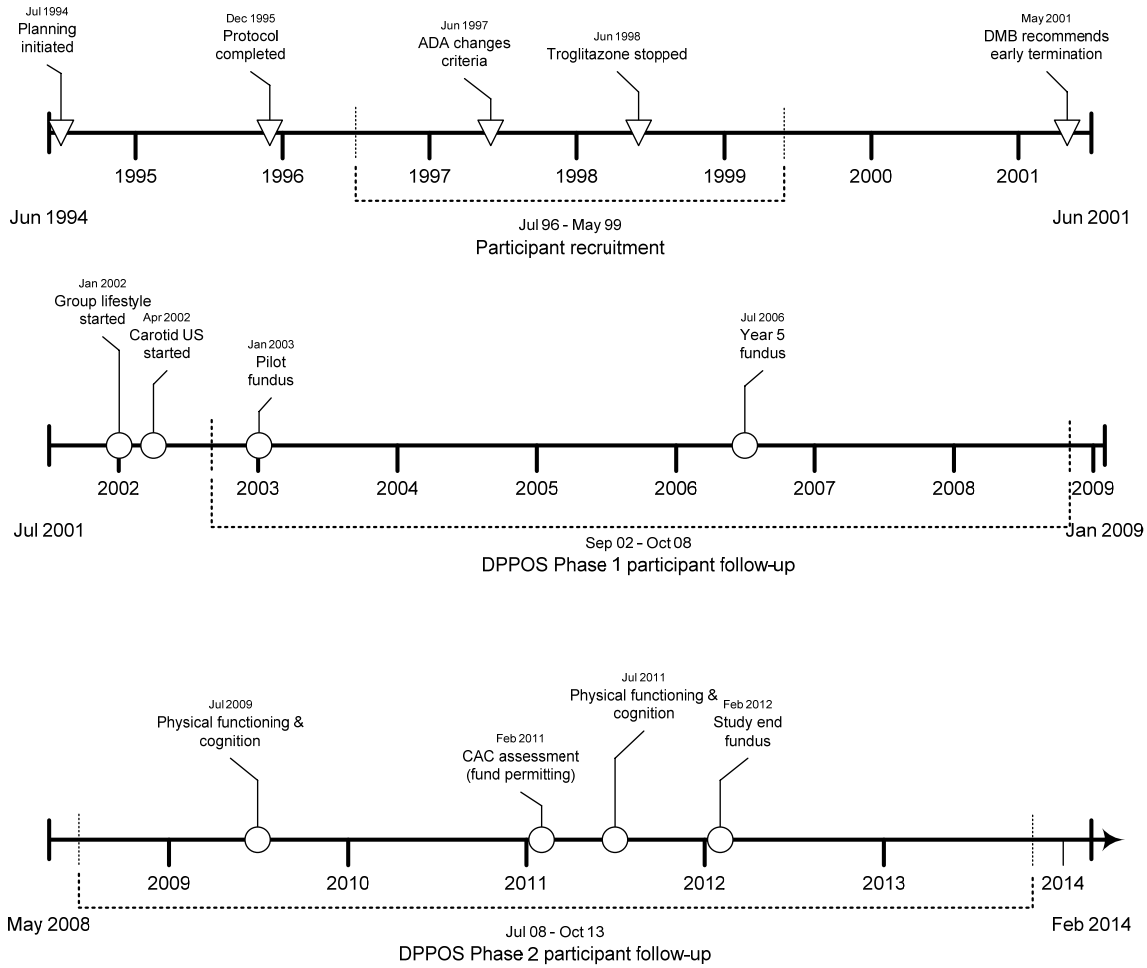

Figure 2 Summaries of DPP Timeline and Proposed Follow-up

3.1.5. Bridge Period Between End of Masked Intervention and Initiation of DPPOS

A summary of important dates in DPP history and the proposed follow-up is shown in Figure 2.

The DPP Research Group decided before the study results were known, to offer effective therapy to the cohort at study end, should one of the study interventions prove to be effective. This decision was made not from any scientific imperative, but based on the sense of the DPP Research Group and NIDDK that initiating effective therapy was consistent with our obligation to the participants who had made the DPP possible. During the final six months of the DPP (January – June 2002), under a "bridge" protocol, all participants were offered an intensive Lifestyle program with the same goals used in the DPP, but offered in a group, rather than individual, setting. In addition, during this period, the former ILS group was offered continued ILS, albeit with a less frequent contact than during the DPP. Placebo therapy was stopped after

individual unmasking took place between August and November 2001. MET was continued, during this period, with participants and staff unmasked to treatment assignment.

3.2. Rationale for Extended Follow-up of DPP Cohort

The DPP was designed to ascertain whether metformin treatment and/or intensive lifestyle modification reduced the development of diabetes, compared to placebo, in subjects with IGT during a period of intervention averaging ≅4 years. (2) Owing to the large and statistically significant reduction in development of diabetes in the lifestyle intervention group (58%) and in the metformin-treated group (31%), compared with placebo treatment, the DPP was ended, by consensus of the external Data Monitoring Board, NIDDK, and the Study Group, approximately one year earlier than planned. (Figure 2) The prevention – or delay - of diabetes should be associated over time with a reduced rate of diabetes-related clinical events, namely diabetic microangiopathy and neuropathy and cardiovascular disease (CVD). The relatively brief study period of the DPP, with a mean follow-up of 2.8 years (range 1.8-4.8 years), precluded an examination of the long-term clinical impact of diabetes prevention. An appreciation of the long-term clinical impact of diabetes prevention is critical in order to understand the role of the DPP interventions in improving health. Moreover, the long-term epidemiological follow-up of the DPP cohort will increase our understanding of the clinical course of IGT and new-onset Type 2 diabetes.

3.2.1. Duration of Diabetes Prevention

The major question that arises is whether the therapies that were effective during the DPP continue to prevent diabetes and how long the effect persists. Long-term follow-up of the DPP cohort will reveal whether the differences in diabetes development decrease, remain the same or increase over time. The duration of the effect of DPP interventions on the development of diabetes has an obvious impact on the interpretation of the study's effect, given the life-long risk for developing diabetes, and the duration-dependent impact of diabetes on health. Other controlled clinical trials such as DASH (9), examining the impact of a lifestyle intervention with salt restriction on hypertension, the EDIC follow-up of the DCCT (10), and the long-term follow-up of the United Kingdom Prospective Diabetes Study (UKPDS) cohort (12) have demonstrated persistent, or even expanded, benefits of initial therapy over time. Such long-term follow-up studies are critical to understand the effects of therapy on chronic conditions.

3.2.2. Long-term Impact of DPP Interventions on Composite Outcomes Including Microvascular and Cardiovascular Disease

3.2.2.1 Microvascular and Neuropathic Disease

The second question addresses the long-term clinical impact of having prevented or delayed the onset of diabetes. As noted above, the ultimate health care benefit of diabetes "prevention" will be a function of the time period during which diabetes is delayed, and whether and to what extent organ damage can be prevented or delayed. Although epidemiological data suggest that prevention or delay of diabetes should result in less disease over time, no study has ever addressed this critical public health question directly.

The development of diabetic retinopathy, nephropathy and neuropathy is believed to require chronic exposure to levels of glycemia at or above the diagnostic limits for diabetes (5). Thus, based on conventional thinking, the appearance of these complications in DPP participants would be expected to be restricted to those who develop diabetes, and would be expected to occur only some years after biochemical conversion. The decreased development of diabetes with intensive lifestyle and metformin would, therefore, be expected to reduce the frequency and extent of these disease entities compared with their occurrence in the former placebo-treated group. Although an assessment of the development of microvascular complications during the DPP was discussed during the planning stages, it was not implemented, because of the added expense and the likelihood that event rates would not be high enough within the planned DPP duration to enable group differences to be detected. However, a difference between treatment groups in these duration-dependent outcomes, if one exists, is more likely to be demonstrated with longer follow-up. The ultimate benefit of preventing diabetes is predicated, to a large extent, on the projected decrease in the development of long-term complications. Follow-up of the DPP cohort during DPPOS will determine whether this effect has been achieved.

3.2.2.2 Cardiovascular Disease (CVD)

Whether CVD, the complication associated with greatest morbidity and mortality in diabetes (10), was altered by DPP therapies was examined during the DPP, albeit with limited power owing to a low event rate. Previous studies have demonstrated that diabetic subjects have higher rates of CVD than individuals with IGT, who in turn have higher rates than persons with normal glucose tolerance (NGT). (13,14) Therefore, prevention or delay in development of diabetes and/or reversion to NGT from IGT, both of which occurred in the DPP, could influence the course of CVD in a significant proportion of DPP participants. In addition, both metformin and lifestyle modification have been shown to improve CVD risk factors directly. (15-19) Metformin has modest beneficial effects on the lipid profile, and lowers PAI-1 levels. (15,16) In obese diabetic subjects, metformin treatment may reduce the incidence of myocardial infarction by mechanisms that may be at least partly independent of blood glucose lowering. (17) Weight reduction and increased physical activity also improve the lipid profile, lower blood pressure and increase fibrinolytic activity. (18,19) Increased physical activity has been associated with a reduced incidence of CVD in non-diabetic and diabetic subjects. (20-22)

Unfortunately, the DPP had insufficient power to detect an effect of the two active DPP interventions on CVD events owing to the relatively low rate of CVD events during the study (0.0029 major clinical CVD events per year). However, the effect of interventions on several subclinical markers of CVD (ankle/brachial index and silent ECG changes) and on CVD risk factors was examined. Although the low event rates of major CVD precluded demonstrating a difference in event rates between the treatment groups, CVD risk factors were variably affected by the different DPP interventions. (Table 3) Blood pressure was significantly lower, lipid levels were less atherogenic, and insulin levels were lower in the Lifestyle treatment group, and to a lesser extent with metformin therapy, than in the placebo group. Longer follow-up of the DPP cohort will be highly informative regarding the effects of therapy on clinical outcomes that are likely to take longer to observe than the initial 3 years of the DPP.

Table 3: CVD Risk Factors during DPP-Mean Change from Baseline

CVD Risk Factors	Placebo	Metformin	Lifestyle
Blood pressure (mmHg)			
Systolic	-0.77	-1.12	-3.26
Diastolic	-0.74	-0.86	-3.27
Lipoproteins (mg/dL)			
Total cholesterol	-3.26	-4.72	-8.14
Triglycerides	-3.39	-3.04	-21.98
LDL-cholesterol	-1.37	-4.00	-4.37
HDL-cholesterol	-.27	0.39	0.69
Insulin level (μU/ml)			
Fasting	0.74	-2.93	-4.52
30 min Post-OGTT	1.45	-6.92	-13.49

3.2.2.3 Economic Implications

The economic impact of the DPP treatments will be a function of any significant differences in health outcomes over time. There is evidence that diabetic subjects experience higher health care costs than do non-diabetic subjects. (23) Analysis of the cost-effectiveness of the DPP interventions has demonstrated a cost per quality adjusted life year that is within the range usually considered affordable.(24) These analyses have not considered the potential long-term effects of the DPP on complications. In order to understand the true costs and benefits of DPP interventions, we must delineate the long-term clinical outcomes associated with the interventions. Reduced long-term health care costs associated with the DPP interventions that delay diabetes and, presumably, diabetes-associated complications, would offset the costs of the interventions and therefore favorably affect the cost-effectiveness and cost-utility ratios.

3.2.3. Summary

In view of these issues, an examination of the putative reduction in diabetes complications and health care costs that may result from the DPP interventions is the requisite next step in providing the clinical evidence that medical intervention in subjects with IGT yields important and tangible health benefits. The DPPOS will analyze the health care outcomes discussed above on the basis of the intention-to-treat groups in DPP. This approach has been used to good effect in several completed clinical trials; e.g. the DCCT (EDIC) (10), the Coronary Drug Project (25,26) and 4S (27). Long-term follow-up of controlled clinical trials involving chronic diseases is predicated on the notion that the study intervention influences certain chronic disease processes in a manner that takes more time to manifest than the duration of the treatment being studied. One of the best examples of such a study was the Coronary Drug Project, in which coronary and all-cause mortality were not altered at the completion of a 6-year period of niacin therapy even though cholesterol levels were significantly lowered. (25) However, these clinical endpoints were significantly reduced after 9 years of further observational follow-up. (26) The ongoing EDIC follow-up of the DCCT cohort has demonstrated widening differences in

outcomes as early as 4 years after the termination of assigned therapies. In addition, longer follow-up has demonstrated differences in more advanced and costly complications, including the need for laser therapy for proliferative retinopathy atherosclerosis and CVD events, between the treatment groups that were not apparent at the end of the DCCT. (10,10a) Lastly, evaluation of the United Kingdom Prospective Diabetes Study cohort 10 years following completion of the intervention phase of the study has demonstrated significant differences in a number of outcomes in subjects previously randomized to the intensive and conventional treatment arms. Thus, despite glucose control not differing between the subjects following completion of the intervention, in those who had received the intensive glucose-lowering regimen, continued significant reductions in risk were observed in any diabetes-related endpoint and microvascular complications and a significant reduction in risk became apparent for myocardial infarction and all-cause mortality. (11)

3.3. Clinical Course of IGT and New-onset Type 2 Diabetes

3.3.1. Epidemiology of Microvascular Disease and Neuropathy in IGT and New-onset Type 2 Diabetes

The "specific" long-term complications of diabetes mellitus have been used to establish the glycemic thresholds at which diabetes occurs. Therefore, the nosologic definition and diagnostic criteria for diabetes mellitus are based on elevated glycemia and the risk for development of retinopathy. (5) The 1997 report by the Expert Committee of the American Diabetes Association was based on a relatively small number of observational, cross-sectional studies that established a threshold below which retinopathy was generally not detected. (5) Other cross-sectional studies also suffer from inaccurate assessment of diabetes onset (41,42), and only a few have been performed in minority populations (43-45), leaving our understanding of the frequency and clinical course of retinopathy incomplete. Longitudinal studies, such as WESDR and studies in the Pima Indians, also suffer from inadequate dating of diabetes onset. In the study in the Pima Indians, the diagnosis of diabetes onset could not be more accurate than within 4 years. (45) Of interest, retinopathy was present in 11.2% of 169 subjects "at the time of diagnosis" and in 12% of persons with IGT. The suggestion in the high diabetes-prevalence population of Pima Indians of a greater risk for "diabetes-specific" complications in non-diabetics than previously appreciated may or may not be relevant in other populations. While duration of diabetes is a well-known risk factor for retinopathy, and other complications, in most populations, when the "clock starts ticking" is unknown. Finally, only a small number of studies (45-47) have examined the prevalence of retinopathy in IGT populations. They have been limited in being generally cross-sectional with poor appreciation of the glycemic history of the participants. Of note, the results of a pilot study during DPP/DPPOS, in which we have excellent measures of glycemia over time, have shown a prevalence of diabetic retinopathy of 7.9% in participants who had not developed diabetes compared with 12.6% prevalence in the sample of DPP participants who had developed diabetes with a mean duration of 3.1 years during DPP.(47a)

Epidemiologic (48,49) and interventional studies, such as the Diabetes Control and Complications Trial (50) and the United Kingdom Prospective Diabetes Study (51) have contributed to our understanding of the relationship between glycemia and complications by performing secondary analyses that plot the development (or risk for progression) of retinopathy against mean hemoglobin A1c over time. These studies have had to extrapolate to the non-diabetic range; there were too few patients with "normal" hemoglobin A1c results to provide reliable estimates of risk in the low diabetic or high normal levels of hemoglobin A1c.

Despite the sometimes fierce ideological battles regarding the correct threshold at which diabetes can be diagnosed, the data on which such decisions have been made have not included patients studied from time of true onset. Moreover, all of the epidemiological studies to establish glycemic thresholds for the diagnosis of diabetes have relied on retinopathy as the complication that is most easily measured quantitatively and objectively. There are relatively few studies that examine the occurrence of kidney dysfunction, and specifically microalbuminuria, early in the course of diabetes, although it is known that microalbuminuria occurs in IGT and in the normal glucose tolerant (NGT) population, where it appears to impart increased risk for CVD events and

mortality. (52,64) A few studies show that increased albumin precedes the onset of Ty2DM. (52) There is very little hard data on microalbuminuria (MA) prevalence rates in IGT. A study in Nauruans (55) found it to be ~60% higher than in NGTs (absolute prevalence of 43%) and newly diagnosed diabetic subjects had a ~2.5 fold increased prevalence. The Finnish data (52) are probably more representative at 11.0%. The rates in most studies of clinically newly diagnosed diabetic subjects indicate a prevalence of 10-30%; in 2 studies the prevalence was at least 5-6 times higher than that in a control population (52,54,55,59,60,61). The incidence tends to progress with duration, but it is not a clear linear progression (53,56,57). In one study the prevalence almost doubled over 10 years from the value at the time of diagnosis (53). Since an important relationship exists with insulin resistance (52), the appearance of microalbuminuria may be less closely related to glucose levels per se, and interventions may reduce MA independently of glucose tolerance categories.

Table 4: Prevalence of Microalbuminuria

	NGT	IGT	Newly diagnosed DM	Established DM
Niskanen	3%		18.2%	33%
Fujikawa	4.1%			
Collins	26%	43%	63%	75%
Standl			19%	
Olivarius	5.6%		32%	
Kuusisto	>20%			
Forsbloom		11.0%	10.0%	
Mykkanen	15.6% (+IGT)			
Giuzar			10.6%	

There are relatively few studies of neuropathy in IGT or newly diagnosed diabetes (65-76). The literature varies on whether there is an increased prevalence of neuropathy in IGT. Surveys suggest prevalence rates in IGT varying from 0.5 - to 3-fold those in NGT (11-16% absolute prevalence rates using clinical measurements). This suggests the possibility that neuropathy may begin to emerge in the prediabetic state. A major problem in these studies is the lack of a uniform test to diagnose neuropathy and the lack of longitudinal studies, especially in IGT population. The prevalence was 4-6 times greater in clinically newly diagnosed diabetic subjects (14-43%) compared to NGT (66,70,73) and about 7 fold greater in established diabetic subjects (65,73,76), but it was not increased in diabetic subjects identified in a glucose intolerance screening program (67). Progression in either newly diagnosed diabetic subjects or individuals with established diabetes without baseline neuropathy was 2-5%/year (70,71,72,74,75).

Table 5: Prevalence of Neuropathy

	NGT	IGT	Newly diagnosed DM	Established DM
Ratzmann -Abnormal T&PP* -Loss of reflex			 14.7% 13.6%	
Sosenko		As NGT	As NGT	
Partanen	2%		8%	
Franklin (SLV)**	3.5%	11.2%		27.8%
Hoorn -Absent VS+ -Absent reflex	 0.5% 6.0%	 16.2% 15.6%	 43.3% 32.2%	 68.5% 67.1% 6.6 years duration
Fedele				32.3%

*Touch and pin-prick
**San Luis Valley Study
+Vibrating sensation

Better understanding of the clinical course of IGT and Ty2DM from the time of onset is critical for several reasons. Establishing the precise relationship between glycemic levels and the occurrence of "diabetic" complications plays a significant role in determining the level(s) of glycemia at which diabetes is diagnosed and therapy is considered. Moreover, such knowledge will contribute to our understanding of the pathogenesis of diabetic complications. Among the major hypotheses to explain the pathophysiology of diabetic complications, the "glycation" hypothesis is probably the most in vogue and has the most mechanistic data associated with it. (77,78) Since glycation occurs not only in red blood cells and hemoglobin, but also in all tissues and circulating proteins exposed to glucose, it should come as no surprise that there may be no specific threshold where one finds diabetic complications; rather, there may be a continuum of risk associated with glycemia, including in the sub-diabetic range. Only through studies of pre-diabetic patients, i.e. IGT, and new onset diabetes, will we have the opportunity to explore the pathophysiology of diabetic complications.

3.3.2. Epidemiology of CVD in IGT and New-onset Type 2 Diabetes

In addition to examining potential differential effects of the randomized interventions on CVD, atherosclerosis and CVD risk factors, further follow-up of the DPP cohort, with its IGT and newly diagnosed Ty2DM subjects, should shed light on the clinical course of CVD, atherosclerosis, and CVD risk factors in various states of glucose intolerance and during the transition from IGT to diabetes. Numerous studies have demonstrated that subjects with diabetes have a 2-4 fold increased likelihood of developing CVD. (11) It is generally believed that this increased risk for atherosclerotic vascular disease is driven by multiple risk factors, including dyslipidemia, hypertension, a procoagulant state and hyperglycemia itself, which frequently cluster in these individuals, linked together by insulin resistance and decompensating beta cell function. (14,28,29) The natural history of atherosclerotic vascular disease in IGT and diabetic subjects is not well understood. An increased risk for CVD in Ty2DM subjects is clearly present at the time of clinical diagnosis of diabetes. (30) Moreover, CVD risk factors associated with insulin resistance, such as higher blood pressure, and triglyceride levels, fibrinogen and PAI-1,

and reduced HDL-cholesterol levels, are found in normoglycemic adult subjects who go on to develop diabetes 8 years later, compared to those who do not, suggesting that the substrate for the increased risk for atherosclerosis is present many years prior to the development of diabetes. Atherogenic risk profiles accompany increasing glycemia in the sub diabetic range. (28,29) However, little is known about the subclinical and clinical course of atherosclerosis during the period when glucose tolerance becomes impaired, followed by development of diabetes.

Most reported studies suggest that the risk for CHD in IGT is intermediate between that in the general population and that in diabetic individuals. (14) However, some studies have not detected any difference in CHD frequency between normal glucose tolerance (NGT) populations and those with IGT, and others have found differences in men or women only. (13,31) Most of these studies were cross-sectional and many of the older surveys did not utilize the WHO diagnostic criteria to define IGT and are therefore difficult to interpret. Among prospective studies in subjects categorized into NGT and IGT groups according to WHO criteria, a Finnish investigation found no difference in CHD incidence. (32)

In addition to differences in the demographics, categorization of subjects, and study design influencing the apparent risk of CVD, the prognostic and metabolic heterogeneity of individuals with IGT inevitably must influence the intrinsic natural history of CVD in these subjects. Although there is little disagreement that Ty2DM is associated with a higher risk of CVD than is IGT, the reason(s) for these differences are not known. It is likely that those individuals with IGT who develop diabetes within a given period have a greater risk than those who do not; however, this has not been studied. Furthermore, there is no information about the risk factor profile or CVD incidence in newly converted diabetic subjects relative to those with IGT, or with longer duration diabetes. Finally, the relationships between established and newer CVD risk factors to subclinical and clinical CVD measures in subjects with IGT and newly diagnosed Ty2DM diabetes, and whether they differ between these two entities has not been studied. Of particular interest is whether glycemia per se is a determinant of increased CVD risk in subjects who convert from IGT to diabetes. Thus, a long-term prospective follow-up study of CVD risk factors, and subclinical and clinical measurements of CVD in a population with IGT, some of whom develop diabetes within the study period and continue to be studied, will provide critical information on the evolution of cardiovascular disease and the factors that influence it, in the preclinical phase of diabetes.

With the advent of the modified ADA diagnostic criteria (4) and the definition of the new category of impaired fasting glucose (IFG), several studies have suggested that IFG does not increase CVD risk compared to those with NGT (33) or alternatively that IGT increases susceptibility for CVD significantly more than IFG (34,35) does. In addition, in a recent large prospective study, HbA1c was continuously correlated with CVD mortality within a non-diabetic population. (36) Lastly, some studies have suggested that post-challenge glucose levels are more predictive of CVD than are fasting glucose levels in those with diabetes or impaired glucose tolerance. (37,38) In none of these studies was any attempt made to assess the unfolding role of the evolution of diabetes in non-diabetic subjects, which is clearly a crucial issue in attempting to clarify the nature of the relationship between glycemia and CVD over time.

DPPOS provides the opportunity to examine CVD, atherosclerosis, and CVD risk factors in a large, demographically diverse, prospectively studied population with IGT and newly diagnosed diabetes. Repeated measures of glycemia and CVD risk factors during and after the DPP make possible a large number of analyses that have never been possible before. By extending this assessment for a further 5-10 years, there should be a sizable group of diabetic

subjects who will have been studied through a phase of IGT and into a phase of diabetes, each lasting several years. Since the date of development of diabetic hyperglycemia is known within 6 months, it will be possible for the first time to track CVD risk factors, and subclinical and clinical outcomes as a function of this transition.

The DPPOS cannot strictly be viewed as a natural history study of IGT, nor of "undiagnosed diabetes" since both of these groups of subjects will have received more study- as well as non-study-based treatment in DPP and in the post-DPP period of follow-up than would occur naturally in the population. However, it is entirely possible that the most important determinant of CVD incidence in our entire study population may be found to be whether participants develop diabetes or not, irrespective of the interventions they have received. Such a finding would be of great importance to the conception of diabetes prevention. In addition, the relationships found to exist in this study between CVD risk factors and CVD subclinical and clinical outcomes will be informative, independent of interventions. We will carefully assess concurrent medication use during the follow-up study, since several effective medications for hypertension, dyslipidemia, and renoprotection are now available and will increase in use over time. Since there is evidence that blockade of the angiotensin system may slow progression to diabetes use of these agents will also be assessed (39,40).

3.3.3. Summary

In summary, the DPPOS provides the opportunity of addressing the clinical course of IGT and new onset Type 2 diabetes as it relates to microvascular disease and neuropathy. Specifically, the epidemiologic part of DPPOS will address the following: the level of glycemia at which retinopathy, neuropathy, and nephropathy develop; the incidence of complications in IGT and truly new onset Type 2 diabetes; the effect of conversion from IGT to diabetes on the development of these complications; the relative effects of fasting and post-prandial glucose levels and HbA1c on risk for developing complications; and the interactions among glycemic and non-glycemic risk factors on the development of the complications. In these epidemiological analyses, previous DPP therapy assignment will be included as one of many covariates.

3.4. Effects of Race-ethnicity and Gender

Over 45% of the DPP participants belong to a US minority racial or ethnic group: at baseline, 19.9% were African American, 15.7% Hispanic American, 5.3% American Indian, and 4.4% were Asian American. The majority of clinics enrolled >25% of participants from at least one non-Caucasian group. The major DPP study results suggested that the active interventions were effective across all racial-ethnic groups in the study, based on a negative test for heterogeneity. (4) However, the same questions posed for the entire DPP cohort in DPPOS are highly relevant in the individual ethnic-racial groups. The long-term effects of DPP interventions on clinical outcomes and the clinical course of IGT and new-onset Ty2DM is especially important in the minority populations because of the increased prevalence of Ty2DM in these groups, compared to the general population (6,78-83), and the suggestion, based on limited data, that the clinical expression of diabetes with regard to complications may be different between ethnic-racial groups. The long-term follow-up may shed light on ethnic-specific contribution of vascular risk factors for the development of micro- and macrovascular complications associated with diabetes or IGT. Similarly, there are limited data regarding the impact of gender on the

development of diabetes and its complications. Finally, though epidemiological studies have characterized the prevalence of diabetes in minority racial/ethnic populations, such studies have generally not provided ethnic, age, or sex-specific incidence rates. The highly compliant and motivated DPP cohort represents an excellent opportunity to examine these issues.

3.4.1. Risk Factors for Type 2 Diabetes and Diabetes-related Complications in Minority Populations

Risk factors for diabetes and its vascular complications such as IGT, decreased insulin sensitivity, hyperinsulinemia, central obesity, overweight, hypertension and gestational diabetes are more prevalent in African Americans. (84) Diabetic retinopathy also appears to be more common in African Americans with Ty2DM (85), though it is not clear whether the higher prevalence of diabetes is responsible. In the cross-sectional Baltimore Eye Study, there were equal rates of blindness secondary to diabetic retinopathy in Blacks and Whites. (86) Other studies have reported the prevalence of blindness to be twice in Black compared to White individuals and of severe visual impairment to be 40% higher among African Americans. (87) The prevalence of retinopathy in Blacks with Ty2DM in the 1988-1991 phase of NHANES III was higher than the rate in non-Hispanic Whites (NHW) but similar to that in Mexican Americans, though these data may reflect the higher rates of hypertension and poor diabetes control. (87)

Similar confounders complicate the interpretation of the 2.6 to 5.6 fold higher rates of end-stage renal disease (ESRD) in Black compared to White Americans with diabetes. (88) Complications of diabetes including retinopathy, nephropathy, ESRD, lower extremity amputation (LEA), heart disease and stroke are all more prevalent among American Indians than among Whites. (80) Complications of diabetes among Hispanics have largely been studied in Mexican Americans. The San Antonio Heart Study and NHANES III reported a greater prevalence of microvascular complications with 4.5 to 6.6 fold higher rates of ESRD than the general diabetic population and diabetic retinopathy being ~2 times more frequent in Mexican Americans, though this has not been confirmed in all studies. (88-90) These data regarding ESRD cannot be easily extrapolated to milder degrees of nephropathy.

Diabetic neuropathy is inherently difficult to study since measurement of nerve dysfunction has not been commonly performed in large epidemiological cohorts. While lower extremity amputations (LEA) may be a robust marker for severe peripheral sensory neuropathy, it represents a late stage of disease, frequently coincident with peripheral vascular disease and is relatively infrequent.

Cardiovascular disease is the major factor underlying the high mortality rates observed in Ty2DM. It is generally accepted that CVD rates in African Americans with diabetes are lower than the rates in NHWs. (91) Lower rates of heart disease have been reported in Mexican American men, compared with NHW men, but not in Mexican American women compared with NHW women. (92)

In none of these cross-sectional reports are minorities and NHW as well matched for demographic characteristics, risk factors, and comorbidities as in the DPP. The longitudinal follow-up and careful characterization of the DPP cohort should help to delineate the risks of developing diabetes and its long-term complications in men and women and in the ethnic-varied groups represented in the study.

4. DEFINITION OF OUTCOMES

4.1. Primary

4.1.1. Glycemia: OGTT and FPG (primary during Phase 1 and secondary during Phase 2)

The DPPOS primary outcome for Phase 1 is progression of oral glucose tolerance test (OGTT) results to confirmed diabetes, by ADA criteria (5). To assess progression to this outcome, an OGTT will be performed routinely on an annual basis under conditions described in the Manual of Operations. All biochemical laboratory outcomes will be measured at the DPPOS Central Biochemistry Laboratory. If the OGTT result meets ADA criteria for diabetes, the participant will be called back for a repeat OGTT within 6 weeks. In order to minimize the unmasking of participants and investigators to a positive but unconfirmed OGTT result, a subset of participants who do not have OGTT results positive for diabetes will be chosen by the Coordinating Center for repeat OGTT. If two sequential OGTTs, performed within a goal of 6 weeks of each other, are positive for diabetes, the clinic and the participant will be notified of the results and the participant will be considered as having reached the primary outcome. If the second test does not meet ADA criteria for diabetes (unconfirmed status), no such notification will be made and the participant will continue on the assigned treatment.

In addition, as a safety measure, participants will be monitored with a fasting plasma glucose (FPG) semi-annually or at any time symptoms suggestive of decompensated diabetes are noted. If this FPG is $\geq$ 126 mg/dL [7.0 mmol/L], the participant will be called back for a repeat FPG within 6 weeks. If the repeat is also $\geq$ 126 mg/dL [7.0 mmol/L], the participant will be considered as having reached the primary outcome, the participant and treatment team will be informed (see section 7.5.6), and an OGTT will be performed for data collection purposes to assess insulin secretion and sensitivity. Again, to maintain masking, the Coordinating Center will ask for a repeat FPG on a subset of non-diabetic participants with FPG < 126 mg/dL [7.0 mmol/L].

Finally, any participants who develop symptoms consistent with hyperglycemia will be encouraged to contact the clinic as soon as possible so that an FPG can be measured. If the FPG is $\geq$ 126 [7.0 mmol/L], the testing strategy outlined above will be followed.

Criteria for the primary outcome:

1 FPG $\geq$126 mg/dL confirmed within a goal of 42 day interval
2 2 hour OGTT sample $\geq$200 mg/dL confirmed within a goal of 42 day interval
3 one FPG $\geq$ 126 mg/dL and one 2 hour OGTT sample $\geq$ 200 mg/dL on two separate visits within a goal of 42 day interval.

During Phase 2 of DPPOS, the further development of diabetes, and the effects of the original interventions on the development of diabetes over the entire course of the DPP/DPPOS, will remain important secondary outcomes.

4.1.2. Composite Diabetes-related Microangiopathic and Neuropathic Primary Outcome

The composite diabetes-related microangiopathic primary outcome is defined as having one or more of the following during year 11 of DPPOS: a) nephropathy: microalbuminuria (≥30 mg/gram creatinine) or renal dysfunction (end-stage renal disease or GFR < 30 ml per min based on serum creatinine and using the MDRD equation),or b) retinopathy: retinopathy by fundus photography (ETDRS grade of 20 or higher) or history of documented laser surgery for retinopathy, or c) reduction or absence of monofilament light touch in either foot (< 8 detected applications of the 10 gram Semmes Weinstein Monofilament).

4.1.3. Composite Diabetes-related Cardiovascular Disease Secondary Outcome

The composite diabetes-related cardiovascular disease secondary outcome is defined as the time to first occurrence of one or more of the following: a) cardiovascular disease (CVD) events (CVD death, 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) hospitalized CHF, f) hospitalized unstable angina/acute coronary syndrome, or g) revascularization or amputation in lower extremity not caused by major trauma.

CVD events are determined at the time of their report and classified and adjudicated by an outcomes committee whose members are blinded to treatment group.

4.2. Other Secondary Outcomes

The DPPOS secondary outcomes were selected for their importance to the clinical and scientific interpretation of the study. They might help explain the mechanism of the primary outcome results, or shed light on how the interventions affect outcomes such as cardiovascular disease and its risk factors, which is at least as clinically meaningful as the primary outcome. Secondary outcomes may be assessed in the study population as a whole or in subsets of the study population, depending on feasibility, cost and the likelihood of deriving significant results from a subset. All biochemical laboratory outcomes will be measured at the DPPOS Central Biochemistry Laboratory. Clinical center staff and study participants are notified if a secondary outcome result falls outside a clinically acceptable range for that participant, constituting a concomitant condition. The timing of outcome assessments is described in Section 12.

Following is a brief summary of secondary outcomes that will be measured at specified intervals (see section 12) in all participants:

4.2.1. Glycemia and insulin secretion:

- HbA_{1c}: Hemoglobin A_{1c} will be assessed to reflect recent average glycemia, to test its relationship to OGTT results and its utility as an indicator of glucose intolerance for

the purposes of diabetes prevention, and as a predictor of microvascular and macrovascular endpoints.
- Insulin and glucose measurements during the OGTT.

4.2.2. Cardiovascular disease and risks, assessed by:

- Electrocardiogram
- Cardiovascular symptom and disease assessment
- History of serious cardiovascular disease events
- Arm blood pressure
- Ankle/arm systolic blood pressure: Ankle-brachial index
- Coronary artery calcium (funds permitting)
- Fibrinolysis and clotting factors: Fibrinogen, tissue plasminogen activator and C-reactive protein
- Lipoproteins: Lipid profile (total cholesterol, total triglyceride, HDL-cholesterol and derived LDL-cholesterol), or beta quantification in the setting of hypertriglyceridemia (specifically measuring LDL-cholesterol), LDL particle size and sub fractions
- Cardiovascular risk profile

4.2.3. Retinopathy, assessed by:

- Fundus photography
- History of documented laser surgery for diabetic retinopathy

4.2.4. Nephropathy, assessed by:

- **Albumin excretion:** Urinary albumin and creatinine concentrations for albumin excretion, using a spot collection.
- **Kidney failure:** defined as GFR < 30 ml per min based on serum creatinine and using the MDRD equation, or transplantation or dialysis
- **Serum cystatin**
- **Serum creatinine**

4.2.5. Neuropathy, assessed by:

- **Semmes Weinstein 10 gram monofilament examination**
- **Symptom assessment**
- **Michigan Neuropathy Screening Instrument**
- **EKG rhythm strip:** to measure heart rate variability

4.2.6. Physical activity, nutrition, behavioral, and body mass and obesity, assessed by:

- **Physical measurements:** Height, weight, waist circumference, BMI
- **Physical activity:** Standardized questionnaire assessment

- **Nutrient intake:** A semi-quantitative food frequency questionnaire.
- **Behavioral:** Dietary restraint, Exercise Self-Efficacy, Low Fat Diet Self-Efficacy

4.2.7. Health related quality of life, assessed by:

- **Psychosocial:** Beck Anxiety and Depression Inventories and the MOS SF-36, to assess mood and general adjustment and health related quality of life.
- **Cognitive performance**
- **Physical functioning**
- **Urinary incontinence**

4.2.8. Resource Utilization, Costs, Health Utilities, and Effectiveness of treatments, assessed by:

- **Quality of Well-Being Scale:** A preference-based measure for overall health used for quality-adjusted life year's computations.
- **Resource utilization instruments:** Questionnaires to capture resource utilization from the perspectives of the participant, and of the DPPOS staff
- **Hospitalizations**

4.2.9. Safety tests:

- **Routine chemistry testing:** Annual serum creatinine, and creatinine clearance annually for metformin participants over 80 years of age
- **Serious adverse medical events and symptoms:** Queries for serious adverse events. Medical records will be gathered in the case of significant cardiovascular intercurrent medical events.
- **Pregnancy testing:** As needed for metformin-treated participants, based on symptoms and menstrual history.
- **CBC:** Annually, for metformin-treated participants, measured locally

4.2.10. Serologic evidence of type 1 diabetes, assessed by:

- Samples for IA2 and GAD antibodies at time of diabetes conversion

4.2.11. Stored specimens:

- **Sample storage:** Samples of plasma will be stored for possible future analyses related to IGT and Type 2 Diabetes, and their complications. Samples for DNA were collected during the DPP.

4.2.12. Other chemistries:

- Relevant biological markers related to the pathogenesis of diabetes and its complications

4.2.13. Other research outcomes:

Other outcomes of the DPPOS include the incidence and determinants of these health outcomes in participants with new-onset diabetes and IGT, as well as the effect of age, race/ethnicity and gender on health outcomes.

5. STUDY DESIGN

5.1. Overall Design

The DPPOS is a prospective study of the effects of DPP interventions on continued prevention or delay of diabetes, and on preventing or ameliorating its complications, specifically diabetic microangiopathy, neuropathy and cardiovascular disease. The rationale for the overall design is to provide maintenance of therapies found to be effective in DPP to assess the long-term impacts on diabetes prevention and complications.

All DPP participants were offered the opportunity to participate in the group lifestyle intervention protocol during the Bridge period, January through June 2002. They will be offered the opportunity to continue a long-term maintenance of lifestyle intervention program, consisting of quarterly Healthy Lifestyle Program (HELP) meetings. In addition, DPP intensive lifestyle participants will be offered 4 weekly or bi-weekly behavior boost sessions in groups twice yearly, and DPP metformin participants will be provided open label metformin (850 mg bid) These are summarized below:

Treatment group name during DPP	Treatment group name during DPPOS
Intensive lifestyle intervention (ILS)	Boost Lifestyle (BLS)
Metformin with standard lifestyle (MET)	Metformin/Group Lifestyle (MLS)
Placebo with standard lifestyle (PLB)	Group Lifestyle (GLS)
Troglitazone with standard lifestyle (TRO)	Group Lifestyle (GLS) (will no longer be research volunteers as of protocol version 3.0)

All DPPOS participants will have twice-yearly clinic visits. Health outcomes assessment will include a brief medical history and fasting glucose measurements at the midyear interval, and an OGTT, HbA1c, questionnaires, and anthropometric measures and biochemical measurements annually. Fundus and neurologic examinations, and measures of subclinical atherosclerosis and cardiovascular events will be performed as stipulated in Section 12.

Assessment of microangiopathic and cardiovascular measures will be performed in both diabetic and non-diabetic DPP participants during the 11 years of the DPPOS. Both individual and composite endpoints will be assessed. The long-term effects and cost-effectiveness of interventions on the incidence and determinants of these outcomes will be assessed based on the original randomly assigned interventions during DPP.

In addition to the primary and secondary objectives, separate analyses will be performed to assess the importance of development of diabetes and other determinants on the development of microangiopathic and cardiovascular outcomes. Subgroup analysis will be performed based on gender, age and race/ethnicity.

5.2. Participation Criteria

All DPP participants will be eligible to participate in the DPPOS. For DPPOS protocols prior to version 3, participants included both diabetic and non-diabetic subjects from each of the four original intervention groups. Beginning with protocol version 3.0, the original troglitazone

participants will no longer participate in DPPOS research activities. Inability to attend group sessions for logistical or heath reasons will not be a criterion for exclusion.

5.3. Principles Guiding the Selection of a Study-wide Group Lifestyle Intervention

The decision to offer effective therapy to the DPP cohort at study end was based on the sense of the DPP Research Group and NIDDK that initiating effective therapy was consistent with our obligation to the participants who had made the DPP possible. Although this decision was not based on any scientific imperative, the Research Group did not think that it would interfere with the follow-up study as designed. Continuing to apply the DPP interventions during DPPOS was based on the expectation that a positive effect of DPP interventions on long-term health outcomes would more likely be obtained if the interventions that were effective in DPP were maintained to some degree in the DPPOS, recognizing that the DPP placebo group would now receive lifestyle intervention as well. This design for DPPOS was thought more likely to minimize confounding of the effects of the past DPP interventions through the introduction of non-standardized therapies by participants and their health care providers.

During the final six months of the DPP (January – June 2002) all participants in the original MET, PLB, and TRO groups were offered the Healthy Lifestyle Program (HELP), an intensive program with the same goals used in the DPP, but provided in a group, rather than an individual setting (DPP Bridge Protocol, version 4.5). During this period, the former ILS group continued with the DPP ILS program, albeit with less frequent contact than during the DPP, owing to resource limitations, and attended the HELP sessions if they desired. In DPPOS all participants will be offered quarterly group sessions to encourage the maintenance of their lifestyle interventions. These meetings should, in addition, help to encourage continued participation in the DPPOS. The use of twice yearly behavior boost groups for the DPP ILS participants is intended to reinvigorate their previous efforts at achieving weight reduction and increased physical activity in a manner that requires only modest staff involvement. Metformin will be provided to all participants who were receiving metformin treatment in DPP in order to maintain long-term intervention with this agent. Although the provision of lifestyle training to the DPP PLB group may reduce differences in long-term outcomes between intervention groups, it is unavoidable. Moreover, the potential benefits of the active interventions during DPP on long-term outcomes, combined with efforts to boost the earlier impact of intensive lifestyle management, and continuing with metformin treatment, provide the opportunity to examine and compare the long-term effects of these interventions on an intention-to-treat basis.

5.4. Timing and Condition of Outcomes Assessment

5.4.1. Development of Diabetes

Progression from impaired glucose tolerance (IGT) to diabetes is assessed by OGTT testing annually, or by fasting plasma glucose (FPG) at the intervening 6-month visit, or any visit at which symptoms consistent with hyperglycemia are reported. Conditions for the OGTT are specified in the Manual of Operations and remain unchanged from the DPP. The annual OGTT will be postponed for up to six weeks if a temporary concomitant condition exists that would affect glucose tolerance. An OGTT that is positive for diabetes, or a FPG that is ≥ 126 mg/dL [7.0 mmol/L], will be repeated for confirmation before the participant is considered to have

developed diabetes. When a participant has been in a "time-out" (other than for pregnancy), such as for a concomitant disease known to affect glucose tolerance, the fasting glucose assessment or OGTT will not be assessed at the mid-year or annual visit. Limited random repeat testing will be done to maintain masking to the occurrence of development of diabetes until the result of the confirmation test is available.

5.4.2. Other Outcomes

Individual and composite microangiopathy, neuropathy, cardiovascular, quality of life and health cost outcomes will be assessed according to the schedule listed in Section 12.

5.5. Masking

There will be no masking of participants to OGTT or lipid results, other than in the case where confirmation of a positive test for diabetes is pending (or during a random repeat fasting glucose or OGTT). Metformin is dispensed as open label.

6. PARTICIPANT MANAGEMENT PROTOCOLS

Each participant is asked to continue treatment according to his or her original DPP randomized assignment:

- Participants in the DPP original Intensive lifestyle intervention, now called the Boost Lifestyle (BLS), are offered the Healthy Lifestyle Program (HELP), plus the Boost Lifestyle program.
- Participants in the original Metformin group, now called Metformin/Group Lifestyle (MLS), are offered continued treatment with metformin, plus the HELP.
- Participants in the original Placebo group, now called the Placebo/Group Lifestyle (GLS), are offered the HELP.
- Participants in the original Troglitazone group, now called the Troglitazone/Group Lifestyle (GLS), are offered the HELP, but will not participate as research volunteers in DPPOS beginning with protocol version 3.0.

6.1. Schedule of Follow-up Visits

Follow-up visits for outcome measurements will be scheduled at 6-month intervals throughout the duration of the DPPOS. Annual visits will be targeted for the anniversary of the participant's original DPP randomization date. HELP group meetings will be offered four times per year, at several different times at each clinic in order to make convenient meeting times available for a large number of participants. Boost sessions will be offered twice per year, and similarly scheduled multiple times for purposes of convenience. Except for participants from the original Troglitazone group, who will cease study participation beginning with protocol version 3.0, all participants will continue their scheduled follow-up visits for the duration of DPPOS regardless of their level of compliance with the assigned treatment. Outcome and safety assessments will be conducted according to the schedule in section 12.

6.1.1. Interim Visits

An interim visit refers to all visits other than scheduled follow-up visits. Interim visits may be required for the monitoring or management of an emerging or existing medical condition, or to repeat procedures that were found to be deficient at a previous visit. Such visits may be held as frequently as deemed necessary.

6.1.2. Confirmation (CON) Visits

In order to confirm the diabetes outcome, confirmation (CON) visits are required whenever a participant has an elevated fasting ($\geq$ 126 mg/dl) or stimulated ($\geq$ 200 mg/dl) glucose.

6.1.3. Suspension of Follow-up Visits

The occurrence or presence of the following will constitute inactive follow-up and suspension of the scheduled follow-up protocol: Voluntary withdrawal by the participant, or

condition that, in the opinion of the principal investigator, makes it unsafe for the participant to continue. Efforts to return participants to an active status will be made regularly, as appropriate.

6.1.4. Home Visits

A home visit is any visit outside the DPPOS clinical center. Home visits will be used as needed and should not be used regularly to take the place of a clinic visit unless the participant is permanently unable to attend the clinical center. Local IRB issues should be addressed concerning off-site blood draws. All guidelines regarding the collection of outcome measures (such as fasting glucose) must be followed. A medical staff person who is certified to perform the listed outcomes should perform the home visit.

The purpose of a home visit is to retain and /or reactivate participants and to collect important outcome data on participants who are having difficulty attending a clinic visit. Information on Serious Adverse Events will be collected at a home visit. In rare cases, the visit may also be utilized to perform a safety blood draw when a medication participant is unable to attend a clinic visit. Home visits should only be conducted for participants who live relatively near the clinical center. Clinic staff is not expected to travel great distances to visit any inactive participant. Clinics will decide whether or not a specific home visit is feasible, taking into account time, cost and risk.

6.2. Lifestyle

Recognizing that long term adherence to healthy eating and exercise behaviors and maintenance of moderate weight loss and physical activity require ongoing support and intervention, lifestyle intervention efforts will be continued during the DPPOS for <u>all</u> previously randomized participants until the end of Phase 1, and for all but the former Troglitazone participants, who will not participate in DPPOS research beginning with protocol version 3.0. To maximize the chances of all participants achieving and/or maintaining the 7% weight loss goal and 150 minute weekly physical activity goal which was the cornerstone of the lifestyle intervention during DPP and the DPP Bridge, Healthy Lifestyle Program (HELP) maintenance sessions will be provided quarterly to all DPPOS participants. In addition, participants who were previously randomized to the intensive lifestyle arm in DPP will be given Boost Lifestyle Sessions in a group format, two times each year. The goals of lifestyle treatment for all DPPOS participants are the same as in DPP:

- Achieve a weight reduction of at least 7% of initial (at DPP baseline) weight and maintain this weight reduction
- Achieve at least 150 min/week of moderate intensity exercise (such as walking and bicycling), and maintain this level of physical activity

6.2.1. Lifestyle Resource Core and Lifestyle Advisory Group

The Lifestyle Resource Core (LRC) and the Lifestyle Advisory Group (LAG) which is comprised of co-investigators and staff representing several DPPOS centers will develop the materials for the HELP maintenance and BLS sessions and provide on-going training and support for the lifestyle interventionists. All materials are reviewed and approved by the DPPOS Executive Committee prior to implementation.

6.2.2. Staff for Lifestyle Interventions

Case managers, group lifestyle interventionists, and/or consultants at each clinical center will carry out both arms of the lifestyle intervention. Interventionists will be individuals with experience and/or training in nutrition, exercise, behavior modification, or group treatment. Other staff (e.g. peer counselors and exercise leaders) is employed as appropriate at each center.

6.2.3. HELP Program

Following the delivery of the 16 session Healthy Lifestyle Program (HELP) that was offered to all previously randomized participants during the DPP Bridge, quarterly HELP maintenance sessions will be offered to all participants. The purpose of the quarterly lifestyle sessions is to reinforce the basic content, as well as the weight loss and physical activity goals. In addition, the quarterly sessions will serve a participant retention purpose. Small incentives, such as gift certificates and lifestyle-relevant materials such as recipe books (gifts are valued in the range of $2.00-10.00) will sometimes be used to reward attendance and participation at these group education sessions. Every effort will be made to make the sessions topical, interesting, and fun (e.g. may involve doing cooking demonstrations, muscle resistance training, stress management and relaxation training etc.) The quarterly sessions will rotate annually through the following content areas:

- Nutrition
- Physical activity
- Stress management/motivation/behavioral self-management
- Diabetes prevention research updates
- Diabetes research and management updates

Each of the four sessions will be offered up to 5 times in the quarter at each clinical center with approximately 20-40 DPPOS participants attending any one-class session. Topics and lesson materials, handouts, and homework assignments are being developed by the Lifestyle Resource Core and will be outlined in detail in the Lifestyle Intervention Manual of Operations for DPPOS. The first quarterly session will begin within 2-3 months after DPPOS begins.

6.2.4. Boost Lifestyle (BLS)

During the DPP Bridge period, DPP intensive lifestyle participants (ILS) either attended the HELP group sessions and/or were encouraged to be seen individually by their lifestyle case managers at least every 8 weeks. During DPPOS these participants will be offered Boost Lifestyle sessions in addition to Group Lifestyle sessions. The purpose of BLS is to offer periodic, structured "restarts" for lifestyle arm participants who have already received intensive, long-term, individual lifestyle intervention. The BLS sessions are intended to reinforce specific behavioral self-management activities (e.g., self-monitoring of fat, calories, and/or physical activity minutes as well as weight checks), which are important for weight loss and physical activity adherence and/or maintenance. An additional focus of the BLS will be to promote home-based behavioral self-management of weight and physical activity through the use of

motivational campaigns. In addition to reinforcing attendance at group sessions, incentives (valued at $5.00 - $20.00) will also be used to reward lifestyle behavior change such as designated weight loss goals, activity goals, self-monitoring of diet and other healthy lifestyle changes. The BLS sequences for each clinical center are characterized as follows:

- The four session restart program will be offered over a period of 4-8 weeks
- A new sequence will be offered in the Spring and Fall of each year
- The program will be conducted in groups of approximately 10-20 participants
- Approximately 1-3 groups will be conducted during each Spring and Fall sequence, as necessary at each clinic to accommodate the BSL (former ILS) participants

Centers will be encouraged to help participants who have been working primarily in intensive, individual lifestyle treatment to make the transition to the group Boost sessions. However, if staff is available, they will be permitted to conduct individual visits, mailings, and/or phone calls to support lifestyle participants in making this transition to group intervention. Topics and lesson materials, handouts, and homework assignments to be utilized in BLS are being developed by the Lifestyle Resource Core and are in the Lifestyle Intervention Manual of Operations for DPPOS. The first BLS session will begin within 2-3 months after DPPOS begins.

6.2.5. Indices of Adherence

Adherence to the HELP program and BLS will be assessed in the following manner:

- Group contacts will be recorded primarily to assess attendance at both HELP sessions and BLS visits
- Adherence to the 7% weight loss goal is determined from measured body weight at mid-year and annual clinic visits for all participants
- Weight data and self-reported physical activity minutes will be collected at the BLS sessions
- Performance of physical activity is determined from interviewer administered questionnaires that assess physical activity at annual clinic visits for all participants

6.3. Metformin Pharmacological Treatment

6.3.1. Description of Intervention

The pharmacological intervention is metformin 850 mg bid, as tolerated. DPP participants who had been randomized to active metformin and are still eligible to take medication will remain in the medication arm of the follow up study. This will allow the longest possible period of continued exposure to metformin to determine its longer-term effects.

Participants who are not eligible to continue study-supplied metformin are those who cannot tolerate metformin, whose creatinine is outside the normal range, who reached the fasting hyperglycemia ($\geq$ 140 mg/dL) outcome during DPP, who have been taken off metformin for

other medical reasons, and/or those who have diabetes and whose HbA_{1c} was measured $\geq$ 7% by the DPPOS Central Biochemistry Laboratory. Metformin is an investigational drug for the treatment of IGT and is used under an Investigational New Drug (IND 49,782) application with the Food and Drug Administration (FDA).

6.3.2. Mechanism of Metformin Action

Metformin is an antihyperglycemic drug of the biguanide class used in the management of Type 2 diabetes in over 90 countries for over 30 years. It was approved for use in the U.S. in 1995 and is distributed by Bristol Myers-Squibb under the trade name Glucophage, and manufactured by Lipha, a French pharmaceutical firm. Generic products are now available as well.

Metformin reduces the excess hepatic glucose production that characterizes Type 2 diabetes without increasing insulin secretion. With reduced hyperglycemia, glucose uptake by muscle and other insulin sensitive tissues is enhanced while insulin levels remain stable or decline. In addition to its antihyperglycemic action, metformin also has antihyperlipidemic effects; particularly the lowering of serum triglyceride levels and is sometimes associated with weight loss.

Metformin has been found to cause lactic acidosis rarely (about 0.03 cases per 1,000 person years) and then only when used in persons with renal or hepatic insufficiency or during episodes of hypoxia or circulatory failure.

Before its 1995 release in the U.S., and after review of extensive metformin use in Canada, Europe and other parts of the world, Bristol-Myers Squibb issued an FDA approved package insert providing detailed contraindications, precautions and safety monitoring recommendations for its use in Ty2DM. During the DPP all of these recommendations (including periodic assessment of serum creatinine) were strictly adhered to and the maximum dosage used (1.7 gm/day) was less than the maximum recommended (2.55 gm/day).

Metformin is not currently approved for use as a preventive medication for the development of Ty2DM. However, the DPP demonstrated that metformin is effective in persons with impaired glucose tolerance, reducing the development of diabetes by 31%.

The most common side effects associated with metformin are gastrointestinal. As many as 30% of persons report diarrhea, nausea, metallic taste, abdominal bloating, flatulence or anorexia. These symptoms are generally transient, resolve spontaneously and can be avoided by gradual escalation of dosage. Metformin is not associated with hypoglycemia unless used in conjunction with other glucose-lowering medications (sulfonylurea or insulin). About 4% of participants were unable to continue metformin in U.S. clinical trials.

About 6-9% of persons on metformin develop reduced vitamin B12 levels. However, megaloblastic anemia is rare and metformin use has not been reported to cause peripheral neuropathy.

6.3.3. Dosing Schedule and Restarts

Administration of metformin will be 850 mg twice each day, taken with food, and with doses recommended to be at least eight hours apart.

If a participant has a lapse in treatment due to illness, hospitalization or other cause and is eligible to restart the medication, then a plan for restart and titration should be considered. This

plan should be based on clinical judgment taking into account the amount of time off metformin and the individual's history of side effects.

6.3.4. Safety Monitoring and Measures to Reduce and Manage Potentially Drug related side Effects

A. Laboratory Safety Monitoring

During the DPPOS all participants assigned to open label metformin will have an annual CBC with differential count and serum creatinine. Women in the metformin treatment group will be asked to get immediate pregnancy testing if their menstrual cycles are more than one week overdue or they otherwise suspect they are pregnant. At the annual visit following their 80th birthday, for participants who are over the age of 80 years, annual creatinine clearances will be initiated.

B. Potential Non-Gastrointestinal Side Effects

Potential non-gastrointestinal side effects include, but are not limited to: headache, mild edema, leg cramps, arthralgia, myalgias, dizziness, mild rashes, and dysmenorrhea. If non-gastrointestinal side effects considered likely to be due to metformin occur and require cessation of metformin, it will be stopped for four weeks. If the non-gastrointestinal symptoms disappear, a second attempt to introduce medications is made after the four weeks. If symptoms re-occur, the metformin will again be discontinued. Clinical judgment should be used to decide continuing attempts. The plan for restart and titration of metformin is based on clinical judgment taking into account the amount of time off metformin and the individual's history of side effects. See MOO for suggested steps for restart.

C. Discontinuation of Metformin Use During Hospitalizations

Metformin should not be used in patients with hypoxia or circulatory failure and should be discontinued before the administration of contrast dyes and surgery requiring general anesthesia. To avoid having metformin administered inadvertently to hospitalized participants in whom it may be contraindicated, medication will be discontinued during hospitalizations. Testing of glucose tolerance for DPPOS will be delayed until medication has been resumed for at least two weeks. However, glucose tolerance testing will be performed within 6 weeks even if medication has not been restarted, assuming that the subject does not have a concomitant condition that substantially interferes with glucose tolerance. If the participant has a serious condition (e.g., recovering from major surgery, on high doses of steroids, ongoing febrile illnesses) known to affect the glucose tolerance adversely, the testing will be postponed until the next regularly scheduled testing of glucose tolerance. Participants will have a GTT or FPG at least annually.

D. Gastrointestinal Symptoms

These symptoms include diarrhea, abdominal pain, vomiting, nausea, a metallic taste, bloating, flatulence and anorexia. If these symptoms are mild and tolerable, medications will be continued. If they are moderate or difficult to tolerate, they will be presumed initially to be due to metformin and metformin will be withheld, at least temporarily. In the event that diarrhea, abdominal pain or vomiting becomes severe enough to cause dehydration or volume depletion, metformin will be discontinued immediately and the participant will be evaluated and treated appropriately.

E. Renal Insufficiency

Serum creatinine safety measurements will be made yearly in participants in the metformin arm who are taking metformin. Metformin is not known to cause renal insufficiency. However, it is associated with an increased risk for lactic acidosis if used in persons whose glomerular filtration or creatinine clearance rates are below 60 mL/min (per 1.73 m^2 surface area). Thus, metformin use is contraindicated with serum creatinine ≥ 1.5 mg/dL [133 μmol/L] in men and ≥ 1.4 mg/dL [124 μmol/L] in women. If creatinine levels are high, metformin will be discontinued and the serum creatinine will be rechecked in two weeks. Metformin will be restarted if the repeat serum creatinine is < 1.5 mg/dL in men or < 1.4 mg/dL in women. If the serum creatinine is again ≥ 1.5 mg/dL [133 μmol/L] in men or ≥ 1.4 mg/dL [124 μmol/L] in women, regardless of the cause, metformin will be stopped permanently and participants will be referred to their health care providers for an evaluation of potential causes of elevated creatinine. For participants who are permanently off study medication, elevations in serum creatinine do not require confirmation, but will be reported to the health care provider. A creatinine clearance will be performed for all participants who are 80 years of age or older, and yearly thereafter. Metformin will also be discontinued in individuals who have a post-randomization creatinine clearance (based on a 24 hour urine collection) level < 75 mL/min.

F. Anemia

A CBC will be determined for safety reasons at yearly intervals in participants in the metformin treatment group who are taking metformin. If anemia (defined as a hematocrit < 36.0% in men and < 33.0% in women) or significant macrocytosis develop, or if the hematocrit decreases by 4 or more points from the level at study entry (e.g., from 44% to 40%) the participant and primary care provider will be notified. Medication may be continued if the cause of the anemia is identified and treated. This includes the administration of vitamin B-12 when indicated.

G. Pregnancy and Nursing

Female DPPOS participants of childbearing age who are fertile have been informed of the potential risks to a pregnancy conceived while on metformin treatment. These women will be asked to practice reliable birth control including systemic hormones, intrauterine devices or barrier methods (diaphragm, male or female condom, cervical cap) with concomitant intravaginal spermicide.

Women in the metformin treatment group will be asked to get immediate pregnancy testing if their menstrual cycles are more than one week overdue or they otherwise suspect they are pregnant. If a woman plans to become pregnant or becomes pregnant, metformin will be discontinued. Following the pregnancy and nursing, metformin will be restarted with consideration of titration from one 850 mg tablet to two tablets over four weeks. See the Protocol Section 7.5 for more details about metformin use following pregnancy.

H. Radiological Studies Using Contrast Dyes

Because of the potential danger of contrast induced renal insufficiency and lactic acidosis associated with metformin, under these conditions, the last dose of medication will be administered on the day prior to administration of contrast dyes. Serum creatinine level will be checked 48 hours or more after dye administration. Metformin will be re-started if the serum creatinine levels are in the acceptable range (< 1.5 mg/dL (133 μmol/L) for men and < 1.4 mg/dL (124 μmol/L) for women). A wallet ID will be given to all participants and a warning letter will be sent to all primary care providers to alert them to the fact that participants are taking metformin and that metformin needs to be discontinued prior to any radiological studies involving contrast dyes.

I. Lactic Acidosis

Metformin may rarely be associated with the development of lactic acidosis, defined as a metabolic acidosis with lactate ≥ 5.0 mM. If hospitalization or an unexplained metabolic acidosis occurs, metformin will be discontinued immediately and not restarted. The participant will be evaluated and treated appropriately.

J. Hypoxic States - Congestive Heart Failure

States of hypoxia or hypo perfusion, including acute congestive heart failure and acute myocardial infarction, may lead to lactic acidosis and require discontinuation of metformin and treatment of the underlying condition. If the underlying hypoxic state is corrected or if CHF is transient (for example, after an acute MI), reinstitution of medication may be considered. Medication arm participants who develop CHF (NYHA Functional Class > 2) during the study should have their metformin stopped. Medication arm participants who develop NYHA Functional Class 2 and require a loop diuretic or digitalis should have their metformin stopped.

K. Surgical Procedures

Because of the risk of metabolic acidosis during general anesthesia and major surgical procedures, medication will be suspended prior to such anticipated surgical procedures, with the last dose administered on the day prior to surgery. Medication will obviously be held while participants are NPO for procedures. Serum creatinine should be checked 48 hours or more after such procedures and medication will be restarted if the serum creatinine levels are in the acceptable range < 1.5 mg/dL (133 μmol/L) for men and < 1.4 mg/dL (124 μmol/L) for women). If an outpatient procedure is scheduled, a letter will be sent to surgeons to alert them to the fact that medication must be discontinued prior to surgery.

L. Dermatological Reactions

In the event of major dermatological reactions such as generalized urticaria, bullous rashes, exfoliative dermatitis or Stevens Johnson Syndrome, medication will be discontinued immediately and not restarted. For localized skin reactions, medication may be discontinued if the skin reactions are potentially drug related. If the rashes clear, medication may be restarted after four weeks, starting at the Step I dosage level and then progressing to Step II after another four weeks. If localized skin reactions recur with restarting the metformin, metformin should be discontinued.

M. Headaches

Metformin has sometimes been associated with transient headaches, although not more frequently than placebo. However, headache is not a reason to decrease or discontinue the metformin unless severe and no other causes are found.

6.3.5. Indices of Adherence

The goal of the pharmacological treatment is to optimize adherence to the pharmacological regimen, while maximizing retention of participants in the DPPOS. Assessment of adherence to the prescribed medication will provide clinic staff a means to identify participants having problems with adherence.

The following will assess adherence to the pharmacological treatment:

- Visual inspection of participant's returned pill containers including a pill count estimating the percent of prescribed medication taken.

- A brief, structured interview, during which the case manager will assist participants to identify problems with adherence to metformin and to develop strategies to promote adherence, as needed.

7. DEFINITION AND MANAGEMENT OF CONCOMITANT CONDITIONS

Clinical centers are neither sufficiently staffed nor funded to provide primary care or ancillary care to participants involved in DPPOS. Whenever possible and acceptable to the referring primary care provider, conditions significantly affecting either the primary or secondary outcomes of the DPPOS should be cared for as specified by protocol within the context of the DPPOS in order to protect the integrity of the DPPOS research questions. Treatments for concomitant conditions can potentially affect either the primary or secondary outcomes. The following sections provide guidelines for therapy, which should be vigorously recommended. However, investigators and staff must be sensitive and at times flexible with regard to the prerogative and needs of the primary care providers who have participants enrolled in DPPOS. If the following conditions arise during the course of DPPOS, the investigator will contact the primary care provider by letter, informing him/her of the condition and provide a copy of the treatment options developed for DPPOS participants. Discussions with the primary care provider should be conducted in the spirit of negotiation and collegiality, with the intent of including the referring primary care provider in DPPOS operations. Referring to primary care providers, community resources will treat all other conditions not directly related to DPPOS outcomes or the clinical center as determined by referral patterns.

7.1. Hypertension

There is a strong association between type 2 diabetes and hypertension, apparently independent of age and obesity (93). The baseline characteristics of the DPP cohort reveal 29% of men and 26% of women with a history of hypertension at entry. These percentages varied by ethnicity, with African American men as high as 35% and Hispanic women as low as 20%. Following are recommendations for treatment:

7.1.1. Goals of Therapy

For those individuals developing diabetes during the course of DPPOS, therapy should aim at meeting the Standards established by the American Diabetes Association (94) maintaining BP < 130/80 mmHg. For those participants who have not developed diabetes, the goal of therapy should be those of the 6th Joint National Commission to maintain BP < 140/90.

7.1.2. Monitoring

Outcome assessment for the categorical outcome of hypertension as well as the continuous variables of blood pressure will be undertaken semi-annually during DPPOS. A new diagnosis of hypertension will be made on the finding of either:

- Initiation of pharmacologic therapy for the treatment of hypertension, or
- For those who are non-diabetic: Systolic BP $\geq$140 or diastolic BP $\geq$90 on a mean of two (2) measurements, or
- For those who are diabetic: Systolic BP $\geq$130 or diastolic BP $\geq$80 on a mean of two (2) measurements

The DPPOS staff will communicate findings of elevated blood pressure to the participant and to the health care provider for follow-up and possible treatment.

7.1.3. Diet

Non-pharmacologic therapy should be employed initially, consisting of a prudent diet aimed at weight reduction if necessary and moderate sodium restriction (<2.3 g of sodium), limitation of alcohol intake, and encouragement of physical activity. The participant and primary care provider will receive a standard printed set of instructions outlining the goals. Participants will be advised to lose weight if overweight, limit alcohol intake to <1 oz per day of ethanol, exercise aerobically regularly, maintain adequate potassium, calcium and magnesium intake, stop smoking, and reduce dietary saturated fat and cholesterol intake. These guidelines will reinforce the standard lifestyle recommendations already in place by DPPOS.

7.1.4. Drug Therapy

Drug therapy should be based on specific needs of the participants, potential side effects of therapy, and consideration of other factors such as cost and availability. The choice of antihypertensive therapy and the monitoring of both its efficacy and side effects will be up to the primary care provider outside of the DPPOS.

7.2. Hyperlipidemia

A fasting lipid profile, consisting of triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol and VLDL-cholesterol will be obtained at annual visits

7.2.1. Diabetic Participants

For those individuals who develop diabetes during the course of DPPOS, the ADA Standards of Care will be followed (95). The categories of risk as defined by lipoprotein levels are shown below:

Risk	LDL-cholesterol	HDL-cholesterol	Triglycerides
High	$\geq$ 130	< 35	$\geq$ 400
Borderline	100-129	35-45	200-399
Low	<100	>45	<200

Category of risk based on lipoprotein levels (mg/dl)

(Note, for women, the HDL cholesterol values should be increased by 10 mg/dl).

Diagnosis of dyslipidemia in diabetic participants will be made on the basis of either an LDL-cholesterol > 100mg/dl, HDL-cholesterol < 45mg/dl for men or < 55mg/dl for women, or a triglyceride > 200 mg/dl. Achieving improvement of these parameters beyond the diagnostic limits will be the treatment goals, as defined by the ADA in its most current recommendations. The consideration of lipid lowering therapy will be left to the discretion of the primary care provider, but the current ADA guidelines are to be strongly recommended.

7.2.2. Non-diabetic Participants

For those individuals in DPPOS who have not developed diabetes, the guidelines established by the Adult Treatment Panel (ATP) III of the National Cholesterol Education Program (96) should be followed. These call for identification of those individuals with established diabetes to be automatically placed in the same high-risk group as those with established CVD.

7.2.3. Other High Risk Participants

Additional individuals may qualify as high risk based upon risk factor identification as delineated by ATP III. Goals of therapy are then individualized based upon the participant's risk of developing atherosclerotic heart disease. More precise long-term risk estimation may be undertaken at the discretion of the primary care provider through calculation of Global Risk. Treatment strategies will be left to the discretion of the primary care provider, with the ATP III guidelines being strongly recommended.

7.3. Cardiovascular Disease

Cardiovascular disease events have been chosen to be one of the secondary outcomes in DPPOS. The incidence of CVD is increased in participants with newly diagnosed Ty2DM, and the risk of deaths in non-diabetic participants with IGT is two times higher than in participants with normal glucose metabolism. Although the CVD event rate during the course of the DPP was quite low and showed no effect of randomized therapy, long-term follow-up may reveal differences based on DPP assignment as incidence of CVD increases with age. CVD events in participants recruited to the DPPOS are significant for several reasons:

- CVD outcomes might be differentially affected by the assigned interventions,
- CVD may have an effect on prognosis of the participants recruited,
- The symptoms of CVD may have an effect on the capability of participants to follow the guidelines of treatment, and
- The conversion rate from IGT to Ty2DM may be higher in participants with CVD than in participants without CVD.

Mid-year and annual history will ascertain the incidence of new CVD events as was performed during the DPP. ECGs will be obtained at the annual visits for central reading and adjudication of silent infarcts.

7.3.1. Myocardial Infarction or Unstable Angina

Their PCP according to the community standards should treat participants who have myocardial infarction or unstable angina during the DPPOS. According to the American Heart Association Guidelines a submaximal exercise test should be performed within three weeks after an acute MI (97). The decision whether participants are allowed to continue the exercise program or whether their exercise program should be modified is based upon the recommendation of their primary care providers.

7.3.2. New Angina Pectoris

Participants who have new symptoms suggesting angina pectoris during the DPPOS should be treated by their Primary Care Providers (PCP). DPPOS will recommend to the primary care provider that participants be treated according to the community standards including cardiological evaluation and possible exercise tolerance testing may be recommended to them. Participants will have their exercise program discontinued until the cardiological evaluation has been performed and their eligibility to continue the exercise protocol should be reconsidered after the results of the evaluation are available.

7.3.3. PTCA or Coronary By-Pass (CABG)

According to the American Heart Association Guidelines, exercise tolerance testing should be performed in the routine follow-up of patients who have undergone PTCA, and to any patient who complains of chest pain during exercise after these procedures. Participants of DPPOS who undergo PTCA or CABG should be allowed to discontinue the exercise component of the DPPOS protocol for up to six months, if necessary. After this period their health status should be re-evaluated by their primary care provider to determine their continuation in the exercise portion of the protocol.

7.3.4. Medical Treatment

The participant's PCP will determine medical treatment of CVD. Beneficial effects of beta-blockers and ACE inhibitors on mortality and recurrent CVD events after myocardial infarctions are clear. The participants with heart failure should be treated according to community standards. The PCP's for all DPPOS participants with diabetes or diagnosed CVD will be advised (98) regarding the value of aspirin therapy (81-325 mg daily).

7.4. Psychological Diseases and Use of Psychoactive Agents

Certain psychiatric disorders, including depression, can affect behavior and may affect glucose metabolism. Some drugs used to treat psychiatric disorders, including antidepressant medications such as those in the tricyclic and SSRI classes, can affect appetite, weight, and glucose metabolism. The presence of depressive symptoms among DPPOS participants will be monitored by means of annual assessment using the Beck Depression Inventory (BDI). Use of antidepressant medications will be monitored during clinic visits, and use will be noted as a confounding variable in relevant data analyses.

7.5. Pregnancy and Contraception

Women with a history of gestational diabetes (GDM) are a substantial subgroup of the DPP. Some of these women, together with other participants in DPP, will be of childbearing potential during the course of the DPPOS. Data from available cohorts suggest that about 6 percent of women of childbearing age may be expected to get pregnant each year.

Female DPPOS participants of childbearing age who are fertile have been informed of the potential risks to a pregnancy conceived while on metformin treatment. These women will be asked to practice reliable birth control including systemic hormones, intrauterine devices or barrier methods (diaphragm, male or female condom, cervical cap) with concomitant intravaginal spermicide.

7.5.1. Safety Monitoring

Women in the metformin treatment group will be asked to get immediate pregnancy testing if their menstrual cycles are more than one week overdue or they otherwise suspect they are pregnant.

7.5.2. Use of Study Interventions During Pregnancy and Breast-feeding

Metformin is contra-indicated in pregnancy although data on adverse effects on the fetus or the mother are scant. The embryo toxic effects of biguanides have been evaluated in the *in vitro* cultured mouse embryo model (99). Because of the lack of teratogenicity of metformin in the few available studies, this drug is classified by the FDA as pregnancy category B (no evidence of risk in humans, animal findings negative). In recently reported studies, metformin has been shown to increase fertility in women with PCOS and some practitioners are investigating potential benefits of continuing its use during gestation. In the absence of definitive evidence indicating the safety of this practice, we will continue to recommend that during pregnancy and for the duration of breast-feeding; metformin should be discontinued in DPPOS participants.

There is no general contraindication for women continuing the recommended levels of exercise during pregnancy (100). The 150-min/wk target for activity levels should not require added monitoring during pregnancy, but because of the lack of data on ketosis with vigorous exercising, regimens that exceed 1000 kcal per week of energy expenditure may require monitoring of ketosis. Recommendations that exercise should continue with a target of 150 min/wk will be forwarded to the providers of obstetrical care for participants who get pregnant during the course of the DPPOS.

Dieting for weight loss during pregnancy can be dangerous; therefore, guidelines for calorie intake for healthy pregnancy and lactation (100) will be recommended. The recommended average daily caloric intake for pregnant women is 30-35 kcal/kg IBW. These recommendations will be forwarded to the provider(s) of obstetrical care for participants who get pregnant during the course of the DPPOS.

The lifestyle intervention, with caloric requirements adjusted to account for breast-feeding, can be introduced as soon after delivery as is feasible; we recommend within the first month. Women who choose not to breast-feed should return to their pre-pregnancy lifestyle intervention, including dietary targets, within the first month following delivery. For women who choose not to breast feed, weight targets should return to pre-pregnancy levels regardless of extra weight that may have been gained during pregnancy. For women who breast-feed, weight targets should be suspended until lactation is finished and then should be re-established at pre-pregnancy levels.

7.5.3. Outcomes Assessment Following Pregnancy

Participants who become pregnant during the DPPOS are likely to develop gestational diabetes, and many of these women will require insulin. The standard of care for follow-up after gestational diabetes is to assess glucose tolerance at six to eight weeks post-partum. Women who become pregnant during the DPPOS will have outcome assessments suspended until 6-8 weeks following delivery. This outcome measure following pregnancy will always be an OGTT. They will then attend the next regularly scheduled outcome assessment visit based on their original DPPOS follow-up schedule. Women meeting ADA criteria for diabetes will have reached the DPPOS primary outcome.

For those DPPOS participants who require insulin during pregnancy, assessing the ongoing need for insulin should begin in the hospital immediately post-partum. Women discharged on insulin should be evaluated with home glucose monitoring, followed by their providers of obstetrical care, to determine the ongoing need for insulin. Based upon post-partum monitoring, some women may remain on insulin or be started on oral hypoglycemic agents by their obstetrical/primary care provider(s). Participants treated with insulin or oral agents will not be re-started on their metformin unless and until their need for therapy resolves.

There may be some women who are still being treated by their primary care provider(s) with insulin or oral agents at the time of their first outcome assessment following pregnancy (i.e., 6-8 weeks following delivery). To ensure standardized assessment of outcomes, therapy must be stopped for the OGTT. If cessation of therapy is not possible, two elevated fasting plasma glucose determinations may be used to define an outcome of diabetes in place of the OGTT.

7.6. Smoking

The prevalence of smoking among the people with IGT is estimated to have declined to about 20 - 25% and is consistent with overall reduction in smoking in the U.S (101). Although 800-1000 of the original DPP participants were expected to be current smokers at the time of randomization, only 7% (approximately 250) of the participants were current smokers at baseline.

DPPOS will continue to follow established public health policy to reduce the prevalence of smoking by discussing smoking as a compounding risk factor for CVD and emphasizing the overall benefits to health for those who quit. DPPOS will emphasize to participants that the risks associated with smoking far outweigh the risks associated with weight gain associated with quitting smoking but will also note that exercise and healthy diet are excellent ways to minimize or eliminate that weight gain.

Following recommendations from the National Cancer Institute and the Agency for Healthcare Research and Quality, DPPOS staff will ask participants about smoking and provide brief messages encouraging them to quit. For those expressing interest in quitting, staff will provide printed materials and/or referral to primary care providers or community based programs. Through regular DPPOS visits, staff will follow up to encourage and support continued abstinence or further attempts to quit.

7.7. Type 2 Diabetes

7.7.1. Interim Visits for Symptoms

Following enrollment and randomization in the DPPOS, participants will be seen on a semi-annual basis for assessment of adverse events. If a participant develops symptoms consistent with uncontrolled hyperglycemia, he or she will be instructed to come to the clinical center for assessment of an adverse event and undergo a fasting plasma glucose determination. This test may be performed locally if needed for safety reasons; however, a sample must be sent to the CBL for outcome assessment. If the centrally read fasting glucose is ≥ 126 mg/dL, a repeat test will be performed within 6 weeks to confirm the diagnosis. The participant will have reached the DPPOS primary outcome if fasting glucose ≥ 126 mg/dL persists.

7.7.2. Intervention and Follow-up for Participants with Diabetes

Participants, investigators, and primary care providers will be unmasked to the diagnosis of diabetes. The participant and the primary care provider will be informed of the diagnosis and the significance will be explained. It will be recommended that the PCP see the participant at one and three months following diagnosis and scheduled thereafter by the PCP. Participants will be offered self-monitoring of blood glucose (SMBG) with the option of monitoring glucose levels routinely two to three times weekly as well as during any acute illness or in the event of symptoms such as polydipsia, polyuria or polyphagia. SMBG results may be reviewed at mid-year and annual visits. DPPOS participants will continue to be seen at six monthly intervals for clinical assessment, and fasting glucose and hemoglobin A_{1c} determinations will be obtained and sent to the CBL. Secondary outcome measurements will continue to be performed as scheduled.

All participants will be encouraged to attend the group lifestyle sessions to reinforce the intervention that they have received. Subsequent individual reinforcement of standard lifestyle recommendations will occur at the scheduled annual visits. For persons taking study assigned metformin, the investigator, in conjunction with the primary care provider, will endeavor to maintain the participant on assigned metformin as long as the hemoglobin A_{1c} remains <7%. In the event that a participant progresses to a hemoglobin A_{1c} ≥7%, study metformin will be discontinued. In all participants with diabetes, when the hemoglobin A_{1c} is ≥ 7%, a stepped care protocol for treatment of diabetes mellitus, as recommended by the American Diabetes Association, will be recommended to the primary care provider.

7.8. Retention Monitoring and Recovery of Inactive Participants

Retention of participants throughout the study period is key to both the power and generalizability of DPPOS findings. Retention of DPPOS participants will be encouraged through the provision of social support from DPPOS staff during clinic visits, quarterly group lifestyle meetings, and other incentives. All participants receive an honorarium, twice a year at scheduled visits, in recognition of the time and effort spent in the DPPOS.

Monitoring activities that track participants' attendance at scheduled clinic visits guide efforts to maximize retention. Missing semi-annual and annual data collection visits triggers a graded hierarchy of recovery efforts designed to maintain participants' involvement in DPPOS.

8. ADVERSE EVENT REPORTING

8.1. Definitions

Only adverse events meeting the criteria for serious will be ascertained and reported following FDA guidelines. Serious adverse events have been defined to include any adverse experience that results in any of the following outcomes:

- Death
- A life-threatening adverse experience
- Overdose to any medication
- Inpatient hospitalization or prolongation of existing hospitalization
- A permanent or severe disability
- A congenital anomaly/birth defect
- Important medical events that do not result in death, are not life-threatening, and/or do not require hospitalization will be considered as serious if, based on appropriate medical judgment, they jeopardize the participant and would require medical or surgical intervention to prevent a serious adverse event.

8.2. Eliciting and Recording Serious Adverse Events

Reporting of serious adverse events will be accomplished by collecting information on these adverse experiences during annual, semi-annual and interim follow-up visits. In order to avoid bias in eliciting serious adverse events, these adverse events will be assessed using a standardized checklist based on study outcomes and total body system assessment.

For all participants, serious adverse events will be assessed semi-annually at the clinic, as well as collected during the interim, as reported. Serious adverse events will be reported to the Coordinating Center as they occur through routine data entry (within 2-3 days), with the exception of death or other life threatening and unexpected adverse events. All deaths or other life threatening and unexpected adverse events, regardless of intervention assignment, must be reported to the Coordinating Center within 24 hours of clinic notification.

For participants assigned to the metformin treatment group, the NIH-NIDDK must provide a written report of all serious and unexpected adverse events to the Food and Drug Administration (FDA) in their annual IND report. If the event is a death or life threatening and unexpected, the FDA must be notified by phone or fax within seven calendar days, followed by the written report within fifteen days.

All serious adverse events will be reported to IRBs by the local clinic following individual institutional guidelines.

9. DATA PROCESSING

9.1. Data Forms

DPPOS data forms are completed to document protocol performance and to collect participant data relevant to the research questions. The section that follows outlines each type of data form that is used to collect participant data and is contained in the master database maintained by the Coordinating Center (CoC). Chapter 12 is the schedule of outcomes collection. The list of DPPOS data forms appears in the study Manual of Operations, and includes administrative as well as data collection instruments.

The CoC creates the DPPOS data form templates. At each clinic, the clinic staff, directed by the program coordinator, reviews completed data forms prior to data entry. Completed forms are edited as they are entered into the data management system, and then again via the central data management system at the CoC.

- **Follow-up visit inventories**:
  Completed semi-annually: serious adverse event assessment, diabetes management, current concomitant prescription medications, and physical measures; and for the metformin treatment participants, pregnancy questions, and medication compliance and dispensing. In addition,
  - at each annual visit: neuropathy screening and neuropathic history, interval history and interval cardiovascular history.
  - at each mid-year visit: Beck depression scale, interval history and interval cardiovascular history.
  - during year 5: retinal photography, ankle brachial index, SF-36 questionnaire, nutrient intake, and selected biochemical markers
  - during year 8: physical functioning, cognition questionnaires, Quality of Well Being, Resource Utilization, and SF-36 questionnaire
  - during year 10: Quality of Well Being, Resource Utilization, SF-36 questionnaire, physical functioning, cognition questionnaires
  - during annual year 11 visit: selected biochemical markers.
  - At study end: retinal photography, ankle brachial index, and coronary artery calcium (if funded)
- **Interim follow-up visit inventory:**
  Reason for interim visit, serious adverse event assessment, interval history, pregnancy questions, and for metformin treatment participants, medication compliance and dispensing.
- **Missed follow-up visit report:**
  Completed anytime a participant misses a scheduled follow-up visit: reason for missed visit and inactive follow-up status.
- **Home visit report**
  Completed for outcome visits: serious adverse event assessment, interval history, current concomitant prescription medications, and physical measures (as appropriate); and for the metformin treatment participants, pregnancy questions, and medication compliance and dispensing.

The following data forms are completed to collect information on lifestyle sessions:

- **Group Session Log:**
  Completed for each GLS or BLS group session. Includes type of session and participants.

9.1.1. Other Forms

The following instruments are completed according to the schedule in Chapter 12:

- Beck Questionnaire
- MOS SF-36 Health Survey Questionnaire
- Modifiable Activity Questionnaire
- Nutrition Interview
- Resource utilization for participants
- Interval History Questionnaire
- Quality of Well-Being Scale
- Urinary Incontinence Questionnaire
- Neuropathy Questionnaire
- Dietary Restraint, Exercise Self-Efficacy, Low Fat Diet Self-Efficacy
- Cognition questionnaires
- Physical functioning: Grip strength, Gait Speed, Chair Stand, Balance

The following event data forms are completed as needed:

- Adverse event reports
- Diabetes confirmation report
- Pregnancy confirmation and outcomes reports
- Mortality report

The following procedure worksheets collect participant status or physical information (see Section 12 for frequency of procedures):

- OGTT procedures
- Urine collection procedures
- ECG procedures
- Fundus photo procedures
- Coronary artery calcium procedures (if funds become available)

The following report data forms are completed as needed:

- CHD Risk Status Report
- Consent and specimen status

9.2. Data Entry and Management System

9.2.1. Clinical Centers

The data entry and management system uses a client-server model. Data entry software corresponding to the data forms completed at a clinical center is developed and maintained by the staff at the Coordinating Center (CoC). Reports are developed for use at the clinical centers to assist clinical center staff in data collection and study management. For reasons of security, the data that are entered by clinical center staff are transmitted via password protected direct telecommunications link. DPPOS computers provided by the CoC containing participant data are kept in a safe location in a site that is locked when not attended, may not be used to access the Internet, and may not be connected to any network of other computers. Additional data entry is available via a secure, password-protected website to the CoC.

9.2.2. Central Biochemistry Laboratory

The Central Biochemistry Laboratory (CBL) uses a relational database to manage analyses performed within the laboratory using a custom-developed Laboratory Information Management System (LIMS). Automated analyzers are connected to the database via communication interfaces developed and maintained by the CBL staff. Reports to the CoC are transmitted via secure FTP to the CoC with the original reports stored in the relational database as well as on a file server. All storage media containing clinical data in use at the laboratory utilize hardware fault redundancy and the data are backed up daily to a secure and remote data storage facility.

9.3. Centralized Data Management System

Participant data stored on clinical center computers are transmitted from the clinical centers and at regular intervals from the central units to the CoC. Data entered via the web are stored on the CoC's server. Both sources of data are converted to SAS data sets after being uploaded to the CoC's server. All new data are edited for unavailable, out of range, or inconsistent values. Weekly audit programs produce more detailed edits across forms for an individual participant. Summaries are prepared for reports to the Steering Committee.

Access to the server and databases is secured by use of login user accounts and passwords. Remote access is granted only to authorized users and is accomplished using a secure virtual private network (VPN). Appropriate filtering/firewall setup is used to prevent unauthorized access.

9.4. Performance Monitoring

9.4.1. Training Workshop and Site Visits

The CoC, Central Units, and the Lifestyle Resource Core (LRC), with appropriate investigator subcommittee members, will establish procedures to train and certify clinical investigators in the protocol, manual of operations, and data processing procedures. Workshops

are held for training personnel from the clinical centers to address the appropriate DPPOS procedures including the use of the DPPOS data forms and data processing systems. CBL personnel will instruct the program coordinators on proper packaging and mailing of specimens for analysis by the CBL. Central units also instruct, train and certify the program coordinators and technicians (as needed) to promote standard assessments. The CoC and the LRC will maintain close contact with the program coordinators and will provide additional training or review as needed.

Based on clinic performance monitoring, appropriate representatives from the CoC, the LRC, the NIDDK, and clinic investigators will visit the clinical centers, as required. These site visits will review procedures with the program coordinators/technicians, assess proficiency in executing the DPPOS protocol, review deficiencies detected in monitoring the performance of the clinical centers, review the utilization of personnel relative to the amounts budgeted, and receive feedback on the adequacy of the centralized support operations.

9.4.1.1 Periodic Performance Reports

During the DPPOS, the CoC will monitor the performance of the clinical centers and produce periodic reports summarizing protocol performance for the Protocol Oversight Program (POP) committee.

9.4.1.2 Retention

The CoC and the POP will monitor the performance of the clinical centers in retaining participants. The CoC will also prepare monthly reports on participant compliance with the DPPOS protocol and participants on inactive follow-up.

9.4.1.3 DPPOS Data Form Completion

The CoC will prepare periodic reports presenting tabulations for data completion and quality. Missing data, particularly on outcome variables, will effectively reduce the power of analyses. In fact, systematic patterns of missing data could bias the study results. Therefore, many of the procedural details outlined in the Manual of Operations are designed to minimize the amount of missing data.

9.4.1.4 Other Reports

Other reports will be developed, as needed, based on requests from the Steering Committee and associated subcommittees.

9.5. Interim Statistical Reports

Interim reports to the Data Safety Monitoring Board (DSMB) will include adverse events by treatment group, study progress, major issues considered and decided by the Steering Committee, protocol modifications, ancillary studies approved, protocol compliance, and data quality. Highlights of completed analyses related to study papers will be presented as they

become available. There will be two formal interim analyses of safety and efficacy pertaining to macrovascular events for purposes of possible "early stopping" of an intervention.

10. STUDY ADMINISTRATION

10.1. Organizational Units

10.1.1. Clinical Centers

Each of the participating clinical centers has agreed to implement the DPPOS Protocol. The clinical centers will follow participants according to protocol; assume responsibility for the completion of the protocol for each participant enrolled in the study; record participant data related to the above; review and enter information from data forms using the data entry and management system; and respond to edit queries from the Coordinating Center (CoC). Each clinical center has a Principal Investigator, a Program Coordinator, and additional staff to carry out the protocol.

10.1.2. Coordinating Center

The Coordinating Center (CoC) is responsible for all aspects of biostatistical design, analysis, data processing and study communications of the DPPOS. In collaboration with the Steering Committee, the CoC is responsible for editing and document processing of the protocol and Manual of Operations and data collection forms development and testing. The CoC provides protocol performance monitoring data, and conducts the interim and final statistical analyses. The CoC collaborates with the Steering Committee members in the preparation of publications based on study results.

Central resource units include the Central Biochemistry Laboratory (CBL), Nutrition Coding Center (NCC), ECG Grading Center (ECG), Fundus Photo Reading Center (FPRC), Quality of Well Being Coding Center (QWB), Coronary Artery Calcium Reading Center (if funded), Cognition Center, and DPPOS Central Genetics Core. Other than the Genetics Core and the Cognition Center, these units function as subcontracts to the CoC. Each is required to be in compliance with its IRB and institutional requirements for human subjects protection and HIPAA. They establish and provide baseline and/or repeated measures of study outcomes as described in Sections 5 and 12. Quality control systems are established for these centrally performed assessments and reports will be furnished periodically to the Research Group. In addition, the units will lend expertise to help formulate the protocol and detailed procedures for participant preparation, specimen and record labeling, handling and shipping. Secure communication systems are maintained for data transfer to the Coordinating Center.

10.2. Funding Mechanism/Study Resources

The DPPOS is supported by the National Institutes of Health through the National Institute of Diabetes and Digestive and Kidney Diseases, other co-funding NIH Institutes and Centers, and other DHHS co-funding Agencies. All support to the clinical centers and the Coordinating Center will be provided through the NIDDK using the mechanism of the Cooperative Agreement.

The NIDDK program officer will provide program involvement as a participant in the scientific efforts of the DPP Research Group through development of protocols and assistance in the conduct of the DPP.

10.3. Working Committees

10.3.1. Steering Committee and Subcommittees

The Steering Committee (SC) is the representative body of the research group. The Committee consists of the Principal Investigator from each clinical center and the CoC, and the NIDDK project manager. This committee is the policy and decision making group, and will oversee the administrative aspects of the DPPOS Research Group. It provides overall scientific direction through consideration of recommendations from the subcommittees and Executive Committee. The committee will approve the details of study design and all procedure manuals and participant management policies. The SC will monitor protocol adherence at the clinical centers including proper data generation, recording and transmittal. Members unable to attend a meeting may designate an alternate to act on their behalf. The members of the Steering Committee select the Study Chairperson and Vice-Chairperson.

Steering Committee recommendations for changes in the Protocol require prior consideration by the appropriate subcommittee or Planning Committee, and an affirmative vote by two-thirds of the Steering Committee members present and voting.

Although the Steering Committee is the decision and policy-making group of the DPPOS, a smaller group has been appointed to direct day-to-day activities. This Executive Committee consists of the Chair of the Steering Committee, the Vice-Chair of the Steering Committee, the Chair of the Publications and Presentations Committee, the NIDDK Project Manager, and the Principal Investigator and Project Coordinator of the CoC. The committee meets by telephone conference, as necessary, and generally on a weekly basis. Other members of the Steering Committee, such as chairs of Sub-Committees, are asked to attend the weekly conference call on a regular basis and as needed to address specific issues.

Subcommittees comprise members of the research group. Their function is to develop detailed policies and procedures and make recommendations to the Steering Committee. The following subcommittees are active during the start-up of the DPPOS. During DPPOS the subcommittees will be reformed and new subcommittees and working groups formed, as necessary to address different tasks and functions.

Initial DPPOS Subcommittees:

- Ancillary Studies
- Economic Evaluation Workgroup
- Outcomes Classification
- Program Coordinator
- Protocol Oversight Program
- Publications and Presentations
- Quality Control

10.3.2. Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) members will serve as external reviewers and advisors to the NIDDK-NIH and the Steering Committee. The DSMB will consist of experts in relevant biomedical fields, Biostatistics and medical ethics. Prior to the initiation of the DPPOS, the DSMB members will review the protocol and study material to ensure the scientific

validity of the study and safety of participants. The DSMB will also assess the performance of the CoC and clinical centers. Its principal responsibility will be to monitor the emerging results to assess treatment effectiveness, or ineffectiveness, and participant safety. Based on these considerations, the DSMB may recommend to the NIDDK that the protocol be modified or that the study be terminated.

10.4. Policies

10.4.1. Publications

The Publications and Presentations Subcommittee (PPS) will coordinate, monitor, review, and assume responsibility for arranging the preparation of all study-wide communications (press releases, interviews, presentations, and publications) relating to the scientific aspects of the study. There will be no publication or presentation of study plans or results which have not been reviewed and approved by a majority of the PPS, and for some types of communications, a majority of the Steering Committee.

With respect to publications and presentations from the DPP, the goals of the PPS are to:

1. Ensure accurate, uniform, timely, and high quality reporting of the DPP activities and results;
2. Preserve the scientific integrity of the study;
3. Safeguard the rights and confidentiality of participants;
4. Assure that the timing of publications and presentations serves the right of the public to know the results of the program without jeopardizing its conduct.

The PPS will organize a writing group for each publication or presentation proposed by the DPP investigators. Members of the writing group will include volunteers from the DPP investigators at large, and will not be restricted to members of the PPS. The PPS will coordinate the efforts of the writing group, establish priorities for data analysis by the Coordinating Center, and help edit the manuscripts produced by the writing groups.

There will be several categories of publications and presentations, with different rules for authorship, ranging from publications of the main results of the study (with authorship by the entire research group) to other types of publications with named authors. The authorship rules balance the need to recognize the contributions of all investigators and staff with the need to recognize individuals for specific contributions to certain types of publications and presentations. Detailed policies are found in the MOO.

10.4.2. Ancillary Studies

The Ancillary Studies Subcommittee will evaluate all proposals for studies that involve DPPOS participants and that are not a part of the protocol. These studies will, in general, be done only on a subset of participants in the DPPOS. However, studies that include all participants and studies that analyze study data in ways extracurricular to the Protocol must also be submitted to the Ancillary Studies Subcommittee. Ancillary studies will have to obtain funding from outside the study.

Major factors in consideration of ancillary studies will include:

- Clinical importance and scientific validity
- Compatibility of goals with those of DPPOS
- Amount of burden on study subjects and staff

Ancillary studies will receive a primary, secondary and statistical review. An outside reviewer may be used if there is no expertise within the study in a specific area. Reviews will be returned to the applicant and appeals from the decision of the Ancillary Studies Subcommittee may be made to the Steering Committee.

Approved ancillary studies will be reviewed by the DSMB.

Detailed policies are found in the MOO.

11. STATISTICAL CONSIDERATIONS

11.1. Data Relevant to the Primary Outcome

After approximately 2.8 years of mean study time, the DPP's external Data Safety Monitoring Board and sponsoring institute, the NIDDK, concluded that the DPP had convincingly demonstrated that the intensive lifestyle intervention and metformin therapy decreased the development of diabetes. Compared with placebo, intensive lifestyle and metformin reduced the development of diabetes by 58% and 31%, respectively. Both results were highly significant and lifestyle was significantly more effective than placebo (4). The therapies were effective across all ethnic and racial groups and in men and women. The intensive lifestyle intervention cohort achieved the target goal of 7% mean weight loss and at least 150 min of activity per week at year 1. The hazard rates for development of diabetes were: placebo 11.0, metformin 7.8, and lifestyle 4.8 per 100 person-years.

At the end of DPP, 99.6% of the study cohort was alive. The entire cohort proved to be remarkably compliant, with 94% retention of volunteers over time, and completion of > 90% of study requirements. Adherence (>80% of assigned medication) to metformin was 72%.

11.2. Study Power

The duration of follow-up in the first five years of DPPOS was extended by one year from 5 to 6 years, by NIDDK. Power calculations have been modified based on actual enrollment, and to correspond to the reordering of outcome measures.

The following assumptions were used to make revised estimates of the power of the DPPOS for the Phase 1 primary outcome, development of diabetes:

- The study will enroll approximately 900 participants per treatment group
- The Phase 1 primary outcome is time to the confirmed development of diabetes assessed through DPPOS Phase 1.
- Type I error rate (α) of 0.05 (two-sided) with a Bonferroni adjustment (99) for two pair-wise comparisons of the intervention groups vs. "control".
- Control (formerly placebo) group's time to the development of diabetes is exponentially distributed with a diabetes development hazard rate of at least 0.066 per year.
- In the intervention groups (i.e., intensive lifestyle or metformin), the diabetes development hazard rate is reduced by at least 30%.
- 84% participation of DPP participants in the follow-up study and a dropout rate of not more than 2%/year.

For the comparison of lifestyle vs. control, assuming a type 1 error .025 and a 2-sided test, the study will have 84% power to detect a 35% reduction in the hazard rate for development of diabetes and 94% power to detect a 40% reduction. For the comparison of metformin vs. control (type 1 error .025, 2 sided test), the study will have 82% power to detect a 35% reduction in hazards.

For the composite primary microangiopathic outcome at year 11, assuming N=850 remaining participants per group and 1% per year dropout, and applying the resulting numbers of participants expected to develop diabetes during the follow-up study, we estimate the power of the study to be 91 percent or greater to detect 25% or greater reductions for each intervention

from the control group proportion with the microangiopathic outcome, and 74% power to detect 20% reductions, using 2-sided pair-wise comparisons vs. placebo with α =0 .025.

11.3. Analysis

11.3.1. Analysis of Development of Diabetes

The primary objective for the first Phase of the DPPOS study is to compare the durability of the original effect during the DPP, i.e., estimation of the hazard rates for development of diabetes *going forward* among participants who did not develop diabetes during DPP among those who enrolled into DPPOS. The analysis will be based on comparing the hazard rates between the two intervention groups (the former Intensive Lifestyle and Metformin groups) and the former placebo group. The primary null hypothesis is that among those who had not developed diabetes by the start of DPPOS, the intervention groups do not differ from the controls in the hazard rates for development of diabetes over the interval from the beginning of the long-term follow-up study. Reasons for comparing across the interval from the start of the long-term follow-up study as the primary analysis rather than from the beginning of DPP are: 1) we will have already published the comparison of the three groups over the DPP interval, and any subsequent comparison encompassing that interval would not be an independent analysis; and 2) if the interventions are indeed effective over the earlier DPP interval, the cumulative incidence curves may have too much separation from the early DPP effects to be able come together again, even if the interventions are not effective over the longer term. The primary analysis from DPPOS baseline does not preclude secondary analyses from the beginning of DPP.

The cohort of participants for this analysis are a subset of the original DPP study population, and as such are no longer "randomized", but rather selected by having survived DPP without developing diabetes. Beyond that selection, each participant will be included in the group to which s/he was randomly assigned, regardless of compliance with study treatment. The number of participants who had not developed diabetes at DPP study end was 870 in the metformin group, 951 in the ILS, and 809 in the placebo group. The primary outcome analysis will use an overall significance level of $\alpha = 0.05$ (2-sided). Two pair-wise comparisons between the intervention groups and the former placebo group, set at the $\alpha= 0.025$ level, will be performed if the overall comparison is statistically significant.

The analysis will compare the treatment groups vs. the former placebo group on DPP baseline characteristics, and any factors on which they differ will be considered for inclusion as covariates in the analysis. The primary analysis will be a life-table analysis of the time to confirmed development of diabetes. Modified product-limit life-table estimated cumulative incidence curves will be calculated for each treatment group and the groups compared using a log rank test (102). Participants will be considered "administratively censored" if they complete the full duration of follow-up without confirmed development of diabetes. Participants who prematurely discontinue their follow-up visits prior to confirmed development of diabetes will be "censored" as of their last follow-up visit. A proportional hazards regression model will be used to evaluate potential covariates that may modify the time to development of diabetes. Graphical procedures will be used to assess the proportionality assumption. If the proportionality assumption is found to be unreasonable then other models such as the accelerated failure time model (103) or the proportional odds model (104) will be used to evaluate the covariates.

Mortality prior to the development of diabetes may be a competing risk event for the primary outcome (105). To account for mortality as a competing risk event, the treatment groups will be compared on the composite event defined as confirmed development of diabetes or all-cause mortality, whichever occurs first, using the same methods described above for the primary outcome. The analysis will also be conducted within subgroups (one-way stratification) based on the following characteristics: racial/ethnic origin, gender, and age (<60, 60+).

The primary analyses that focus on the intention-to-treat assignment during DPP will include all participants in the original DPP placebo, lifestyle and metformin intervention groups who have enrolled in DPPOS. Since the participants originally assigned to troglitazone only had a limited exposure to that intervention, owing to the premature termination of the troglitazone arm, and were not included in the primary DPP outcome analyses, they will not be included in the primary DPPOS analyses.

11.3.2. Composite Outcomes of Microangiopathic, Neuropathic and Cardiovascular Disease

The analysis of the composite primary microangiopathic outcome at year 11, and composite secondary cardiovascular disease outcome will be performed in an intent-to-treat fashion on the DPP groups, as randomized, including participants who have developed diabetes.

For both composite outcomes, the objective is to determine the effect of the interventions on the proportion of participants experiencing the outcome through follow-up visit year 11. For the composite primary microangiopathic outcome, the groups will be compared using the global test using general estimating equations (GEE) among DPPOS enrolled participants. For the composite secondary cardiovascular outcome, the groups will be compared on the time to event from DPP randomization through DPPOS year 11 using all participants randomized into DPP.

11.3.3. Secondary Research Questions

Secondary objectives of the post-DPP study are to evaluate the long-term effects of DPP interventions on selected individual health outcomes. These are:

- Further development of diabetes
- Diabetic retinopathy
- Diabetic neuropathy
- Albuminuria
- Renal failure
- Macrovascular disease
- Cardiovascular disease events
- Subclinical atherosclerosis outcomes
- Risk factors for cardiovascular disease
- Amputation in a lower extremity not resulting from major trauma
- Hospitalizations
- Physical activity, nutrition, body mass and obesity
- Dietary and exercise behaviors
- Physical functioning
- Quality of life indices

- Health care costs
- Cognitive performance
- Urinary incontinence

Other Analyses. Other research questions will examine the clinical course of IGT and newly diagnosed diabetes with regard to the development of microvascular, neuropathic and cardiovascular disease and their respective risk factors. These "epidemiologic" analyses will largely be descriptive. Appropriate statistical methods will be applied to analyze the interactions among putative and established risk factors and the development of different outcomes. In these analyses, treatment assignment during the DPP will be considered a covariate.

The former troglitazone participants who continue in the DPPOS through visit year 6 will be included in the "other" outcomes exploring the relationship between incident diabetes and determinants of long-term complications of new-onset diabetes and IGT. No research data will be collected in this group beginning with protocol version 3.0.

11.4. Monitoring

An external Data Safety Monitoring Board will review reports of study progress and safety regularly throughout the study. They will alert the NIDDK and the Steering Committee if they believe the study should be stopped for reasons of patient safety.

Because we have already shown both interventions to be effective in delaying or preventing diabetes over 3 years, there would be no compelling reason to stop the follow-up study for having demonstrated further benefit. The assessment of the composite microangiopathy will occur after the year 11 visits. Therefore, we do not intend to implement a formal statistical monitoring plan for either of these outcomes. The DSMB will review two interim analyses of time to macrovascular event for safety.

12. Outcomes Schedule

Outcomes Schedule, Visit Years 1-6

Participant DPPOS visit year number	PPT Year 1		PPT Year 2		PPT Year 3		PPT Year 4		PPT Year 5		PPT Year 6	
Visit calendar year	9/1/02-10/31/03		7/1/03-10/31/04		7/1/04-10/31/05		7/1/05-10/31/06		7/1/06-10/31/07		7/1/07-10/31/08	
DPPOS funding calendar year	2/1/03-1/31/04		2/1/04-1/31/05		2/1/05-1/31/06		2/1/06-1/31/07		2/1/07-1/31/08		2/1/08-1/31/09	
Mid-year or Annual visit	Mid	Ann	Mid	Ann	Mid	Ann	Mid	Ann	Mid	Ann	Mid	Ann
Glycemia												
Fasting glucose	X	X	X	X	X	X	X	X	X	X	X	X
30', 120' glucose++		X		X		X		X		X		X
HbA1c ++		X		X		X		X		X		X
Insulin Secretion and Sensitivity												
Fasting, 30' insulin++		X		X		X		X		X		X
Inflammatory, clotting and fibrinolytic factors												
Fibrinogen		X								X		
TPA		X								X		
CRP		X								X		
Lipids												
Lipid profile		X		X		X		X		X		X
Particle size and sub fractions		X								X		
Kidney Function												
Urine albumin & creatinine		X		X		X		X		X		X
Serum Cystatin		X								X		
Serum Creatinine		X		X		X		X		X		X
History												
Symptoms and Events	X	X	X	X	X	X	X	X	X	X	X	X
Physical												
Weight	X	X	X	X	X	X	X	X	X	X	X	X
Height		X								X		
Waist Circumference		X		X		X		X		X		X

Outcomes Schedule, Visit Years 1-6, Continued

Participant DPPOS visit year number	PPT Year 1		PPT Year 2		PPT Year 3		PPT Year 4		PPT Year 5		PPT Year 6	
Visit calendar year	9/1/02-10/31/03		7/1/03-10/31/04		7/1/04-10/31/05		7/1/05-10/31/06		7/1/06-10/31/07		7/1/07-10/31/08	
DPPOS funding calendar year	2/1/03-1/31/04		2/1/04-1/31/05		2/1/05-1/31/06		2/1/06-1/31/07		2/1/07-1/31/08		2/1/08-1/31/09	
Mid-year or Annual visit	Mid	Ann	Mid	Ann	Mid	Ann	Mid	Ann	Mid	Ann	Mid	Ann
Blood Pressure												
Arm BP	X	X	X	X	X	X	X	X	X	X	X	X
ABI		X								X		
Quality of Life												
Beck	X		X		X		X		X		X	
SF-36		X								X		
Urinary Incontinence		X		X		X		X		X		X
Physical Activity and Nutrition												
MAQ		X		X		X		X		X		X
Nutrition Intake		X		X						X		
Cardiovascular												
ECG		X		X		X		X		X		X
Carotid Ultrasound+												
Eye												
Retinal photography#		X								X		
Neurologic												
Symptom Assessment		X		X		X		X		X		X
MNSI with monofilament		X		X		X		X		X		X
Heart rate variability		X		X		X		X		X		X
Saved Specimens												
Fasting EDTA Plasma		X		X		X		X		X		X

Outcomes Schedule, Visit Years 1-6

Participant DPPOS visit year number	PPT Year 1		PPT Year 2		PPT Year 3		PPT Year 4		PPT Year 5		PPT Year 6	
Visit calendar year	9/1/02-10/31/03		7/1/03-10/31/04		7/1/04-10/31/05		7/1/05-10/31/06		7/1/06-10/31/07		7/1/07-10/31/08	
DPPOS funding calendar year	2/1/03-1/31/04		2/1/04-1/31/05		2/1/05-1/31/06		2/1/06-1/31/07		2/1/07-1/31/08		2/1/08-1/31/09	
Mid-year or Annual visit	Mid	Ann	Mid	Ann	Mid	Ann	Mid	Ann	Mid	Ann	Mid	Ann
Safety Measures												
Serum creatinine		X		X		X		X		X		X
CBC*		X		X		X		X		X		X
Serious Adverse event report**	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy##		X		X		X		X		X		X
Serology												
IA2***, GAD***												
Other Chemistries												
Relevant biological markers related to the pathogenesis of diabetes and its complications		X								X		
Economic Evaluation												
Resource Utilization								X				
QWB		X		X		X		X		X		X

Fundus photos were obtained in Year 1 or 2 on a subset of diabetic and non-diabetic participants. Year 5 photos were completed on all participants in the former lifestyle, metformin and placebo arms.

Pregnancy tests as needed for participants on metformin based on symptoms and menstrual history and measured locally.

* In the Metformin treatment group on study metformin measured locally. Additionally, creatinine clearance will be performed annually on those metformin participants who have reached their 80th birthday.

** Serious Adverse events will be collected at Annual, Mid-year and Interim follow-up visits.

*** Specimen for IA2 and GAD antibodies will be collected at the time of confirmation and will be analyzed for those who converted.

+ Carotid ultrasounds were collected during the DPP bridge period as a baseline for DPPOS

++ For diabetic participants: HbA1c is collected at Mid-Year visits; the 30' insulin and 30/120' glucose collections are discontinued

+++ The following outcomes are not obtained for participants in the former troglitazone arm: carotid ultrasound, fundus photographs, other chemistries

Outcomes Schedule – Visit Years 7-11

Participant DPPOS visit year number	PPT Year 7		PPT Year 8		PPT Year 9		PPT Year 10		PPT Year 11	
Visit calendar year	**9/1/08-10/31/09**		**7/1/09-10/31/10**		**7/1/10-10/31/11**		**7/1/11-10/31/12**		**7/1/12-10/31/13**	
DPPOS funding calendar year	**2/1/09-1/31/10**		**2/1/10-1/31/11**		**2/1/11-1/31/12**		**2/1/12-1/31/13**		**2/1/13-1/31/14**	
Mid-year or Annual visit	**Mid**	**Ann**	**Mid**	**Ann**	**Mid**	**Ann**	**Mid**	**Ann**	**Mid**	**Ann**
Glycemia										
Fasting glucose	X	X	X	X	X	X	X	X	X	X
30', 120' glucose+		X		X		X		X		X
HbA1c +		X		X		X		X		X
Insulin Secretion and Sensitivity										
Fasting, 30' insulin+		X		X		X		X		X
Inflammatory, clotting and fibrinolytic factors										
Fibrinogen										X
TPA										X
CRP										X
Lipids										
Lipid profile		X		X		X		X		X
Particle size and subfractions										X
Kidney Function										
Urine Albumin & Creatinine		X		X		X		X		X
Serum Cystatin		X		X		X		X		X
Serum Creatinine		X		X		X		X		X
History										
Symptoms and Events	X	X	X	X	X	X	X	X	X	X
Physical										
Weight	X	X	X	X	X	X	X	X	X	X
Height										X
Waist Circumference		X		X		X		X		X

Outcomes Schedule – Visit Years 7-11, Continued

Participant DPPOS visit year number	**PPT Year 7**		**PPT Year 8**		**PPT Year 9**		**PPT Year 10**		**PPT Year 11**	
Visit calendar year	**9/1/08-10/31/09**		**7/1/09-10/31/10**		**7/1/10-10/31/11**		**7/1/11-10/31/12**		**7/1/12-10/31/13**	
DPPOS funding calendar year	**2/1/09-1/31/10**		**2/1/10-1/31/11**		**2/1/11-1/31/12**		**2/1/12-1/31/13**		**2/1/13-1/31/14**	
Mid-year or Annual visit	**Mid**	**Ann**	**Mid**	**Ann**	**Mid**	**Ann**	**Mid**	**Ann**	**Mid**	**Ann**
Blood Pressure										
Arm BP	X	X	X	X	X	X	X	X	X	X
ABI ++								X		
Quality of Life										
Beck	X		X		X		X		X	
SF-36			X				X		X	
Urinary Incontinence		X		X		X		X		X
Physical Activity, Nutrition, Behavior, Functional										
MAQ		X	X		X		X		X	
Nutrition Intake										X
Dietary Restraint, Exercise Self-Efficacy, Low Fat Diet Self-Efficacy			X		X		X		X	
Physical Function tests (Grip strength, CES-D Depression, Gait Speed, Chair Stand, Balance)			X				X			
Cognition										
Cognitive function tests			X				X			
Cardiovascular										
ECG		X		X		X		X		X
Coronary Artery Calcium (if funded) ++								X		
Eye										
Retinal photography ++								X		
Neurologic										
Symptom Assessment		X		X		X		X		X
Modified MNSI including monofilament		X		X		X		X		X
Heart rate variability		X		X		X		X		X

Outcomes Schedule – Visit Years 7-11, Continued

Participant DPPOS visit year number	PPT Year 7		PPT Year 8		PPT Year 9		PPT Year 10		PPT Year 11	
Visit calendar year	**9/1/08-10/31/09**		**7/1/09-10/31/10**		**7/1/10-10/31/11**		**7/1/11-10/31/12**		**7/1/12-10/31/13**	
DPPOS funding calendar year	**2/1/09-1/31/10**		**2/1/10-1/31/11**		**2/1/11-1/31/12**		**2/1/12-1/31/13**		**2/1/13-1/31/14**	
Mid-year or Annual visit	**Mid**	**Ann**	**Mid**	**Ann**	**Mid**	**Ann**	**Mid**	**Ann**	**Mid**	**Ann**
Saved Specimens										
Fasting EDTA Plasma (no serum is stored)		X		X		X		X		X
Safety Measures										
Serum creatinine		X		X		X		X		X
CBC*		X		X		X		X		X
Serious Adverse event report**	X	X	X	X	X	X	X	X	X	X
Pregnancy##		X		X		X		X		X
Other Chemistries										
Relevant biological markers related to the pathogenesis of diabetes and its complications										X
Economic Evaluation										
Resource Utilization								X		
QWB		X	X				X			

Pregnancy tests as needed for participants on metformin based on symptoms and menstrual history and measured locally.
* Collected from participant of the metformin treatment group on study metformin measured locally. Additionally, creatinine clearance will be performed annually on those metformin participants who have reached their 80th birthday.
** Serious Adverse events will be collected at Annual, Mid-year and Interim follow-up visits.
*** Specimen for IA2 and GAD antibodies will be collected at the time of confirmation and will be analyzed for those who converted.
+ For diabetic participants: HbA1c is collected at Mid-Year visits; the 30' insulin and 30/120' glucose collections are discontinued
++ The following will be completed at study end: ABI, retinal photography, coronary artery calcium (if funded)

12.1. Visit Schedule

Annual visits will be targeted for the anniversary of the participant's original DPP randomization date. Mid-year visits will take place 6 months before and after annual visits.

13. STUDY TIMETABLE

Diabetes Prevention Program

Phase I	July 1994 - June 1996	Protocol Development and Implementation
	July 1994 - December 1995	Protocol Development
	January 1996 - June 1996	Protocol Implementation
Phase II	July 1996 - June 2002	Participant Randomization and Follow-up
	July 1996 - June 1999	Recruitment and Follow-up
	July 1999 – December 2001	Participant Follow-up
Phase III	June 2001	Initiate Study Close-out and Data Analysis
Phase IV	January 1, 2002	Bridge Period Starts
	August 31, 2002	Bridge Period Ends

Diabetes Prevention Program Outcomes Study

Planning	January 2002 to August 31, 2002	Protocol development
Phase I	September 1, 2002 to January 31, 2009	Participant follow-up
	July 2006 to October, 2007	Year 5 major visit
	February 1, 2008 to January 31, 2009	Phase I Analysis
	June 2008	Submit funding renewal
Phase II	February 1, 2009 to January 31, 2014	Participant follow-up
Phase III	February 1, 2014 to January 31, 2015	Study close-out and data analysis

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15. CONSENT FORM FOR FOLLOW-UP STUDY

IRB Templates - Attached separately.

NAME OF INSTITUTION

INFORMATION AND CONSENT FOR THE DIABETES PREVENTION PROGRAM OUTCOMES STUDY (DPPOS)

INVESTIGATORS

Name of Principal Investigator
Title, Affiliation, Phone Number

Name of Co-Investigator(s)
Title, Affiliation, Phone Number

Name of Program Coordinator
Title, Affiliation, Phone Number

Name of Other Staff (optional as per IRB)
Title, Affiliation, Phone Number

24-Hour Emergency Telephone Number
(List phone number(s) here)

INVESTIGATOR'S STATEMENT:

PURPOSE AND BACKGROUND

This research study is called the Diabetes Prevention Program Outcomes Study (DPPOS) and is an extension of the Diabetes Prevention Program (DPP), of which you were a participant. The purpose of the DPPOS is to look at the effects of the study interventions on the development of type 2 diabetes as well as diabetes related health problems over a long period of time (up to 11 years). In this type of research, health information is combined from many volunteers.

Diabetes is a disease in which there is too much glucose (sugar) in the blood. Diabetes causes damage to blood vessels, heart, kidneys, eyes, and nerves. Diabetes affects at least 24 million Americans. Ninety to ninety-five percent of those affected have type 2 diabetes.

The interventions that were studied during the DPP were intensive lifestyle modification and metformin. An additional medication group (troglitazone) stopped taking the medication during the study due to serious side effects. The results of the DPP showed that the risk of type 2 diabetes was reduced by 58% in the intensive lifestyle group and 31% in the metformin group. The DPPOS will examine the continued effects of these study interventions over a long period of time. You will take part in the DPPOS for up to eleven years. All participants who were in the original DPP study groups randomized to intensive lifestyle modification, metformin or placebo (approximately 3,200) are being asked to continue to take part in the DPPOS.

PROCEDURES

If you choose to take part in the DPPOS you will be assigned to one of the following intervention groups based on your original randomly assigned intervention group.

1. Group Lifestyle Sessions (GLS): For participants formerly assigned to the placebo intervention group - You will be invited to take part in the Healthy Lifestyle Program-Maintenance (HELP-Maintenance). These sessions will consist of a quarterly (four times per year) group session that will focus on lifestyle issues, as well as other health related topics. The original exercise and diet goals of the intensive lifestyle interventions, walking (or similar activity) 2 ½ hours (150 minutes) per week and using healthy eating habits to lose and maintain a 7% weight loss, will be reinforced. You may be asked to keep a record of your food intake and/or physical activity, and you may be invited to take part in additional supervised physical activity sessions. You may be weighed. A trained professional will lead the group sessions. These sessions will be offered

at several different times in order to allow you to attend at a time that is convenient for you. Each class will last about 1 to 1 ½ hours depending on the material to be covered. If you choose not to attend the HELP-Maintenance sessions, you may still take part in the DPPOS.

2. Metformin + Group Lifestyle Sessions (MLS): For participants formerly assigned to the metformin intervention group -You will be invited to attend and take part in the HELP-Maintenance quarterly group sessions as described above. In addition, you will be asked to continue taking metformin open-label (unmasked). If you are unable or choose not to take metformin, and/or you choose not to attend the HELP-Maintenance sessions you may still take part in the DPPOS.

3. Boost Lifestyle + Group Lifestyle Sessions (BLS): For participants formerly assigned to intensive lifestyle intervention group - In addition to being invited to attend and take part in the quarterly HELP-Maintenance sessions described above, you will be asked to take part in Boost Lifestyle Sessions (BLS), a series of lifestyle "boost" classes offered twice a year over four to eight weeks. The exercise and diet goals of the intensive lifestyle program, walking (or similar activity) 2 ½ hours (150 minutes) per week and using healthy eating habits to lose and maintain a 7% weight loss, will be reinforced by providing you with materials to help you to track your fat and calorie intake, as well as monitor your physical activity. You may be weighed at the classes and you may be invited to take part in additional supervised physical activity sessions. Each class will last about an hour. In addition to reinforcing attendance at group sessions, incentives (valued at $20.00 or less) will also be used to reward lifestyle behavior change such as weight loss, activity, self-monitoring of diet and other healthy lifestyle changes. If you choose not to attend the BLS and/or the HELP-Maintenance sessions, you may still take part in the DPPOS.

Clinic Visits: As a participant in the DPPOS, you will be asked to attend a clinic visit twice a year. In some cases, you may be asked to attend an additional interim visit. These visits and procedures to be completed are described below:

Mid-year visit: (Approximately 1-2 Hours)

You will be asked not to eat or drink anything, except water for 12 hours before your appointment:

1. Blood pressure will be measured in your arm. This will take about 10 minutes.
2. You will be weighed.
3. A blood sample (5 ml or 1 teaspoon) for fasting glucose will be taken from your arm. A repeat sample (about 1 teaspoon) may be necessary for some persons. If you are diabetic, HbA1c will also be measured.
4. You may be asked questions regarding your behaviors, physical activity, health and feelings. This will take about 30 minutes.

5. In years 8 and 10 you will be asked questions regarding your cognitive status, such as memory. This will take about 20 to 30 minutes.
6. In years 8 and 10 your physical functioning will be tested. This will take about 20 to 30 minutes.

Annual Visit: (Approximately 2-4 hours):

1. An electrocardiogram (ECG) will be performed. This will take about one-half hour.
2. Blood pressure will be measured in your arm. This will take about 10 minutes.
3. You will have the circulation in your legs checked by measuring your blood pressure in your arms and legs with a doppler at year one (1) and again later in the study. This is a painless test that uses sound waves and cool sticky gel and takes about 20 minutes.
4. Body measurements: Your weight and waist size will be measured. This will take about 10 minutes. You will have your height measured during years one and again later in the study. This will take about 5 minutes.
5. You will receive a test for neuropathy (problems with nerves in the feet). This will involve an examination of the sensation in your feet and testing of your reflexes. This test will take about 10 minutes.
6. Oral glucose test: This test will take about 2 and ½ hours. You will be asked to not eat or drink anything, except water, for 12 hours before your appointment. A blood sample will be taken from your arm. You will then be asked to drink a glassful of flavored sugar water over 5 minutes. Another blood sample will be taken from your arm at 30 and again at 120 minutes. The total amount of blood drawn for this test is approximately 1 tablespoon. A repeat oral glucose test may be necessary for some persons.
7. People with diabetes will not be asked to complete the oral glucose test, but will have a fasting blood glucose drawn (approximately one tablespoon) following the same 12 hour fasting instructions as stated above..
8. Additional blood samples will be taken from your arm at the same time that you are having blood drawn for the oral glucose test, for lipids (blood fats), hemoglobin A1C (measure of the average blood glucose level control over 3 months time) serum creatinine (a measure of kidney function), and other blood tests related to diabetes and heart disease (total amount of blood drawn equals approximately 4 to 5 tablespoons). Some of this blood will be stored for future studies described below if you agree. If you are assigned to the metformin group and taking metformin provided by the study, an additional sample would be drawn for a complete blood count (about 10ml or two teaspoons). A repeat blood sample might be necessary for some persons.
9. You will be asked to provide a urine sample for measurement of urine albumin and creatinine (measures of kidney function).
10. If you are taking metformin and are 80 years old or older, or you will turn 80 years old during the course of the study, you will be asked to complete an annual 24-hour creatinine clearance test. This will involve collecting your

urine in a container for 24 hours and returning it to the clinic. When you return the sample to the clinic you will have a blood sample (5 ml or 1 teaspoon) taken from your arm to measure serum creatinine. Whenever possible, this sample will be collected with the other annual blood sample collections; however, in some cases you may be asked to provide an additional sample.

11. You will be asked to complete several questionnaires. You may be asked questions about your health, medications, physical activity, diet and feelings. Some of the questionnaires will be completed by interview and others you will complete yourself. These will take about 1½ to 2 hours to complete.
12. If you are a woman assigned to and taking metformin provided by the DPPOS and there is a chance that you could become pregnant, you will be asked whether you are willing to use medically effective birth control methods for the duration of the study. If you decide to become pregnant during the study, you must notify the clinic staff immediately. If there is a chance that you could be pregnant, a pregnancy test will be done. If you suspect that you are pregnant you should stop your metformin immediately and notify clinic staff.
13. We have previously asked you to give us personal information such as address, phone numbers, and social security number, to help us to reach you if we lose touch. We will ask you to update this information each year and as necessary.

Interim Visit (approximately 30 minutes to 2.5 hours):

Some participants may be asked at times to attend an interim visit.

At this visit the following tests/procedures may occur:

1. You may be asked to attend an interim visit for a repeat blood sample or oral glucose tolerance test when necessary as indicated above.
2. If you are taking metformin, in some cases an additional blood test (5 ml or 1 teaspoon) for kidney function may be required. This would require an interim visit.
3. You may have your weight measured.
4. You may have your blood pressure measured.
5. You may be asked questions concerning your health, given information about your health and health education, or provided with information about the study.

Diabetes diagnosed during study: We ask that you report any symptoms of diabetes to the clinic for further evaluation. Symptoms of diabetes include:

Extreme thirst
Frequent urination
Blurry vision
Unusual tiredness or drowsiness

Unexplained weight loss
Frequent or recurring skin, gum or bladder infections

If you develop diabetes during the study, you will no longer be asked to have the oral glucose tolerance test; however, you will continue to be asked to provide blood for a fasting glucose and hemoglobin A1c test, as well as the other blood samples and tests listed above. In addition, you will be given a glucose meter as well as basic instruction regarding use of the meter and a general overview of diabetes care. You will be referred to your primary care provider (PCP) for additional diabetes education and follow-up. If you do not have a PCP, we can help you find one. The DPPOS cannot provide individual diabetes counseling and it will be your responsibility to follow-up with your physician for your diabetes care. If you wish, the DPPOS may assist you in locating diabetes care.

If your hemoglobin A1c test reaches 7% or higher and you are taking metformin provided by DPPOS, we will refer you to your physician for evaluation and further treatment, and will no longer provide metformin.

Retinal photographs (1-2 hours):

Retinal photos will be completed during the final years of DPPOS. At this visit the following tests/procedures may occur:

1. You will make one visit to a retinal photograph center [local address if needed] which will last about one (1) to two (2) hours.
2. You will answer some questions about your eyes, including any allergies to eye drops used to open (dilate) the pupil .These drops are [XXX – replace with clinic-specific language]. A brief examination of your eye will be done to see if this will be safe for you. [Replace with clinic-specific language if necessary] This will not be a complete eye examination by an eye specialist (Ophthalmologist) but only for safety and research purposes.
3. Drops will be put in both eyes to dilate your pupils, and you will wait about 30 minutes for the drops to work.
4. You will have pictures taken with a camera of the back or your eyes (retina) using a bright flash. There will be about 20 pictures taken of each eye.
5. The photographs will be sent to the Reading Center in Wisconsin identified only with a study number. Your name will not be sent.
6. You may be asked to return for additional photos if the first ones were not acceptable, or for other reasons.

ALTERNATIVE TREATMENTS FOR IGT

The DPP showed that metformin or the DPP intensive lifestyle program is effective in preventing or delaying the development of diabetes. At the end of DPP all participants were offered the DPP lifestyle training in group sessions.

During DPPOS, continued lifestyle lessons will be offered to all participants on a quarterly basis. However, if you wish to participate in an additional lifestyle modification program outside the study, you are free to do so. Although the DPP proved its effectiveness, metformin is currently not an approved drug for prevention of diabetes. If you are not in the metformin treatment group and you want to take metformin, you should discuss this with your primary healthcare provider.

RISKS, STRESS, AND DISCOMFORT

Oral Glucose Tolerance and Blood Tests: The risks of drawing blood include temporary discomfort from the needle stick, possible bruising or redness of the skin, lightheadedness, and on rare occasion, infection. It is possible that some may get nausea or an upset stomach with the glucose (sugar) drink that is given during the oral glucose test. Rarely some people may experience a mild low blood sugar reaction (symptoms like nervousness or sweating) at the end of the test. You will be given a snack to guard against this.

Electrocardiogram (ECG): The risks associated with the use of the ECG electrodes include possible skin irritation, redness and/or chaffing at the application site.

Metformin: The risks of taking metformin were described to you previously in the DPP and have not changed. This medicine has been used for many years to treat patients with diabetes. Side effects include: loss of appetite, upset stomach, vomiting, stomach pain, diarrhea, bloating or gas, or a funny taste (like metal). These are usually mild and lessen with continued use of the medicine. Mild side effects might happen in one out of five persons. Only one or two persons out of fifty are expected to have to stop metformin because of side effects. Anemia (insufficient Vitamin B-12) might also happen very rarely in some persons. Very few persons (3 in 100,000 and usually persons with poor kidney function or with severe liver disease) have serious problems (a condition known as lactic acidosis) with metformin that might result in death. Lactic acidosis has also occurred in people who are heavy or binge alcohol drinkers. Persons with poor kidney function or severe liver disease, women planning to become pregnant, or persons who are heavy or binge alcohol drinkers should not take metformin. You cannot take the study medication, metformin, if you have poor kidney function or severe liver disease or you plan to become pregnant. For those assigned to and taking metformin provided by the DPPOS, tests will be done annually to check on kidney function and blood cell count, as well as an additional annual kidney test for those taking study metformin who become 80 years old while participating in the study. If you have been diagnosed with or suspect kidney or severe liver problems or disease, you should not take metformin. It is always possible that you could have an unexpected serious reaction to metformin or any other medicine.

Persons with congestive heart failure (CHF) should not take metformin. You should report the symptoms of CHF, shortness of breath or swelling in the ankles, to your healthcare provider immediately, and stop taking metformin until you are instructed to use it again.

If you are a woman assigned to the Metformin Lifestyle group and taking metformin provided by the DPPOS and there is a chance that you could become pregnant, you will be asked whether you are willing to use medically effective birth control methods for the duration of the study. If you decide to become pregnant during the study, you must notify the clinic staff immediately. If there is a chance that you are pregnant, you should stop the metformin, inform us, and a pregnancy test will be done.

Metformin has not been approved for use in pregnancy. Metformin has not resulted in any increased risk during pregnancy. Some medicines might, however, cause birth defects to an unborn baby. It is important that you tell us if you suspect at all that you might be pregnant. Study medicines will be stopped if you get pregnant. You will continue in the DPPOS if you are pregnant, and will be asked to re-start your study medicine after pregnancy and breast feeding.

There are some other circumstances for which metformin should be discontinued temporarily. These include overnight hospitalization, some surgical procedures and tests using a contrast dye. It is requested that you notify the clinic if any of these situations occur so that you may be instructed concerning stopping the study metformin.

Exercise: The risks associated with exercise include fatigue, muscle soreness, and injury such as sprained ankles or pulled muscles. Risks are reduced by proper warm-up and cool-down periods. There may be additional risk of heart problems for those who have a chronic disease or experience symptoms with exercise, although this risk is extremely minimal considering the intensity of the recommended exercise, i.e., walking. The level of exercise that we will recommend for you is thought to be more beneficial than harmful, but there is a very small risk of heart attack or sudden death during exercise. Heart attack has been estimated to occur less than once out of 500,000 hours of exercise in people without known heart disease. The risk is greater in people with heart disease. It is important that you contact your physician before beginning any new physical activity program or if you develop diabetes, heart disease or other related health problems during the study. If you wish to take part in the Help-Maintenance or Boost Lifestyle Sessions (BLS) you will be required to obtain a signed permission letter from your physician before beginning any of the physical activity segments of the program.

Eye drops: Some people feel slight burning or tearing when the eye drops are put in. Your vision may be blurred while the eyes are dilated, and you should not drive for 2-3 hours after the test. There is a less than 1% chance that the drops

could cause closed-angle glaucoma, a rapid increase in the pressure inside the eye. Symptoms could include pain in your eye, decreased vision, headache and/or nausea. If any of these symptoms occur after your visit, you should call the eye center immediately [phone number] and follow their instructions.

Photographs: There is no risk to your eyes from the photos. Some people feel discomfort from the flash, however, this lasts only a few seconds.

This eye photography study is for research purposes only and should not replace regular eye examinations and follow-up. [As with any investigational study, there may be adverse events or side effects that are currently unknown and it is possible that certain of these unknown risks could be permanent, serious or life threatening. insert only if required by local IRB]

Other: Some people may feel uncomfortable about some of the questions we ask. You may decide not to answer any question.

There is also the risk that a breach of confidentiality could occur, however, every effort is made to prevent this from happening.

As with any investigational study, there may be adverse events or side effects that are currently unknown and it is possible that certain of these unknown risks could be permanent, serious or life threatening.

BENEFITS

You may not receive any benefit from taking part in this study.

During your participation in the DPPOS, you will receive medical testing. We will tell you if we find any problem. This information may be given to your doctor if you agree. Problems such as diabetes and diabetes related health conditions might be found and treated sooner than if you were not in the study. This might improve your health.

Intensive lifestyle and metformin were shown to reduce the onset of type 2 diabetes. Participation in a group lifestyle intervention and/or taking metformin may help to reduce your risk of developing diabetes.

Your participation in this study may benefit society by learning more about the onset of type 2 diabetes and the relationships between blood sugar levels and complications.

After detailed central grading of the retinal photographs, you will receive a summary report of the photography that you can share with your health care provider.

CONFIDENTIALITY

To help us further protect your privacy, the investigators have obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS).

With this Certificate, the investigators cannot be forced (for example by court subpoena) to disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. Note however, that if an insurer or employer learns about your participation, and obtains your consent to receive research information, then the investigator may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your own privacy.

Finally, you should understand that the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

Information that we receive from you will be kept confidential to the extent allowed by law. Information we collect about you will be put into a research record that will be sent to a central data site at The George Washington University for statistical analysis. Your central research record will not be directly identified with your name. A code number and/or letters will identify your records. The link between the code and your name is stored in a secure location at the (insert your institution name.) Only authorized personnel at (insert institution name) will have access to the key to the code. Anonymous coded information may be released to a DPP investigator (or other investigator authorized by the DPP) only after determination of the scientific usefulness of a proposed study. [Insert appropriate language as determined by your IRB].

OTHER INFORMATION

[Your IRB may require that some or all of these sections be inserted in other parts of the consent]

Some of the test results will not be made known to you or the clinic staff or your own doctor. This is known as "masking". The only blood tests that will be masked in some cases will be the results of the oral glucose tolerance test or fasting glucose test. When the test is confirmed to be normal or shows that diabetes has developed, the results will be unmasked.

You will be given results from the glucose, lipid, blood pressure, ECG and neuropathy tests, and kidney, complete blood count tests for those assigned to and taking DPPOS metformin. If you wish these results to be sent to your physician, we will ask you to sign a permission form indicating to whom you would like the

results sent. The other tests and procedures performed are for research purposes only and for these you will not receive individual results. Some of the samples collected at your mid-year and annual visits will be stored for future use for studies related to diabetes development and other health related conditions If you do not want your samples to be stored and utilized for future studies of diabetes and related health conditions such as heart disease, please indicate below. No samples for this purpose will be drawn or stored.

[Institutional language as suggested by your IRB should be substituted for the following sections.]

Participation in this study is completely voluntary. You are free to take back your consent and stop taking part in this study at any time. You may ask any questions about the study at any time. Your current or future care will not be affected by your stopping the study

[Each center should incorporate a statement to address medical liability.]

If a test result shows that you should get medical care, you will be referred to your doctor. If you do not have a doctor, we will help you to see a doctor for medical care.

This study can be stopped or modified at any time.

If you have any questions about your rights as a research subject, you may call (IRB contact name) at (IRB phone number.)

COSTS AND PAYMENTS: All study procedures for the DPPOS will be free of charge. You will receive money (up to $100 a year) for your time and effort for participating in the study in addition to other incentives noted above.

PARTICIPANT'S STATEMENT:

The study described above has been explained to me. I understand that I am consenting to participate in the DPPOS. If I have any questions, I know that I can contact one of the investigators listed on the first page.

In addition, I agree to the following:

I give permission for my blood to be stored in a central bank (currently at the University of Washington) for future use by the DPPOS investigators in studies of diabetes, related complications, and heart disease:

_____YES _____NO _____INITIALS

When I die, the specimens I have donated may still be used for the research purposes agreed to above.

_____YES

_____NO (my specimens MUST be destroyed once you have been notified of my death).

_____INITIALS

We are also asking you to allow samples of your blood and your research data to be sent to the NIDDK Central Repositories, a research resource supported by the National Institutes of Health. The Repository collects, stores, and distributes biological samples and associated data from people with many kinds of disorders, from unaffected family members, and from other healthy people. The purpose of this collection is to make samples available for use in research for the study of diabetes, related complications and heart disease after the current study is completed. Sending samples to the Repository may give scientists valuable research material that can help them to develop new diagnostic tests, new treatments, and new ways to prevent diseases.

The Repository will take measures to protect your privacy, although no guarantee of confidentiality can be absolute. Before the DPPOS researchers send samples to the Repository, each sample will be given a code number. Your name and all personal identifying information, such as address, social security number, date of birth, and clinic location will not be included. Therefore, the Repository will not be able to give out your name, or other information that identifies you to the scientists who receive the samples. However, the Repository and scientists will also have some research data about you, such as age, sex, diagnosis, treatment group, race, and outcomes of the study.

You will not receive any direct benefit or payment for participating, but your sample may benefit the future health of the community at large or some particular group. Because other researchers will not have access to your identity, neither you nor your physician will get the eventual results of studies that might be performed using your sample. It is possible that data resulting from use of your sample may eventually be used in a research publication. In that event, your name or other identifying information will not be included, as this information will not be available to the researchers.

It is important for you to understand that there is a small chance that some research may yield results that may indirectly have a negative impact on insurability, employability, and/or family relationships of some individuals or groups of people.

Sometimes, research results in findings or inventions that have value if they are made or sold. These findings or inventions may be patented or licensed, which could give a company the sole right to make and sell products or offer testing based on the discovery. Some of the profits from this may be paid back to the researchers and the organizations doing this study, but you will not receive any financial benefits.

Your donation is voluntary, and if you choose not to participate there will be no penalty or loss of benefits to which you are entitled.

If you agree to have your sample stored in the Repository, you can change your mind up until the end of the DPPOS. When we receive written instructions from you, we will destroy your sample and all information that identifies you. After the DPPOS ends, you will not be able to withdraw your samples because the Repository will not know which one is yours. The samples will stay in the Repository indefinitely or until it is used up.

1) Data

I give permission for my research data to be sent to the NIDDK Central Repository for future use by NIH approved investigators in studies of diabetes, related complications and heart disease.

_____YES _____NO _____INITIALS

2) Blood

I give permission for my blood to be sent to the NIDDK Central Repository after the end of DPPOS for future use by NIH approved investigators in studies of diabetes, related complications and heart disease.

_____YES _____NO _____INITIALS

_____

Participant's Printed Name

_____

Participant's Signature Time Date

_____

Investigator's Signature
Date

_____

Person obtaining consent Date

cc: Investigator
Participant