PROTOCOL

for the

DIABETES PREVENTION PROGRAM OUTCOMES STUDY

(DPPOS)

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1. EXECUTIVE SUMMARY

1.1. Background

Type 2 diabetes mellitus (T2DM) is rapidly becoming the most common chronic disease in the United States, with the most recent estimates of more than 9% of the adult population affected and 1,700,000 new cases per year. T2DM 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, T2DM 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 T2DM 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 T2DM and its attendant long-term complications, total health care costs for diabetes have been estimated at approximately 245 billion dollars per year, or 12% of total U.S. health care expenditures in 2012. The enormous human and financial costs that accompany T2DM, and the difficulty in treating it effectively once it has developed, make it an appropriate target for prevention.

The **Diabetes Prevention Program** (DPP, 1994-2001) 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 ≥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 (**Figure 1**).

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 remained unanswered. Specifically, whether the decrease in the development of diabetes can be sustained was unknown. Moreover, determining whether the delay or prevention of diabetes would 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, was 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** (DPPOS, 2002-2015), was 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 patients with new onset T2DM, 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 joined DPPOS. As of December, 2014 and after 12 years of DPPOS and a mean of 16 years of combined DPP/DPPOS, 84% of the surviving DPPOS cohort continue to attend annual follow-up visits. Analyses performed after 11 years of DPPOS demonstrated a durable effect of diabetes prevention associated with the lifestyle and metformin interventions with 27 and 18% reductions in diabetes incidence, respectively, compared with the placebo group. Analyses through the first 6 years of DPPOS (Phase 1) revealed significant reductions from baseline in CVD risk factors in the lifestyle intervention group, with decreased utilization of glucose-lowering and lipid-lowering medications. Analyses following year 11 of DPPOS Phase 2 (2013) revealed no significant differences in the prevalence of the aggregate microvascular outcome, comprised of fundus photography measured retinopathy, nephropathy based on estimated glomerular filtration rate (eGFR) or increased albuminuria (≥30 mg albumin/g creatinine), or neuropathy detected by abnormal monofilament sensation, among the treatment groups; however, in a pre-specified analysis by sex, women had a 21 and 22% reduced risk of this outcome in the lifestyle group compared with the placebo and metformin groups, respectively. Moreover, among the participants who had not developed diabetes during DPP/DPPOS, the prevalence of the aggregate microvascular outcome was 28% lower compared with those who had developed diabetes. Protocol version 3.4 described the DPPOS including the revisions incorporated to complete the second phase of DPPOS, from 2009 to 2015 (**Figure 1**).

The **DPPOS Phase 3** (2015-2025) is a 10-year study divided into two 5-year funding periods as required by the NIH, and will focus primarily on the effects of randomized metformin therapy on CVD and cancer; the continued, even longer term effects of the original randomized therapies during DPP and DPPOS on selected microvascular complications; and on the clinical course of pre-diabetes and new onset diabetes. Since protocol version 3.4 only covers participant visits through DPPOS study year 13 (ending October 2015), version 4.0 adds

DPPOS study year 14-18 visits (through 2021), which will commence on July 1, 2015. Version 4.0 covers the first 5-year period of **DPPOS Phase 3**.

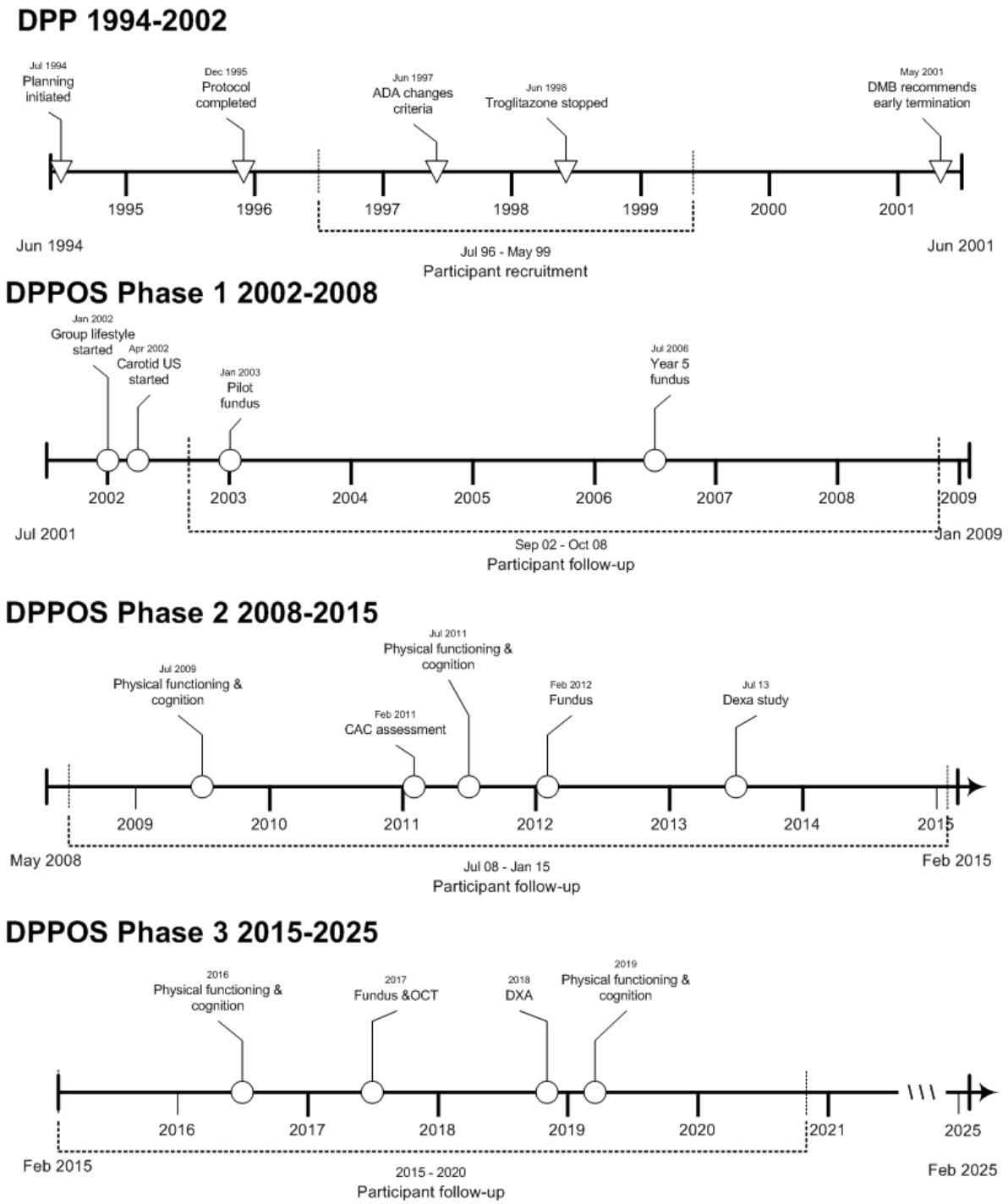

Figure 1. Timeline for DPP and DPPOS

1.2. Objectives

The primary objectives of DPPOS Phases 1 & 2 were to evaluate the long-term effects of active DPP interventions on the further development of diabetes and composite diabetes-related microvascular complications. **DPPOS Phase 3** will evaluate the long-term effects of the original DPP/DPPOS interventions on cancer (first 5 years) and cardiovascular disease (second 5 years), with a particular focus on the effects of the metformin intervention.

The secondary objectives of **DPPOS Phase 3** are to evaluate the long-term effects of DPP interventions on the further development of diabetes, microvascular and selected 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, i.e. the clinical course of dysglycemia, as well as assessing subgroups of participants in order to evaluate the effect of race/ethnicity, age, and sex on health outcomes.

1.3. Study Population

All surviving 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 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, 5% American Indian, and 4% Asian or Pacific Islander-American. A total of 2776 participants consented to participate in DPPOS (86.8% of the 3124 surviving participants). Among intensive lifestyle, metformin, and placebo participants who joined DPPOS, 770 DPPOS participants had been diagnosed as having diabetes as of September, 2002. Through January 2015, an additional 824 DPPOS participants have developed diabetes, for a total of 1594 (56%) of DPPOS participants having developed diabetes. The mean age of the cohort as of January, 2015 was 66 years with 68% women, the same sex distribution as at DPP baseline.

All surviving DPPOS participants will be invited to continue their participation in **DPPOS Phase 3.** For participants who can no longer sign informed consent owing to infirmity, alternate informed consent processes will be put into place according to local practice and institutional permission.

1.4. Study Interventions

Quarterly lifestyle group sessions were held for all participants through summer 2014. These focused on lifestyle lectures as well as other topics of interest to participants with IGT or diabetes. Additional group lifestyle boost sessions were offered to the group originally assigned to intensive lifestyle intervention through spring 2014. During **DPPOS Phase 3**, an annual lifestyle check-up will be offered to the original lifestyle group. Open label metformin therapy (850 mg twice per day) will continue to be provided to the participants originally assigned to metformin. An annual group lifestyle session will be held for all participants.

1.5. Outcomes

DPP

The DPP was originally designed to examine the effects of lifestyle or metformin on diabetes development compared with placebo. DPPOS was designed to assess the longer-term effects of the original DPP interventions on diabetes development and on diabetes complications and cost-effectiveness.

DPPOS Phase 1

The primary outcome for DPPOS Phase 1 was 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).

DPPOS Phase 2

The primary outcome for DPPOS Phase 2 was the prevalence of microvascular and neuropathic disease, defined as a composite of the following at the year 11 visit, or if the participant was deceased or lost to follow-up before year 11, as of his/her last assessment:

a. Nephropathy: increased albuminuria (≥30 mg/gram creatinine, confirmed), or renal dysfunction (end-stage renal disease, dialysis or renal transplant) or eGFR < 45 ml per min based on serum creatinine, using the CKD-EPI equation or another validated algorithm; the qualifying criteria confirmed), or
b. Retinopathy: retinopathy by fundus photography (ETDRS grade of 20 or greater) or adjudicated history of laser or other treatment for retinopathy, or
c. Neuropathy: reduction or absence of light touch sensation to monofilament (Semmes-Weinstein 10 gram) in either foot (< 8 of 10 applications detected).

If a participant was taking antihypertensive drugs at the last assessment and did not meet the ACR or eGFR criteria at that time, he or she was considered to have reached the nephropathy outcome if the nephropathy criteria were met at 2 consecutive past visits. This substitutes for the occurrence of nephropathy at year 11.

DPPOS Phase 3

The primary outcome for **DPPOS Phase 3** is time to the development of cancer and of major atherosclerotic cardiovascular events (MACE). The cancer outcome includes the first occurrence of a new cancer diagnosed since DPP randomization and is the primary outcome during the first 5 years of **DPPOS Phase 3**, while MACE includes any of the following: nonfatal or fatal myocardial infarction or stroke or any cardiovascular death occurring since DPP randomization. The first occurrence of a new MACE event since DPP randomization is the primary outcome during the second 5 years of **DPPOS Phase 3**. The occurrence of cancer and MACE events are collected at every visit using a standard medical history questionnaire and adjudicated by reviewers who are blinded to treatment assignment.

SECONDARY OUTCOMES (outcomes assessed in Phases 1 & 2 but discontinued in **DPPOS Phase 3** are shown in brackets)

- Further development of diabetes
- Diabetic retinopathy

- Diabetic neuropathy
- Diabetic nephropathy
- Cardiovascular disease events
- [Subclinical atherosclerosis]
- Risk factors for cardiovascular disease
- Amputation in a lower extremity not resulting from major trauma
- Hospitalizations
- [Nutrition], Physical activity, body weight and obesity
- [Dietary and exercise behaviors]
- Physical functioning
- Quality of life indices
- Health care costs
- Cognitive performance
- Urinary incontinence
- Sexual function
- Pulmonary function
- Bone density, whole body composition and vertebral fractures
- Healthy Aging Index

1.6. Design and Power

The power analysis at entry to DPPOS Phase 2 was as follows: based on the high rate of adherence during DPP and enrollment in DPPOS Phase 1, we estimated that 85% of all current (at the time) DPPOS participants would elect to continue in DPPOS Phase 2. The global test provided 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, =0.025), and 74% power for a 20% reduction[1,2].

For **DPPOS Phase 3**, the analysis of cancer will take place at end of the first 5 years and of MACE after 10 years, using the log rank test. To detect 28% risk reduction in total cancer associated with metformin, the study requires 170 events in the placebo group using a log-rank test with 85% power and 2-sided significance level of 0.05. Assuming an increasing annual incidence rate of 1.86% by 2020 and an annual loss to follow-up of 1.04%, the projected 199 cancer events in the placebo group will provide 89% power to detect a 28% hazard risk reduction at the end of the first 5-year period. For MACE, we estimate an age related 2.1 fold increase in annual incidence rate in the next 10 years. This conservative increase is used to project events in the placebo participants of 116 and 156 after 5 and 10 additional years of **DPPOS Phase 3** assuming a 1.04% loss to follow-up per year. To detect a 30% hazard risk reduction in MACE incidence in the primary comparison of metformin and placebo with 85% power and a 2-sided significance level of 0.05 using a log-rank test, we require 145 placebo events. With the expected 156 events in the placebo group by 2025, the study will have 89% power to detect a 30% hazard risk reduction. This protocol represents 5 years of study although some of the goals described will require 10 total years of study. We hope to extend this protocol for an additional 5 years once the first 5-year period is completed.

1.7. Analyses

The primary outcome analysis in DPPOS Phase 1 compared the three intervention groups with regard to the cumulative incidence of diabetes. DPPOS Phase 2 compared 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 analysis for **DPPOS Phase 3** will focus on the effects of metformin compared with placebo on the development of a number of diabetes related complications, including cancer and MACE. The primary and secondary outcome analyses will follow the "intention to treat" principle. The time to event analysis uses the date of event or first occurrence for composite outcomes. A participant is considered "administratively censored" if he/she completes the full duration of follow-up without an event. Participants who died or prematurely discontinued follow-up visits prior to any event are "censored" as of their last follow-up visit or contact – hence, participants who did not enroll into DPPOS are censored as of their last contact during DPP. Separate Kaplan-Meier estimates of cumulative incidence curves are calculated for the three treatment groups and are compared using the log rank test[3].

2. OBJECTIVES

2.1. Primary

The primary objective of DPPOS Phase 1 was to evaluate the long-term effects of active DPP interventions on the further development of diabetes. The primary objective of the DPPOS Phase 2 was to evaluate the long-term effects of the DPP interventions (Intensive Lifestyle and Metformin) on the prevalence of the composite diabetes-related microangiopathic and neuropathic outcome.

The primary objective of the **DPPOS Phase 3** is to evaluate the long-term effects of metformin compared with placebo on the incidence of cancer and of major atherosclerotic cardiovascular events (MACE: fatal and nonfatal myocardial infarction or stroke, and other cardiovascular deaths), with the comparisons of lifestyle compared with placebo, and lifestyle compared with metformin, important secondary objectives. Major secondary comparisons will be lifestyle vs. placebo and metformin vs. lifestyle.

2.2. Secondary

The secondary objective of the DPPOS (**DPPOS** outcomes assessed in Phases 1 & 2 but discontinued in **Phase 3** are shown in brackets) is to evaluate the long-term effects of DPP interventions on selected health outcomes including:

- Further development of diabetes
- Diabetic retinopathy
- Diabetic neuropathy
- Diabetic nephropathy
- Cardiovascular disease events
- [Subclinical atherosclerosis]
- Risk factors for cardiovascular disease
- Amputation in a lower extremity not resulting from major trauma
- Hospitalizations
- [Nutrition], Physical activity, body weight and obesity
- [Dietary and exercise behaviors]
- Physical functioning
- Quality of life indices
- Health care costs
- Cognitive performance
- Urinary incontinence
- Sexual functioning
- Pulmonary function
- Bone density, whole body composition and vertebral fractures
- Healthy Aging Index

The outcomes chosen as secondary objectives were selected based on their clinical importance, demonstrated association with diabetes, and the possibility that they would be responsive to the DPP interventions.

2.3. Other Objectives

Other research questions of the **DPPOS Phase 3** 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 sex on health outcomes.

3. BACKGROUND AND RATIONALE

3.1. The Diabetes Prevention Program (1996-2001)

3.1.1. DPP 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)[4-6]. Development of diabetes, defined by 1997 ADA criteria, 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 (T2DM), had become epidemic in the US, currently affecting >9% of the adult population and with almost 1,700,000 new cases per year[7]. 2. The consequences of T2DM including diabetes-specific complications, such as retinopathy, nephropathy, and neuropathy, and cardiovascular disease, cause severe morbidity and mortality with enormous human and financial costs[8]. 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[6]. 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[9], and, finally, 5. Potentially modifiable environmental factors, such as overweight and a sedentary lifestyle, that were known to increase risk for diabetes[10-12], 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 was predicted to manifest as a benefit of diabetes prevention interventions. 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[4]. The ability to demonstrate a reduction in microvascular complications or "hard" CVD outcomes was

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

3.1.2. DPP 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, this population was projected to have a rate of progressing to diabetes of 7.5% per year[4,9]. The baseline characteristics of the study population have been described in detail[5]. (**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) 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 DPP, with the expectation that more would develop diabetes over time[9]. 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	142 (4%)	57 (5%)	36 (3%)	49 (5%)
Fasting glucose (mmo1/L)	5.9 ± 0.5	5.9 ± 0. 5	5.9 ± 0. 5	5.9 ± 0. 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.

3.1.3. DPP Outcome Data

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, 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 were not known or could not be afforded during the study. Samples suitable for *genetic analysis* have also been collected, and have been analyzed as part of a separately funded affiliated project. In addition, samples have been kept in long-term storage for participants who consented to this. All data collected include standardized measurements using uniform methods and central analysis/reading/grading with easily accessible stored data. Data and samples have been provided to the NIDDK repository and thereby made available to the broader scientific community.

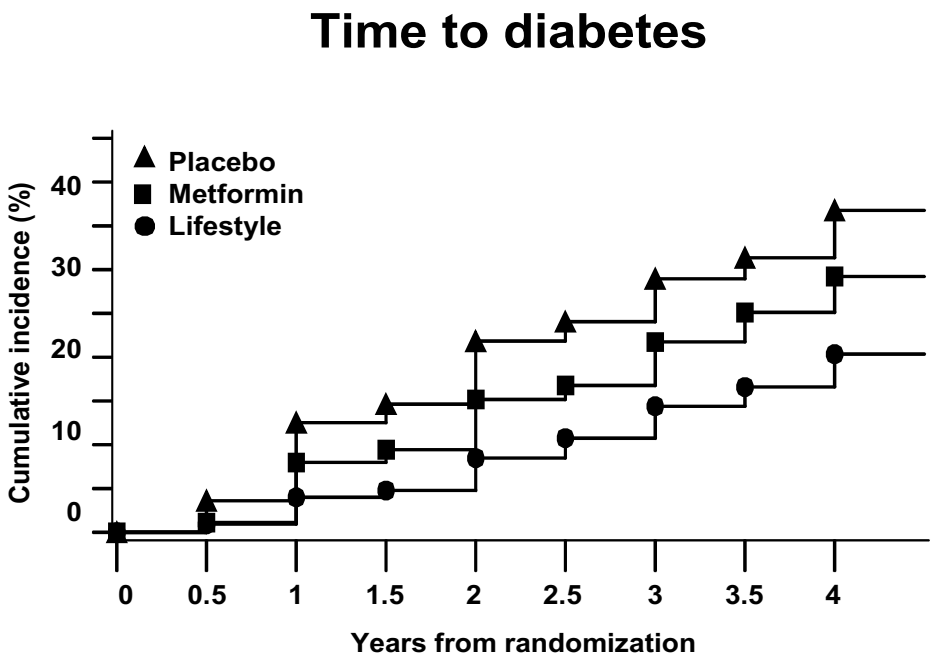

Figure 2: Life-table Analysis of Cumulative Incidence of Diabetes Development During DPP

3.1.4. DPP 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 (**Table 2, Figure 2**). Both results were significant and lifestyle was significantly more effective than metformin[6]. 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 DPP 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 years		13.9	6.9
Weight loss (%)*			
Year 1	0.43 (0.5)	2.72 (2.9)	6.7 (7.2)
Year 2	0.06 (0.1)	2.07 (2.2)	5.4 (5.7)
Year 3	-0.37 (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

*Values are mean percent weight loss (standard error)

3.1.5. Bridge Period Between End of Masked Intervention and Initiation of DPPOS (2002)

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 setting, rather than an 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. Metformin was continued during this period, with participants and staff unmasked to treatment assignment.

3.2. The Diabetes Prevention Program Outcomes Study Phases 1&2 (DPPOS) (2002 – 2015)

3.2.1. DPPOS Study Rationale and Design

The DPP was designed to ascertain whether metformin treatment and/or intensive lifestyle modification reduced the development of diabetes, compared with placebo, in subjects with IGT during a period of intervention averaging 4 years. 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 would increase our understanding of the clinical course of IGT and new-onset type 2 diabetes.

3.2.2. DPPOS Study Cohort

All surviving participants from DPP were invited to join DPPOS. Of the 3,234 three-arm participants randomized to DPP, 68 withdrew during DPP, and 39 died before they could enroll in DPPOS. Of the remaining 3,127 DPP participants, 351 did not enroll in DPPOS or could not be contacted, and 2,776 (88.8%) enrolled. The characteristics of the DPPOS cohort at randomization, DPP end, and at DPPOS Phase 2 end (2013), which will serve as baseline for **DPPOS Phase 3**, are shown in **Table 3**.

Table 3 Characteristics (means) of DPPOS Cohort at randomization, DPP end and DPPOS Phase 2 end

	DPP	DPP End (2001)*			DPPOS Phase 2 End (2013)**				
	Total-2776	PLB-935	MET-926	ILS-915	PLB - 780	MET - 772	ILS - 751	Non-DM-1226	DM-1550
Age (yr)	51	54	54	54	65	66†	66	67	65§
Sex (% women)	68	69	67	68	69	68	68	68	68
Diabetes (%)	0	30	21	14	60	55	52	0	100
BMI (kg/m^2)	34	34	33†	32†‡	33	32†	32†	31	33§
HbA1c (%)	5.9	6.1	6.0†	5.9†‡	6.3	6.1†	6.2‡	5.6	6.6§
SBP (mmHg)	124	123	123	120†‡	121	122	121	121	122
DBP (mmHg)	78	76	76	74†‡	71	71	71	71	71
LDL-C (mg/dL)	125	124	123	124	96	95	98	102	92§
HDL-C (mg/dL)	46	45	47†	47†	53	55†	54	56	52§
Triglycerides (mg/dL)	162	157	153	138†‡	137	137	130	118	147§

Baseline characteristics did not differ across treatment groups except for HDL. Treatment group differences († significant vs PLB, ‡ significant vs MET) in means; at study end by glycemic status with significant glycemic differences noted (§significant vs non-DM) *Final DPP annual visit during masked phase; **DPPOS year 11 annual visit.

3.2.3. DPPOS Phase 1 Results: Diabetes Prevention

The first question addressed in the DPPOS was the long-term impact of the DPP interventions on the development of diabetes. This effect of the DPP interventions was evaluated in two ~6-year phases during DPPOS. After ~6 years of DPPOS (DPPOS Phase 1, ~10 years after randomization), weight regain was evident in the group originally assigned to ILS and a persistent modest weight loss was seen in the group originally assigned to MET. In the cohort followed into the DPPOS, diabetes incidence rates during DPP were 4.8 (95% CI 4.1, 5.7) cases per 100 person-years (P-Y) in ILS, 7.8 (6.8, 8.8) in MET and 11.0 (9.8, 12.3) in PLB (**Figure 3**). Although the rates of diabetes development in the DPPOS period became similar across treatment groups: 5.9 (5.1, 6.8) per 100 P-Y in ILS, 4.9 (4.2, 5.7) in MET, and 5.6 (4.8, 6.5) in PLB, the between-group differences established during the DPP interval produced persistent treatment-related differences in diabetes incidence at 10 years (35% reduced ILS vs PLB and 18% reduced MET vs PLB)[13]. This pattern persisted into the second phase of DPPOS (Phase 2, years 10-15 following randomization). At year 15 (the end of DPPOS Phase 2), cumulative diabetes incidence was 52% of those originally assigned to ILS, 55% of those originally assigned to MET and 60% of those originally assigned to PLB. **(Figure 3**)

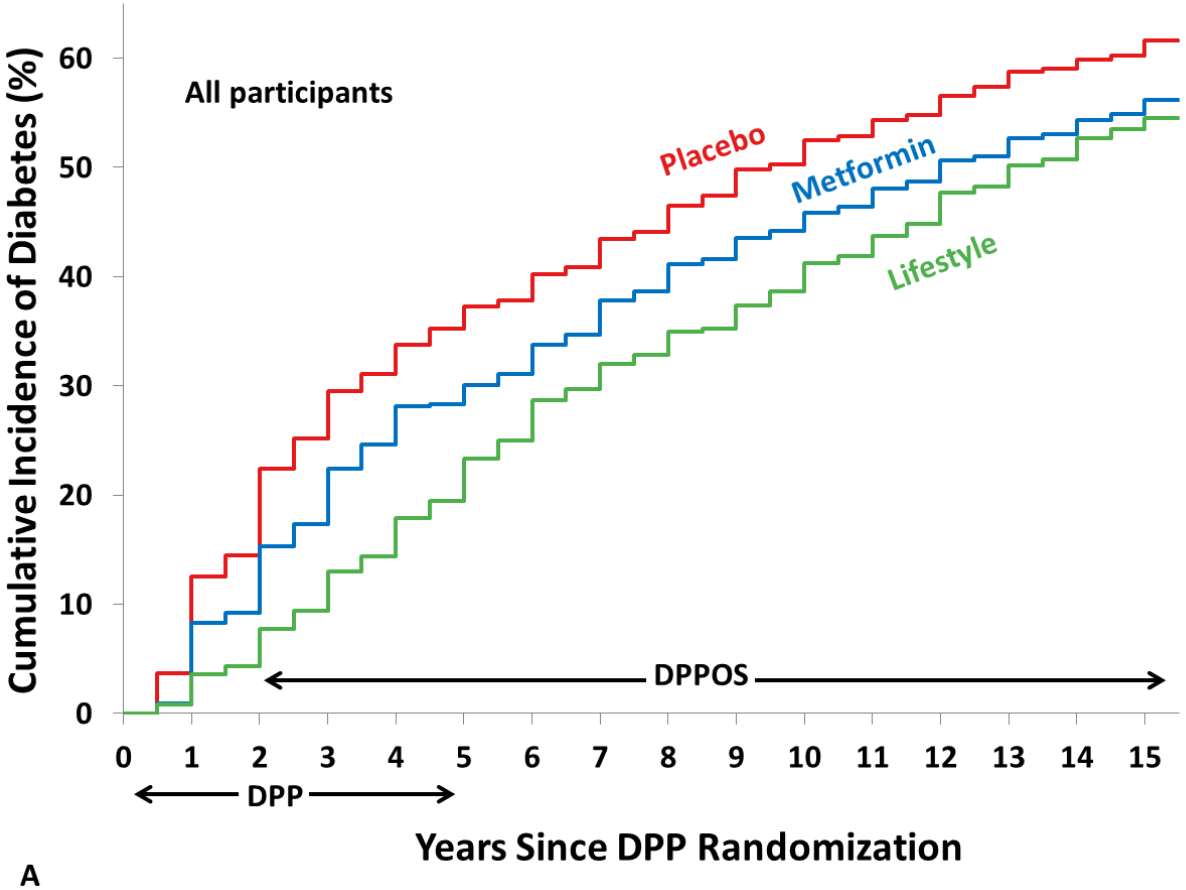

Figure 3. Diabetes outcomes in the DPP and DPPOS

Of note, the diabetes ascertainment methods employed in the DPP/DPPOS identify the transition to diabetes at an earlier stage than is seen in traditional clinical care. The mean fasting

glucose in the study groups at Year 15 was 122 (ILS), 118 (MET) and 123 mg/dl (PLB), and the mean HbA1c was 6.2% (ILS), 6.1% (MET) and 6.3% (PLB). This indicates that the magnitude and duration of exposure to dysglycemia, and to overtly diabetic levels of elevated glucose, are less than would be predicted despite the majority of each group having made the transition to biochemically diagnosed diabetes.

3.2.4. DPPOS Phase 2 Results: Impact of DPP Interventions on Microvascular Disease

The second question addressed in DPPOS Phase 2 was the long-term clinical impact of having prevented or delayed the onset of diabetes, specifically the effects of DPP interventions on diabetes-related complications. The ultimate health care benefit of diabetes "prevention" was expected to 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. Epidemiological data suggest that prevention or delay of diabetes should result in less disease over time, but very few studies have been able to address 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[14]. Thus, based on conventional thinking, the appearance of these complications in DPP participants was expected to be restricted to those who develop diabetes, and was expected to occur only some years after biochemical conversion. The decreased development of diabetes with intensive lifestyle and metformin was therefore expected to reduce the frequency and extent of these disease entities compared with their occurrence in the former placebo-treated group.

For this set of analyses the pre-specified primary outcome was an aggregate of microvascular diseases, defined as the presence of one or more of nephropathy, retinopathy or neuropathy. *Nephropathy* was defined as albuminuria ≥30 mg/g creatinine in a spot urine collection on 2 consecutive tests or an estimated eGFR <45 ml/min/1.73 m^2, based on annual serum creatinine using the CKD-EPI equation[15] on 2 consecutive tests, or renal failure (end-stage renal disease, dialysis or transplantation). Participants taking antihypertensive drugs at the final assessment who did not meet albuminuria or eGFR criteria at that time were considered to have reached the nephropathy outcome if the nephropathy criteria were met at 2 consecutive past visits. *Retinopathy* was diagnosed on 7-field stereoscopic fundus photography as an ETDRS grade 20 or greater[16] in either eye or treatment of retinopathy with laser or intravitreal injections. The presence of *neuropathy* was based on loss of light touch sensation (<8 of 10 applications detected on the dorsum of the great toe) measured with a 10-gram Semmes-Weinstein monofilament[17]. Kidney function and neuropathy were measured annually during DPPOS, while retinopathy was measured during the final year of DPPOS (2012-13). The study was powered based on the global test[1] at 91% power to detect a 25% reduction in microvascular complications due to an intervention, from a projected placebo group average prevalence of 12.1% (powered for each pair-wise comparison, 2-sided, α=0.025)[2].

Despite the group differences in diabetes incidence, the average prevalence of the microvascular outcomes at DPPOS Phase 2 end did not differ significantly among the three treatment groups (**Figure 4**)[18]. We did observe some differences in complication prevalence in subgroup analyses. The prevalence of the microvascular outcome was approximately 50% higher in men than women, and increased with increasing age, but was similar across racial/ethnic groups. The pre-specified sex-specific analysis showed a significant sex-by-lifestyle vs. placebo treatment interaction (P=0.047). In women but not in men, lifestyle intervention reduced

microvascular disease by 21% compared with placebo (P=0.03) and 22% (P=0.02) compared with metformin. Participants who did not develop diabetes during DPP/DPPOS had a 28% lower aggregate microvascular disease prevalence at year 15 than those who did develop diabetes (P<0.001) for all treatment groups combined, with similar patterns in each treatment group (P=0.20 comparing treatment groups).

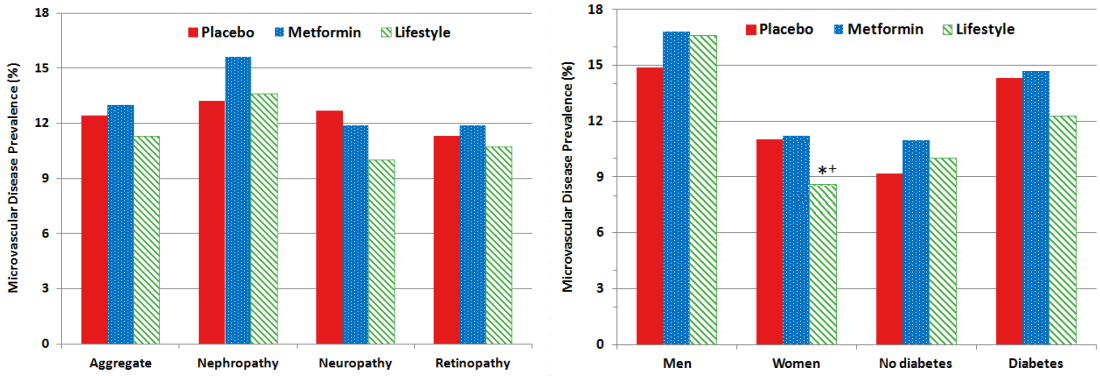

Figure 4. The left panel presents the results for the prespecified aggregate result, and for the treatment effects within each type of microvascular complication. The right panel presents the results for the aggregate result, divided by major groupings.

We observed the expected relationship of duration of diabetes, and exposure to hyperglycemia, with retinopathy and nephropathy, but not with neuropathy. Even 15 years after original randomization in the DPP, the differences in magnitude of hyperglycemia and duration of diabetes between treatment groups were modest. Further follow-up is needed to identify whether DPP treatments that prevent/delay the progression to diabetes, and the early and continuing glycemic separation of treatment groups, will produce a measurable beneficial effect on microvascular disease.

3.2.5. DPPOS Phase 1 & 2 Results: Impact of DPP Interventions on Cardiovascular Disease (CVD) Risk

Diabetes is estimated to account for as much as 25% of all cases of CVD[19]. With the T2DM epidemic, the absolute number of cases and the fraction attributable to T2DM will only grow. A decreased incidence of T2DM would be expected to decrease subsequent CVD; however, whether T2DM prevention reduces CVD is unknown. Similarly, whether ILS or MET has direct preventive effects on the development of CVD in addition to, or independent of, their beneficial effects on T2DM development is unknown.

Metformin has been beneficial in several small prevention trials of CVD in persons with diabetes[20-23]. In addition, metformin reduces myocardial infarct size, prevents heart failure and improves cardiac function in animal models[24,25]. Evidence of beneficial effects on CVD risk factors and cardiac function independent of its antihyperglycemic action[26], combined with the DPP-based recommendation for its use in prediabetes[27,28], has led to recent CVD prevention studies with metformin in non-diabetic cohorts. The first of such studies found no benefit of metformin on carotid intimal media thickness change in patients with coronary heart disease (CHD)[29]. Another showed no effects on left ventricular function[30]. A larger trial with clinical outcomes is in progress[31].

The only published data on the long-term effects on CVD events of lifestyle interventions that target T2DM prevention come from the Da Qing study which recently reported a significant reduction in mortality, largely cardiovascular in origin, after 23 years of total follow-up, between their original control and lifestyle intervention groups[32]. These findings, although intriguing, must be viewed with skepticism because of the cluster (clinic-based) randomization, asymmetric loss-to-follow-up, and differences in age and smoking patterns in the two intervention groups. The recently completed Look AHEAD study, which used the DPP ILS in patients with ~ 8 years T2DM duration, showed no significant effects on the primary CVD outcome over ~12 years of follow-up[33]. The differences between Da Qing and Look AHEAD results suggest that lifestyle interventions may need to be started early in the course of dysglycemia.

Table 4. 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 (U/ml)			
Fasting	0.74	-2.93	-4.52
30 min Post-OGTT	1.45	-6.92	-13.49

The DPP and DPPOS Phases 1 & 2 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. 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 4**) 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 ~15 years of the DPP/DPPOS Phases 1 & 2. Continuation of the study in **DPPOS Phase 3** presents the unique opportunity to evaluate the effects of MET begun during pre-diabetes vs PLB or ILS on CVD, the effects of ILS on CVD, and associations between T2DM prevention and CVD.

3.3. DPPOS Phase 3 (2015-2025)

There is a strong rationale for continued follow-up of the DPP/DPPOS cohort. The randomized study assignments at baseline provide a unique opportunity to evaluate metformin's putative effects on CVD and cancer outcomes, which have been proposed in recent years. More generally, the random assignments allow long-term prospective intention-to-treat analyses. The population has been highly adherent to study procedures and study therapies, and between-group differences in glycemia persist over time prompting projections of between-group differences in outcomes based on diabetes status and on total glycemic exposure.

Long-term follow-up of randomized controlled clinical trials has been highly informative in several completed clinical trials; e.g., the DCCT (EDIC)[34], the Coronary Drug Project[35,36] and 4S[37]. This approach 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[35]. However, these clinical outcomes were significantly reduced after 9 years of further observational follow-up[38]. The ongoing EDIC follow-up of the DCCT cohort demonstrated widening differences in outcomes as early as 4 years after the termination of assigned therapies[34]. In addition, longer follow-up 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[11,34,39,40]. Lastly, evaluation of the United Kingdom Prospective Diabetes Study (UKPDS) cohort 10 years following completion of the intervention phase of the study demonstrated significant differences in a number of outcomes in subjects previously randomized to the intensive and conventional treatment arms[20]. Notably, 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 outcome and microvascular complications and a significant reduction in risk became apparent for myocardial infarction and all-cause mortality.

3.3.1. DPPOS Phase 3: Effects of metformin on CVD

In DPP/DPPOS, intensive lifestyle and metformin reduced body weight and improved insulin resistance, glycemia and cardiometabolic vascular risk factors[13,41-44]. However, whether T2DM prevention reduces CVD has not been shown. More specifically, whether metformin has direct preventive effects on the development of CVD in addition to, or independent of, the beneficial effects on T2DM development is unknown. In **DPPOS Phase 3** we will study the comparative effectiveness of the early initiation of metformin during pre-diabetes vs treatment only after the development of T2DM on CVD prevention.

Metformin has been beneficial in several small prevention trials of CVD in T2DM, including in the UKPDS[22,45]. In addition, metformin reduces myocardial infarct size, prevents heart failure and improves cardiac function in animal models and human studies[24,25]. Evidence of beneficial effects on CVD risk factors and cardiac function independent of its antihyperglycemic action[26], combined with the DPP-based recommendation for its use in pre-diabetes[28], has led to recent studies with metformin for CVD prevention in non-diabetic cohorts. The first of such studies found no benefit of metformin on carotid intimal media thickness change in patients with CHD[29] and a recent trial of metformin in non-diabetic patients showed no effects on left ventricular function[30].

DPPOS is by far the largest of the diabetes prevention studies with a cohort randomly assigned to metformin. Further, the long-term exposure to metformin beginning in pre-diabetes is a unique strength of this study. Although subjects in the other treatment groups can initiate metformin treatment once diagnosed with diabetes, the mean cumulative metformin exposure is currently 10.9, 2.4 and 1.8 y in MET, PLB and ILS. Further, 70% of the MET group subjects who have not developed T2DM continue to take study-related metformin. Projected cumulative metformin exposure will remain considerably greater in MET by virtue of its early randomized

use. **DPPOS Phase 3** will also ascertain whether total years of metformin exposure, much of it during the period of prediabetes, reduces CVD risk.

Although this phase of the study is focused on comparisons of metformin versus placebo treatment groups, we remain interested in the effects of diabetes prevention via the intensive lifestyle intervention. As noted above, the apparent differences between Da Qing and Look AHEAD results using lifestyle interventions to reduce the incidence of CVD suggest that lifestyle interventions may need to be started early in the course of dysglycemia to reduce long-term CVD. This is a question we will be able to address in **DPPOS Phase 3**.

In summary, further follow-up of DPPOS presents the unique opportunity to evaluate the effects of metformin begun during pre-diabetes vs PLB or ILS on CVD, the effects of ILS on CVD, and associations between T2DM prevention and CVD.

3.3.2. DPPOS Phase 3: Impact of DPP Interventions on Cancer

A focus on cancer is new for **DPPOS Phase 3**. The randomized metformin exposure beginning at DPP enrollment presents an unparalleled opportunity to address the putative beneficial effects of metformin on cancer in obese dysglycemic individuals. Accumulating epidemiologic evidence suggests that cancer risk is increased in overweight and obese individuals, with excess body weight accounting for 25-50% of cases of some common cancers (breast, colorectal, endometrial, renal cell, esophageal)[46] The underlying mechanisms are unclear, but may involve obesity-associated hyperinsulinemia or increased IGF-1[47,48]. T2DM also increases the risk of several common cancers (hazard ratios 1.2 to 2.1), although it is not clearly established if this risk is independent of obesity[49-51]. Little is known about whether lifestyle change (in particular, dietary weight loss interventions) for obesity or T2DM prevention can reduce cancer incidence. Metformin has recently received attention as a potential anti-cancer agent, based on promising experimental and epidemiologic data[52,53]. A recent meta-analysis of 11 observational studies showed a 33% reduction in cancer incidence in patients taking metformin compared with other anti-diabetic drugs, and a 34% reduction in cancer mortality[54]. However, whether metformin has direct preventive effects on the development of cancer in addition to, or independent of, the beneficial effects on T2DM development is unknown. In **DPPOS Phase 3** we will study the comparative effectiveness of the early initiation of metformin during pre-diabetes vs treatment only after the development of T2DM on cancer incidence.

Potential mechanisms for metformin's anticancer actions include a direct insulin-independent anti-tumor effect via activation of the cellular energy signal AMPK[55,56] and inhibition of mitochondrial oxidative phosphorylation[57]. In addition, since insulin has mitogenic effects and tumor cells often express high levels of insulin receptor, metformin's insulin lowering effects may also help reduce tumor development and growth. Benefits of metformin against breast, colorectal, pancreas, endometrial and prostate cancer have been suggested, but to date evaluations in clinical trials have focused largely on biomarkers and surrogate in vitro outcome[58]. Definitive trials with randomized exposure and sufficient sample size, duration of exposure and follow up are needed to address the critical public health question of whether metformin reduces cancer risk.

With continued differences in metformin exposure among the original treatment groups, and more cancer cases developing, **DPPOS Phase 3** can examine the effect of randomized MET on cancer risk in an initially pre-diabetic population. A pilot DPPOS project with NCI began in

2012 to lay the groundwork for this project, including providing an estimate of between group differences in cancer rates.

As with the CVD outcomes, we are also interested in whether diabetes prevention via intensive lifestyle treatment is associated with reduction in cancer incidence, and whether any such effects are related to weight and weight loss with DPP interventions. **DPPOS Phase 3** will also allow us to address these important potential public health impacts of DPP/DPPOS.

3.3.3. DPPOS Phase 3: Diabetes Outcomes

We plan to continue to ascertain diabetes development through ongoing testing of fasting glucose and 75g oral glucose tolerance testing. This outcome is no longer primary but the long-term effects of the randomized therapies on diabetes and glycemia-related outcomes remain of interest, and this information will be needed for evaluation of the relationships of glycemia with other outcomes of interest.

3.3.4. DPPOS Phase 3: Effects of Interventions on Microvascular Disease

In **DPPOS Phase 3** we will continue to ascertain microvascular disease components, including retinopathy and nephropathy as a prespecified combined outcome, and neuropathy alone and in combination with the others as secondary outcomes of interest. Some modifications to the measurements will be implemented, explained in detail below (Section 4.1.2). Effects of randomized treatments on progression to early and later microvascular disease will be evaluated, as well as the association with diabetes prevention, and in relationship to glycemia and glycemic exposure and to other outcomes of interest (for example blood pressure and weight changes).

3.3.5. DPPOS Phase 3: Epidemiology of Microvascular Disease and Neuropathy in IGT and New-onset Type 2 Diabetes

Epidemiologic[59,60] and interventional studies, such as the DCCT[61] and the UKPDS[62] 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 HbA1c over time. These studies have had to extrapolate to the non-diabetic range; there were too few patients with "normal" HbA1c results to provide reliable estimates of risk in the low diabetic or high normal levels of HbA1c.

Better understanding of the clinical course of IGT and T2DM 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[63,64]. 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. 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.

In the **DPPOS Phase 3** we hypothesize that continued exposure to treatment-related differences in glycemia, owing to differences across the entire course of time since initiation of the DPP, will manifest as differences in microvascular disease prevalence.

3.3.6. DPPOS Phase 3: 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 T2DM 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. This remains of interest with the transition to **DPPOS Phase 3**, which provides an opportunity for extended evaluations of these relationships into the period when clinically evident CVD will manifest.

Numerous studies have demonstrated that subjects with diabetes have a 2-4 fold increased likelihood of developing CVD[65]. 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[66-68]. The natural history of atherosclerotic vascular disease in IGT and diabetic subjects is not well understood. An increased risk for CVD in T2DM subjects is clearly present at the time of clinical diagnosis of diabetes[69]. 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 with 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[67,68]. 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[66]. 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[70,71]. 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[72].

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 T2DM 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 T2DM 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.

DPPOS Phases 1 & 2 provided 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 made possible a large number of analyses that have never been possible before. We have observed significant treatment-related differences in CVD risk factors[42] (**Figure 5**) with major between-group differences seen in the 3-5 years after randomization. Also, we have analyzed a collection of CVD biomarkers and identified treatment-related differences in C-reactive protein and tissue plasminogen activator[43], as well as adiponectin[73], which suggest graded beneficial effects on CVD risk. By extending this assessment for a further 5-10 years into **DPPOS Phase 3**, 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 to 12 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.

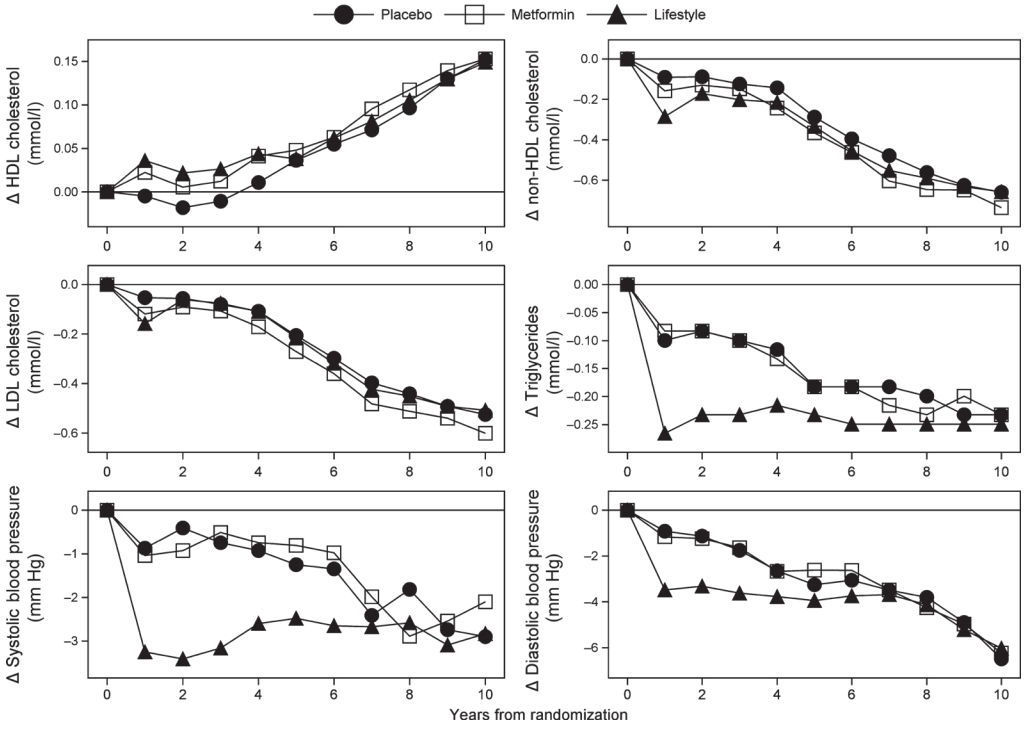

Figure 5. Changes in major CVD risk factors in the DPP cohort

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 whether participants develop diabetes or not, regardless 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[25,74].

3.4. Other important DPP/DPPOS Analyses

3.4.1. Economic Implications

The economic impact of the DPP treatments will be a function of any significant differences in health outcomes over time. Diabetic patients experience higher health care costs than do non-diabetic persons[75]. During DPPOS, an "in trial" health economic analysis was performed, using the actual data regarding health care utilization (e.g., medications, hospitalizations) and the calculated costs of the interventions over time. The results[76] demonstrated that metformin therapy was cost-savings and both the life-style intervention and metformin were cost effective, with improved QALYs in ILS and MET compared with PLB. 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.

In **DPPOS Phase 3** we will be able to extend these analyses to the effects of prevention of diabetes-related complications, incorporating the costs of screening and long-term treatment in order to produce the anticipated prevention effect. These analyses will be considerably strengthened by quantifying the true prevention effect as it relates to micro- and macrovascular disease, as well as any effects on cancer and effects on age-related infirmity.

3.5. Effects of Race-ethnicity and Sex

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. A very similar distribution by race-ethnicity has continued during DPPOS. 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[6]. 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 T2DM are especially important in the minority populations because of the increased prevalence of T2DM in these groups, compared with the general population[77-81], 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 sex 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.

3.5.1. 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[82]. Diabetic retinopathy also appears to be more common in African Americans with T2DM[83]. In the cross-sectional Baltimore Eye Study, there were equal rates of blindness secondary to diabetic retinopathy in Blacks and Whites[84]. Other studies have reported the prevalence of blindness to be twice in Black compared with White individuals and of severe visual impairment to be 40% higher among African Americans[85]. The prevalence of retinopathy in Blacks with T2DM 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[85].

Similar confounders complicate the interpretation of the 2.6 to 5.6 fold higher rates of end-stage renal disease (ESRD) in Black compared with White Americans with diabetes[86]. 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[79]. 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[86-88]. 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 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 T2DM. It is generally accepted that CVD rates in African Americans with diabetes are lower than the rates in NHWs[89]. 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[90].

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.

In the **DPPOS Phase 3** we will continue to perform pre-specified analyses comparing the sex and race/ethnicity subgroups, as these outcomes carry important implications for the entire population and benefits may differ among these groups.

4. DEFINITION OF OUTCOMES

The outcomes for **DPPOS Phase 3** are similar to those from DPPOS Phases 1 & 2, except as noted specifically below.

4.1. Primary Outcomes during DPP and DPPOS

4.1.1. Diabetes and Glycemia: OGTT and FPG

The primary outcome for DPP, DPPOS Phase 1 and a secondary outcome for DPPOS Phase 2 and **Phase 3** is progression of oral glucose tolerance test (OGTT) results to confirmed diabetes, by ADA criteria[14]. To assess progression to this outcome, an OGTT will be performed routinely on an annual basis through DPPOS visit year 12 and biennially thereafter 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 of fasting plasma glucose ≥ 126 mg/dl or 2 hour plasma glucose ≥ 200 mg/dl, 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 diabetes 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 through DPPOS year 12 and annually beginning in year 13 or at any time symptoms suggestive of decompensated diabetes are noted. If this FPG is ≥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 ≥ 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). Again, to maintain masking, the Coordinating Center will ask for a random repeat FPG on a subset of non-diabetic participants with FPG < 126 mg/dL [7.0 mmol/L]. In years without a scheduled OGTT, if HbA1c ≥6.5% and fasting glucose is <126 mg/dl, a confirmatory OGTT will be performed. If the OGTT meets the diagnostic criteria for diabetes, the participant will be notified of the results and the participant will be considered as having diabetes. Otherwise, the participant will have not met the criteria for diabetes.

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 ≥126 [7.0 mmol/L], the testing strategy outlined above will be followed.

Criteria for the diabetes outcome:

1 FPG ≥126 mg/dL confirmed within a goal of 42 day interval
2 2 hour OGTT sample ≥200 mg/dL confirmed within a goal of 42 day interval
3 FPG ≥ 126 mg/dL or 2 hour OGTT sample ≥ 200 mg/dL confirmed on two separate visits within a goal of 42 day interval.
4 HbA1c ≥ 6.5 mg/dL and FPG<126 mg/dl when OGTT sample not collected and confirmation by FPG or 2 hour OGTT within a goal of 42 day interval.

The scheduled OGTT will be postponed for up to six weeks if a temporary concomitant condition exists that would affect glucose tolerance. 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 scheduled visit. Cases of diabetes diagnosed outside the study will be adjudicated by the study's Outcomes Committee.

For DPPOS Phase 2 and **Phase 3**, 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, remain important secondary outcomes.

4.1.2. Composite Diabetes-related Microangiopathic and Neuropathic Outcome

The diabetes-related microangiopathic primary outcome for DPPOS Phase 2 was defined as a composite of the following at the year 11 visit, or if the participant is deceased or lost to follow-up before year 11, as of his/her last assessment:

a. Nephropathy: increased albuminuria (≥30 mg/gram creatinine, confirmed), or renal dysfunction (end-stage renal disease, dialysis or renal transplant) or eGFR < 45 ml per min based on serum creatinine, using the CKD-EPI equation; the qualifying criteria confirmed)
b. Retinopathy: retinopathy by fundus photography (ETDRS grade of 20 or greater) or adjudicated history of laser or other treatment for retinopathy or
c. Neuropathy: reduction or absence of light touch sensation to monofilament (Semmes-Weinstein 10 gram) in either foot (< 8 of 10 applications detected).

If a participant took antihypertensive drugs at the last assessment and did not meet the ACR or eGFR criteria at that time, he or she was considered to have reached the nephropathy outcome if the nephropathy criteria were met at 2 consecutive past visits. This substituted for the occurrence of nephropathy at year 11.

For **DPPOS Phase 3**, the main composite diabetes-related microangiopathic outcome, now a secondary outcome, is defined as time to first occurrence of nephropathy or retinopathy, the two microvascular disease components that are most objectively measured microvascular complications. Nephropathy is adapted from KDIGO[91] for categories of moderately increased albuminuria or moderately to severely decreased eGFR and defined as development of any of the following: (1) confirmed elevated albuminuria (≥30 mg/g creatinine) based on annual spot urine; (2) confirmed eGFR by CKD-epi[15] <45 ml/min; (3) kidney transplant; or (4) dialysis for end-stage renal disease. The definition of the retinopathy outcome will change from microaneurysms (ETDRS≥20) as used in DPPOS Phase 2 to mild diabetic retinopathy (ETDRS≥35)[16] or adjudicated treatment for retinopathy. Macular edema by optical coherence tomography (OCT)[92,93] will be a secondary outcome. The ETDRS grade was modified in recognition of the expected increase in time and level of hyperglycemia that will result in more diabetes-specific lesions and to minimize noise from aging related retinal findings. Spectral domain OCT is a noninvasive imaging technology that uses principles of light interferometry and Fourier analysis to generate a voxel (3-dimensional) rendering of the retinal architecture. OCT has become widely used in medical ophthalmology practice and in clinical research and is the standard of care imaging modality for diagnosis and management of diabetic macular edema. Analyses will be standardized across diverse digital formats. Symptomatic distal symmetric polyneuropathy

(DSPN) will be measured with the symptom questionnaire from the Michigan Neuropathy Screening Instrument used in previous years and, beginning in 2018, signs of neuropathy will be detected using quantitative measurements of vibration, light touch and sharp (pin prick) sensation, as recommended in the 2017 ADA Position statement[94]. The MNSI questionnaire and the monofilament test will be continued, as in past examinations, to allow longitudinal analyses. The principal outcome for DSPN in DPPOS Phase 3 will be defined as the presence of DSPN symptoms (score ≥4 on the MNSI questionnaire)[95] or any signs of bilateral DSPN. The signs of bilateral DSPN require abnormal finding on both toes for pinprick testing (score ≥5)[96], for vibration testing (score≥5)[96], or for light touch sensing (<8 detected from 10 monofilament applications on each toe). Secondary analyses will include the presence separately of DSPN by symptoms or by signs, the presence of symptomatic DSPN confirmed by signs, and the individual elements of the neurologic sensory examination.

4.1.3. Cardiovascular Disease

The primary outcome of the second 5-years of **DPPOS Phase 3** is the incidence of major cardiovascular disease (MACE). MACE is defined as the time to first occurrence after DPP randomization of one or more of the following: fatal and non-fatal myocardial infarction and stroke or other cardiovascular death.

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[97], 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. Secondary outcomes will also consider each of these components separately as well as arrhythmias.

All CVD events are determined at the time of their report using a standardized medical history questionnaire and adjudicated after medical records are available by an outcomes committee whose members are blinded to treatment group.

4.1.4. Cancer

The primary outcome of the first 5-years of **DPPOS Phase 3** is the incidence of new primary cancer (excluding non-melanoma skin cancer) with pre-defined obesity-related cancers and cancer mortality as secondary outcomes. Obesity-related cancers will be defined prior to analysis of this outcome by investigators masked to the cancer outcome results. Due to sex-specific differences in cancer types, stratified analyses by sex are also planned. A recurrence or metastasis of a cancer previously diagnosed prior to DPP randomization does not count towards this outcome. Relevant medical records for all DPP participants with a history of cancer diagnoses or reported cancer deaths are included, even from participants who did not enroll in DPPOS. Medical records are obtained and include pathology reports, notes from biopsy procedures or surgeries, hospital discharge summaries, radiology reports cancer staging forms, and ER/PR/Her2 (breast cancer only). Records are de-identified and redacted to obscure metformin exposure. Cancer events are adjudicated by a trained National Cancer Institute physician.

4.1.5. Determining Vital Status and Cause of Death for Participants

The National Death Index (NDI) or an external people-search service will be used to search for DPP and DPPOS participants who have not been seen at their local center and have not been able to be contacted for more than 1 year, as well for deceased participants. The NDI is a central computerized index of death record information from State vital statistics offices nationwide. Each center will submit their cases to the NDI or people-search service. Coding that includes cause of death will be obtained. Records will be searched for all years for which vital status cannot be confirmed. If permitted by the local IRB, follow-back investigations will be undertaken to obtain medical records and next-of-kin interviews as required. Central review of cause-of-death will be adjudicated by an outcomes committee whose members are blinded to treatment assignment.

4.1.6. Medicare database

The DPPOS may undertake a search of the Centers for Medicare and Medicaid Services (CMS) database for the purpose of determining diagnosis codes and dates for health care utilization to supplement medical records.

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 secondary outcomes and their risk factors. Secondary outcomes may be assessed in the study population as a whole or in subsets, 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 Chapter 12.

Following is a brief summary of secondary outcomes that will be measured at specified intervals (see Chapter 12 for schedule) in all participants. Outcomes measured in DPPOS Phase 1 and/or Phase 2 but not in **DPPOS Phase 3** are noted in brackets:

4.2.1. Glycemia and insulin secretion:

- HbA1c: 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 outcomes.
- 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]
- [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
- Macular edema by OCT

4.2.4. Nephropathy, assessed by:

- Albumin excretion: Urinary albumin and creatinine concentrations for albumin excretion, using a spot collection.
- Serum cystatin
- Serum creatinine
- History of end-stage kidney disease treated with dialysis or transplantation

4.2.5. Neuropathy, assessed by:

- Semmes Weinstein 10 gram monofilament examination
- Examination of vibration sensation
- Examination of pinprick sensation
- Michigan Neuropathy Screening Instrument Questionnaire
- EKG rhythm strip: to measure heart rate variability

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

- Physical measurements: Height, weight, waist circumference, BMI
- DXA: Measures of bone density, whole body composition and vertebral fractures in a sample of participants
- 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
- Healthy Aging Index[98]
- Urinary incontinence
- Activities of Daily Living and Instrumental Activities of Daily Living
- Sexual function (by standardized questionnaires)
- Pulmonary function by spirometry
- Cardiorespiratory fitness measured by the 6-minute walk test
- Fractures (hospitalized spine, hip or appendicular fracture, adjudicated)
- Infections (hospitalized, self report)

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

The study will continue to collect information on resource utilization and costs associated with the interventions and with medical care received outside of the study, as well as information on health-related quality-of-life and survival. From these data, medical costs of the interventions and medical care outside of the study will be computed, and compared among the treatment groups. Differences in quality-adjusted life-years gained will be compared by treatment group. The information used in the health economics analyses will be obtained with:

- 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: Serum creatinine
- 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, reports of cancer diagnosis, and hospitalizations for infection or for spine, hip or appendicular fractures.
- Pregnancy testing: As needed for metformin-treated participants, based on symptoms and menstrual history.
- [CBC: for metformin-treated participants, measured locally]
- Vitamin B12: for metformin-treated participants

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, serum and urine 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]

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, cancer 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 were offered the opportunity to continue a long-term maintenance of the lifestyle intervention program, consisting of quarterly Healthy Lifestyle Program (HELP) meetings through spring 2014. In addition, DPP intensive lifestyle participants were offered 4 weekly or bi-weekly behavior boost sessions in groups twice yearly through 2014, and DPP metformin participants were provided open label metformin (850 mg bid). During **DPPOS Phase 3**, participants will remain in their originally randomized treatment groups, except that those in the original troglitazone group are no longer being followed. All participants will be offered a single Group Lifestyle (HELP) session annually. Participants in the original metformin group will continue to receive study metformin per protocol. Participants in the original ILS group will receive an additional "lifestyle check-up" during their annual visit. These interventions are summarized below:

DPP	DPPOS Phases 1 & 2	**DPPOS Phase 3***
Intensive lifestyle (ILS)	Boost LS + HELP	HELP plus annual lifestyle check-up
Blinded Metformin + standard LS (MET)	Open label metformin + HELP	HELP plus open label metformin
Blinded Placebo + standard LS (PLB)	Group lifestyle (HELP only)	HELP
Troglitazone + standard LS (stopped in 1998) (TRO)	Group lifestyle (until 2008)	N/A

*Single group lifestyle session offered annually to all participants

During DPPOS Phases 1 & 2, participants had twice-yearly scheduled visits. During **DPPOS Phase 3**, participants will have an annual in-person visit. The mid-year assessment will be conducted by telephone, unless an in-person visit is required or is requested by the participant. Study outcomes, including health outcomes assessments , a brief medical history, fasting and OGTT blood draws, questionnaires, anthropometric measures, fundus, and neurologic examinations, and measures of subclinical atherosclerosis are performed as stipulated in Section 12.

Assessment of microangiopathic, cancer, and cardiovascular outcomes will be performed in both diabetic and non-diabetic DPP participants during all years of the DPPOS. Both individual and composite outcomes 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, cancer and cardiovascular outcomes. Subgroup analysis will be performed based on sex, age and race/ethnicity.

5.2. Participation Criteria

All DPP participants are eligible to participate in the DPPOS, except for those originally randomized to troglitazone. Inability to attend group sessions for logistical or heath reasons will not be a criterion for exclusion.

5.3. Procedures for obtaining surrogate consent

The following surrogate consent issues will require approval by local IRBs. Some IRBs may require different procedures for following participants who do not have the capacity to consent. Each clinical center will follow procedures approved by its IRB. Participants who have the capacity to consent will be given the opportunity to decide in advance whether they do or do not want a surrogate to make decisions for them to continue their participation in the study should they lose capacity to consent in the future. This will be documented on the procedures consent note in their research chart. For those participants who choose not to have a surrogate make enrollment decisions for them in the future and lose the capacity to consent, this will be documented and the participant will be excluded from further participation after losing the capacity to consent.

- Staff persons will discuss with the participant who they have chosen as a surrogate or who they would like to serve as a surrogate decision maker.
- Staff persons will ascertain that the following can serve as a surrogate: first-degree family members (sibling, spouse, or an adult son or daughter), health care proxy, legally appointed guardian, or participant-chosen surrogate, in accordance with local, state and IRB regulations.
- Participants will be encouraged to discuss their future research participation with the surrogate.

Participants may also provide consent to have a surrogate provide health information including the assessment of cognitive ability.

5.4. 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 Phases 1 & 2 all participants were offered quarterly group sessions to encourage the maintenance of their lifestyle interventions until June 2014. These meetings helped to encourage continued participation in the DPPOS. The use of twice yearly behavior boost groups for the DPP ILS participants was intended during DPPOS years 1-12 to reinvigorate their previous efforts at achieving weight reduction and increased physical activity in a manner that requires only modest staff involvement. Beginning in year 13 and continuing in **DPPOS Phase 3**, lifestyle messages will be reinforced during regularly-scheduled outcomes visits and at one annual HELP lifestyle class offered to all participants. During DPPOS Phases 1 & 2, and **Phase 3**, metformin was and will be provided to all participants who were receiving metformin treatment in DPP, assuming that HbA1c is <7.0% and the participant has not developed a contraindication or intolerance to metformin, in order to maintain long-term intervention with this agent. (See section 7.2.2 regarding HbA1c ≥ 7.0%.) The provision of lifestyle training to the DPP PLB group during years 1-12 may reduce differences in long-term outcomes between intervention groups. 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.

5.5. 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 continues follow-up according to his or her original DPP randomized assignment. Metformin will continue to be provided to the original Metformin participants throughout DPPOS. The HELP program will be held once annually and Boost programs were discontinued beginning with DPPOS year 13.

6.1. Schedule of Follow-up Visits

During DPPOS Phases 1 & 2, follow-up visits for outcome assessments were scheduled at 6-month intervals. Annual visits were targeted for the anniversary of the participant's original DPP randomization date. HELP group meetings were 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 for years 1-12 and annually thereafter. Boost sessions were offered twice per year, and similarly scheduled multiple times for purposes of convenience for years 1-12. Except for participants from the original Troglitazone group, who ceased 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.

Beginning in study year 13 and continuing in **DPPOS Phase 3**, in-person annual visits will continue with reduced intensity of outcome measurements according to the outcomes schedule (See section 12). Mid-year visits will be brief, and held primarily by phone or in person as needed. The original DPP ILS participants may participate in a brief annual lifestyle check-up to reinforce lifestyle goals. Participants originally assigned to metformin who have not developed diabetes, or who have developed diabetes but have continuously maintained HbA1c <7% at (based on results from their annual visit) will continue to be provided study metformin. (See section 7.7.2 regarding HbA1c ≥ 7.0%.)

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 selected outcomes, confirmation (CON) visits are required whenever a participant has an elevated fasting (≥126 mg/dl), stimulated (≥200 mg/dl) glucose, or for annual visits without a scheduled OGTT collection, an HbA1c ≥6.5%. If urine albumin level ≥30 mg/gm creatinine or eGFR < 45 is first demonstrated in DPPOS year 11 and 16 visits, participants will be asked to return so that a repeat urine or blood sample can be obtained for confirmation.

6.1.3. Suspension of Follow-up Visits

The occurrence or presence of the following will constitute suspension of the scheduled follow-up protocol: Voluntary withdrawal by the participant, or a 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 or Telephone 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 study staff person who is certified to perform the listed outcomes will 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 home 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 are 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.

For those individuals who cannot travel and for whom a home visit is not possible, a telephone visit may be conducted to collect updated health history, Serious Adverse Events, CVD and cancer event information.

6.1.5. Remote Visits

For participants who have moved far away from any DPPOS clinic or have physical limitations that make them unable to come to a DPPOS clinic, a remote visit might be performed by a non-DPPOS staff person trained and certified in DPPOS procedures. The purpose of a remote visit is to retain participants and to collect important outcome data. Clinical center staff will arrange for the visits, and provide clear instructions to participants about what to expect. Weight and blood pressure will be measured, and routine annual visit blood and urine samples and safety specimens will be obtained at remote visits. Samples will be sent to the DPPOS laboratory identified by only the participant study number and data will be returned to the clinical center.

6.1.6. 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, group meetings, and other incentives. All participants receive an honorarium, 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.

6.2. Lifestyle Program in DPPOS Phases 1 & 2

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 were continued during the DPPOS for all previously randomized participants until the end of Phase 1, and for all but the former Troglitazone participants, who did 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 were provided quarterly to all DPPOS participants through spring 2014. In addition, participants who were previously randomized to the intensive lifestyle arm in DPP were given Boost Lifestyle Sessions in a group format, two times each year through spring 2014. The goals of lifestyle treatment for all DPPOS participants was the same as for the lifestyle group during 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

During DPPOS Phases 1 & 2, the Lifestyle Resource Core (LRC) and the Lifestyle Advisory Group (LAG) comprised of co-investigators and staff representing several DPPOS centers developed the materials for the HELP maintenance and Boost sessions and provide on-going training and support for the lifestyle interventionists. All materials were reviewed and approved by the DPPOS Executive Committee prior to implementation.

6.2.2. Staff for Lifestyle Interventions

During DPPOS Phases 1 & 2, case managers, group lifestyle interventionists, and/or consultants at each clinical center carried out both arms of the lifestyle intervention. Interventionists were individuals with experience and/or training in nutrition, exercise, behavior modification, or group treatment. Other staff (e.g. peer counselors and exercise leaders) were 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 were offered to all participants during DPPOS Phases 1 & 2 (until the summer of 2014) . The purpose of the quarterly lifestyle sessions was to reinforce the basic content, as well as the weight loss and physical activity goals. In addition, the quarterly sessions

served 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-$10) were sometimes used to reward attendance and participation at these group education sessions. Every effort was 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 rotated 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 was 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 were developed by the Lifestyle Resource Core and outlined in detail in the Lifestyle Intervention Manual of Operations for DPPOS. The first quarterly session began within 2-3 months after DPPOS began.

Annual HELP sessions will continue to be offered to all participants, regardless of randomized treatment group, during **DPPOS Phase 3**.

6.2.4. Boost Lifestyle

During the DPP Bridge period, DPP intensive lifestyle participants 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 Phases 1 & 2, these participants were offered Boost Lifestyle sessions in addition to Group Lifestyle sessions. The purpose of Boost was to offer periodic, structured "restarts" for lifestyle arm participants who had already received intensive, long-term, individual lifestyle intervention. The Boost sessions were 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 Boost was 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 - $20) were 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 Boost sequences for each clinical center was characterized as follows:

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

Centers were 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 were available, they were 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 Boost were developed by the Lifestyle Resource Core and are in the Lifestyle Intervention Manual of Operations for DPPOS. The first Boost session began within 2-3 months after DPPOS began.

Boost sessions will not continue in **DPPOS Phase 3**, but will be replaced, in the former lifestyle intervention group only, with a brief, annual lifestyle checkup, a 10-15 minute review of lifestyle goals and success.

6.2.5. Indices of Adherence

Adherence to the HELP program and Boost were assessed in the following manner:

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

6.3. Lifestyle Program in DPPOS Phase 3

The lifestyle program for **DPPOS Phase 3** for visit years 13-18 will consist of an annual lifestyle check-up for participants originally randomized to the intensive lifestyle group, a 10-15 minute review of lifestyle goals and success, and an annual HELP session for all participants to promote retention and reinforce healthy lifestyle lessons.

6.4. Metformin Pharmacological Treatment

6.4.1. 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 metformin will remain in the metformin 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 eGFR is below 30 mL/minute/1.73 m^2, who reached the fasting hyperglycemia (≥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 ≥7% by the DPPOS Central Biochemistry Laboratory. Metformin is an investigational drug used under an Investigational New Drug application with the Food and Drug Administration (FDA) (IND #142797).

6.4.2. Mechanism of Metformin Action

Metformin is an antihyperglycemic drug of the biguanide class used in the management of Type 2 diabetes worldwide for over 50 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 and provided to DPPOS by Merck KGaA, Darmstadt, Germany. 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 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 T2DM. 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 T2DM. 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.

6.4.3. 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.

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

A. Laboratory Safety Monitoring

During DPPOS Phases 1 & 2, all participants assigned to open label metformin had an annual CBC with differential count and serum creatinine. During **DPPOS Phase 3**, serum creatinine will be measured annually and eGFR calculated, and, in years 14 and 16, vitamin B12 levels will be measured, in participants taking study metformin. 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.

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. The Manual of Operations includes required 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 an OGTT 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 and eGFR calculated in participants in the metformin arm who are taking study metformin. Metformin is not known to cause renal insufficiency. However, it is associated with an increased risk for lactic acidosis if used in persons with reduced kidney function. Metformin is contraindicated in those with eGFR <30 mL/minute/1.73 m^2, and should be used with caution and reviewed in those with eGFR ≥30 and <45 mL/minute/1.73 m^2. If eGFR levels are <30 mL/minute/1.73 m^2, study-supplied

metformin will be discontinued permanently. For participants who have an eGFR ≥30 and <45 mL/minute/1.73 m^2, the local PI can elect to continue metformin or stop it based on clinical judgment that takes into account the cause of renal dysfunction, anticipated clinical course and other factors. An interim serum creatinine measurement and calculated eGFR can be requested for safety monitoring.

F. Anemia

During DPPOS Phases 1 & 2, a CBC was measured for safety reasons at yearly intervals in participants in the metformin treatment group who were taking study 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 B12 when indicated. The annual CBC will be replaced by B12 measured in years 14 and 16 for those taking study metformin.

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 7.1 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 eGFR is in the acceptable range (≥30 mL/minute/1.73 m^2). 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. Metformin will obviously be held while participants are NPO for procedures. As part of usual clinical care, serum creatinine should be checked 48 hours or more after such procedures and before study metformin is restarted if the eGFR is in the acceptable range ($\geq$30 mL/minute/1.73 m^2). If the clinic is notified of a scheduled outpatient surgical procedure, the participant will be instructed to discontinue metformin the day prior to the procedure.

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.

6.4.5. 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. The study recommends that participant health issues be followed by a primary care provider. Treatments for concomitant conditions can potentially affect either the primary or secondary study outcomes and therefore are carefully tracked by the study. If the participant consents, clinically relevant laboratory and medical results are communicated in writing to the primary care provider. The annual HELP session provided to all participants will include reinforcement of healthy behaviors, including smoking cessation.

7.1. 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.

7.1.1. 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.

7.1.2. Use of Study Metformin 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.

7.1.3. 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 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.

7.2. Diabetes

7.2.1. Interim Visits for Symptoms

Following enrollment and randomization in the DPPOS, participants will be evaluated 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 diabetes outcome if fasting glucose ≥ 126 mg/dL persists.

7.2.2. 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. Participants will be instructed to follow up with their PCP following diagnosis. DPPOS participants will continue to be seen at six monthly intervals during years 1-12 and annually beginning in DPPOS year 13 for clinical assessment, and fasting glucose and HbA1c 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 HELP sessions (annual during **DPPOS Phase 3**) 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 HbA1c remains <7%. In the event that a participant progresses to an HbA1c ≥7%, study

metformin will be discontinued. In all participants with diabetes, when the HbA1c 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.

8. ADVERSE EVENT REPORTING

8.1. Definitions

Only adverse events meeting the criteria for serious will be ascertained and reported to the DSMB 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, 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. The Coordinating Center will transmit the death report to the NIDDK Program Official.

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. In addition, the NIDDK must notify the FDA of all life-threatening or fatal SUSARs (Serious Unexpected Suspected Adverse Reaction) within seven calendar days; NIDDK must notify the FDA of all other SUSARs by 15 calendar days.

All serious adverse events will be reported to local IRBs by the 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 according to the schedule in Chapter 12: serious adverse event assessment, diabetes management, current concomitant prescription medications, interval medical history and interval cardiovascular history, neuropathy screening, and physical measures; and for the metformin treatment participants, pregnancy questions, and medication compliance and dispensing. In addition, outcomes outlined in Chapter 4 are completed according to the schedule in Chapter 12.
- **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 and phone 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.

9.1.1. Other Forms

The following instruments were completed during DPPOS Phases 1 & 2, or will be completed during **DPPOS Phase 3**, 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
- Cancer history and risk factor questionnaire
- Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL)
- Sexual Function Questionnaires
- 6-Minute Walk Test Questionnaire

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 Chapter 12 for timing and frequency of procedures):

- OGTT procedures
- Urine collection procedures
- ECG procedures
- Fundus photography and Optical Coherence Tomography (OCT) procedures
- Coronary artery calcium procedures
- DXA procedures
- Spirometry procedures

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

A secure, web-based password protected data entry and management 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 participant management, data collection and study management. DPPOS computers are kept in a safe location in a site that is locked when not attended.

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

Data entered via the web-based electronic data collection system is securely transmitted and stored on the CoC's server. 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 and Protocol Oversight Program. The CoC maintains confidentiality of patient data and emerging results per a confidentiality policy, which every staff member is required to sign.

The CoC adheres to the Biostatistics Center's data backup and security policies to ensure the safety and confidentiality of the data. Backup procedures include: twice-weekly system backup, daily incremental back-up, and off-site disaster recovery backup. Security procedures include: logon and link password protection, and for internet access, separate Web servers which use SSL and encryption algorithms. Virus and malware protection software is used on all computers and is updated on an hourly basis. All portable computers employ full disk encryption. University computing facilities provide support in the event of a disaster. 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, and Central Units, with appropriate investigator subcommittee members, have established 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 instruct the program coordinators on proper collection, 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 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 NIDDK, and clinic investigators will visit the clinical centers virtually or in person, 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 and 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. During DPPOS Phase 2, there were two formal interim analyses of safety and efficacy pertaining to macrovascular events for purposes of possible "early stopping" of an intervention. The DSMB will develop a safety monitoring plan for **DPPOS Phase 3** to include a futility assessment.

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, Cognition Center, DXA Reading 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 Chapters 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 official and project scientist 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 DPPOS.

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, CBL and the CoC, and the NIDDK Project Scientist. 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, 1 or 2 Principal Investigators from the clinical centers, representatives of the Study Coordinators, the NIDDK Project Scientist and Program Official, and the Principal Investigator(s) 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. During DPPOS the subcommittees will be reformed and new subcommittees and working groups formed, as necessary to address different tasks and functions.

Standing DPPOS Subcommittees:

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

10.3.2. Data and Safety Monitoring Board

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

and ongoing through all phases of DPPOS, the DSMB members review the protocol and study material to ensure the scientific validity of the study and safety of participants. The DSMB also assesses the performance of the CoC and clinical centers. Its principal responsibility is to monitor the emerging results to assess treatment effectiveness, or ineffectiveness, and participant safety according to the DSMB-approved interim monitoring plan. 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) coordinates, monitors, reviews, and assumes 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 Manual of Operations.

10.4.2. Ancillary Studies

The Ancillary Studies Subcommittee evaluates all proposals for studies that involve DPPOS participants or stored samples and that are not a part of the protocol. These studies may 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 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 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 are returned to the applicant and appeals from the decision of the Ancillary Studies Subcommittee may be made to the Steering Committee.

Approved ancillary studies that involve participants are reviewed by the DSMB.

Detailed policies are found in the Manual of Operations.

11. STATISTICAL CONSIDERATIONS

11.1. Data Relevant to the Diabetes Outcome

After approximately 2.8 years of mean study time, the DPP's external Data and 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[6]. 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

11.2.1. Power for the Development of Diabetes

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 were 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 from DPP randomization through DPPOS Phase 1.
* Type I error rate of 0.05 (two-sided) with a Bonferroni adjustment 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.

11.2.2. Power for the Microangiopathy Outcome, Year 11

For the composite microangiopathic Phase 2 Primary 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.

11.2.3. Power for Cancer Development

For the cancer outcome for **DPPOS Phase 3**, we estimated the number of cancer cases through the first 5 years of **DPPOS Phase 3** using incidence rates based on both SEER[100] and current DPPOS data. To detect 28% risk reduction in cancer for the primary comparison of metformin vs placebo with 85% power for a 2-sided significance level of 0.05, the study requires 170 events in the placebo group using a log-rank test. Assuming an increasing annual incidence rate of 1.86% by 2020 and an annual loss to follow-up of 1.04%, the projected 199 events in the placebo group will provide 89% power to detect a 28% hazard risk reduction at the end of the first 5-year period. Secondary analysis of the cancer incidence between metformin and placebo separately by men and women will be assessed in the second 5-years.

11.2.4. Power for CVD (MACE) Development

The lower rate of CVD events in pre-diabetes than in diabetes has been documented[14]. It is reasonable to assume that our placebo group, all of whom started with pre-diabetes and with ~56% developing diabetes to date during the course of DPP/DPPOS, will have a CVD event rate that is a blend of pre-diabetes and diabetes. Moreover, our study population has a similar rate of treatment of traditional CVD risk factors (e.g., through use of antihypertensive agent and statins)[7] to that in the general population today. This trend emphasizes the need to use contemporaneous external data to project event rates.

In this light, the most relevant rates of MACE in non-diabetic and diabetic populations, including age-specific rates, come from a recent report on 2010 national data[8]. These data were collected during a period when treatment of established CVD risk factors was widespread, and therefore represent the background rates expected in our cohort. For all persons surveyed, the rate of acute myocardial infarction fell from 8.5 per 10000 person-years in 1990 to 5.7 in 2010. Among those aged 45-64 with diabetes the rate in 2010 was 51.3 per 10000 person-years (or 0.513 per 100 person-years), while those 65-74 had 66.4 and those over 75 had 143.5 events per 10000 person-years (0.664 and 1.435 per 100 person-years, respectively). These rates are within the range of rates that we observed in the Placebo group by DPPOS end (**Table 5**).

Table 5. MACE Event Rates and Numbers to Date in Placebo Group and Projections

	DPP start 1997-1998	DPPOS start 2002-2003	DPPOS end 2014	5 yr projection 2020-2021	10yr projections 2025
Event Rate (% per yr)	0.24	0.50	0.70	1.17	1.57
Total number			64	116	156

We estimated the age related 2.1 fold increase in annual incidence rates in the next 10 years using Cox proportional hazards model using attained age as a time dependent covariate. This conservative increase is used to project events in the placebo participants of 116 and 156 after 5 and 10 additional years of **DPPOS Phase 3** assuming a 1.04% loss to follow-up per year. To detect a 30% hazard risk reduction in MACE incidence in the primary comparison of metformin and placebo with 85% power and a 2-sided significance level of 0.05 using a log-rank test, we require 145 placebo events. With the expected 156 events in the placebo group by 2025, the study will have 89% power to detect a 30% hazard risk reduction. Other important secondary comparisons will be lifestyle vs. placebo and metformin vs. lifestyle.

11.3. Analysis

11.3.1. Analysis of Development of Diabetes

The primary objective for DPPOS Phase 1 was 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 had not developed diabetes during DPP among those who enrolled into DPPOS[13]. The analysis was based on comparing the hazard rates between the two intervention groups (the Intensive Lifestyle and Metformin groups) and the placebo group. The primary null hypothesis was that among those who had not developed diabetes by the start of DPPOS, the intervention groups did not differ from the controls in the hazard rates for development of diabetes over the interval from the beginning of DPPOS. Reasons for comparing across the interval from the start of DPPOS as the primary analysis rather than from the beginning of DPP were: 1) we had 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) since the interventions were indeed effective over the earlier DPP interval, the cumulative incidence curves may have had too much separation from the early DPP effects to be able come together again, even if the interventions were not effective over the longer term. The primary analysis from DPPOS baseline did not preclude secondary analyses from the beginning of DPP.

The cohort of participants for this analysis were a subset of the original DPP study population, and as such were no longer "randomized", but rather selected by having survived DPP without developing diabetes. Beyond that selection, each participant was 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 used 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 = 0.025 level, were performed if the overall comparison was statistically significant.

The analysis compared the treatment groups vs. the former placebo group on DPP baseline characteristics, and any factors on which they differed were considered for inclusion as covariates in the analysis. The primary analysis was a life-table analysis of the time to confirmed development of diabetes. Modified product-limit life-table estimated cumulative incidence curves were calculated for each treatment group and the groups compared using a log rank test[3]. Participants were considered "administratively censored" if they completed the full duration of follow-up without confirmed development of diabetes. Participants who prematurely

discontinued their follow-up visits prior to confirmed development of diabetes were "censored" as of their last follow-up visit. A proportional hazards regression model was used to evaluate potential covariates that may modify the time to development of diabetes. Graphical procedures were used to assess the proportionality assumption. If the proportionality assumption was found to be unreasonable then other models such as the accelerated failure time model[101,102,102] or the proportional odds model[103] was used to evaluate the covariates.

The analysis was also conducted within subgroups (one-way stratification) based on the following characteristics: racial/ethnic origin, sex, and age (<45, 45-<60, 60+).

The primary analyses that focused on the intention-to-treat assignment during DPP included all participants in the original DPP placebo, lifestyle and metformin intervention groups who 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 were not included in the primary DPPOS analyses.

11.3.2. Composite Outcomes of Microangiopathic and Neuropathic Disease

The analysis of the composite primary microangiopathic outcome at year 11 for DPPOS Phase 2, and composite secondary cardiovascular disease outcome was performed in an intent-to-treat fashion on the DPP groups, as randomized, including participants who have developed diabetes.

For this composite outcome, the objective was 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 were compared using the global test using general estimating equations (GEE) among DPPOS enrolled participants[1].

The year 11 data for each component was reviewed with respect to being "missing at random" before selecting the appropriate statistical methods for missing data.

11.3.3. Analysis of Cancer and MACE Incidence

The primary outcomes for **DPPOS Phase 3** are time to the development of cancer (first 5 years) and major cardiovascular disease (MACE, including non-fatal myocardial infarction and stroke, and fatal cardiovascular disease) (second 5 years). The cohort of participants for these analyses includes all participants randomized to the original DPP study. Each participant will be included in the group to which s/he was randomly assigned, regardless of compliance with study treatment. Since the participants originally assigned to troglitazone only had a limited exposure to that intervention, owing to the premature termination of the troglitazone arm, were not included in the primary DPP outcome analyses, and are no longer followed in DPPOS, they will not be included in the primary **DPPOS Phase 3** analyses.

The primary comparison will focus on the metformin vs. the placebo group. The time to event analysis uses the date of the first occurrence of the outcomes. Participants will be considered "administratively censored" if they complete the full duration of follow-up without confirmed disease. Participants who died or prematurely discontinue their follow-up visits prior to developing the event will be "censored" as of their last follow-up visit – hence, participants who did not enroll in DPPOS will be censored as of their last contact during DPP. Separate

Kaplan-Meier estimates of cumulative incidence curves are calculated for the three treatment groups and will be compared using the log rank test.

Mortality prior to the development of cancer or MACE is a competing risk event[104,105,105]. Regression models that censor on death provide an estimate of the coefficient effect on the underlying cause-specific hazard for the outcome event. If there is a difference between groups in overall mortality, we will examine the cumulative incidence functions within groups adjusting for death as a competing risk.

The analysis will also be conducted using subgroups (one-way stratification) to assess treatment effect modification based on the following characteristics: racial/ethnic origin, sex, and age at randomization (<45, 45-<60, 60+).

A proportional hazards regression model will be used to evaluate potential covariates that may modify or mediate the time to development of the outcome[106]. To allow for model misspecification, such as non-proportional hazards, all inferences will be conducted using the robust variance estimate[107] that provides a valid inference in the presence of such misspecification.

11.3.4. Secondary Research Questions

Secondary objectives 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 function
* Quality of life indices
* Health care costs
* Cognitive performance
* Urinary incontinence
* Sexual function
* DXA-derived bone density, body composition and vertebral fractures
* Pulmonary function
* Healthy Aging Index
* All-cause and cause-specific mortality

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 and Timing of Analyses

An external Data and 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 DPPOS for having demonstrated further benefit. The assessment of the composite microangiopathy occurred after the year 11 visits. Therefore, we did not implement a formal statistical monitoring plan for either of these outcomes in DPPOS. The DSMB reviewed two interim analyses of time to macrovascular event for safety during DPPOS Phase 2.

Since the cohort size for **DPPOS Phase 3** is fixed, power is driven by the number of placebo subjects with an outcome event and the projected effect size. Projections for the placebo events assumed an exponential increase in hazard rate for cancer and MACE expressed in terms of a growth factor (i.e. ~2-fold increase over 10 years) and based on accumulated DPP/DPPOS data and results from recent studies. Given our best estimate of the accumulation of events, and using effect sizes of 25 or 30%, we expect to reach the level of required cancer events in the placebo group during the first 5-years of **DPPOS Phase 3**, and the required MACE events in the placebo group during the second 5-years of **DPPOS Phase 3**.

12. OUTCOMES SCHEDULE

Outcomes Schedule, DPPOS Phase 1: Visit Years 1-6

Participant DPPOS visit year	Year 1		Year 2		Year 3		Year 4		Year 5		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, DPPOS Phase 1: Visit Years 1-6, Continued

Participant DPPOS visit year	Year 1		Year 2		Year 3		Year 4		Year 5		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, DPPOS Phase 1: Visit Years 1-6, Continued

Participant DPPOS visit year	Year 1		Year 2		Year 3		Year 4		Year 5		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 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.

** 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, DPPOS Phase 2: Visit Years 7-12

Participant DPPOS visit year	Year 7		Year 8		Year 9		Year 10		Year 11		Year 12	
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		7/1/13-10/31/14	
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		2/1/14-1/31/15	
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		
TPA										X		
CRP										X		
Lipids												
Lipid profile		X		X		X		X		X		X
Particle size and subfractions										X		
Kidney Function												
Urine Albumin & Creatinine		X		X		X		X		X		X
Serum Cystatin				X		X		X		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
Cancer History and Risk Factors										X		
Physical												
Weight	X	X	X	X	X	X	X	X	X	X	X	X
Height										X		
Waist Circumference		X		X		X		X		X		X
DXA (body composition measures)+++												X

Outcomes Schedule, DPPOS Phase 2: Visit Years 7-12, Continued

Participant DPPOS visit year	Year 7		Year 8		Year 9		Year 10		Year 11		Year 12	
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		7/1/13-10/31/14	
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		2/1/14-1/31/15	
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				
Quality of Life												
Beck	X		X		X		X		X		X	
SF-36			X				X		X		X	
Urinary Incontinence		X		X		X		X		X		X
Physical Activity, Nutrition, Behavior, Functional												
MAQ		X	X		X		X		X		X	
Nutrition Intake										X		
Dietary Restraint, Exercise Self-Efficacy, Low Fat Diet Self-Efficacy			X		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		X
Coronary Artery Calcium ++								X				
Eye												
Retinal Photography ++										X		
Neurologic												
Symptom Assessment		X		X		X		X		X		X
Modified MNSI including monofilament		X		X		X		X		X		X
Heart rate variability		X		X		X		X		X		X

Outcomes Schedule, DPPOS Phase 2: Visit Years 7-12, Continued

Participant DPPOS visit year	Year 7		Year 8		Year 9		Year 10		Year 11		Year 12	
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		7/1/13-10/31/14	
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		2/1/14-1/31/15	
Mid-year or Annual visit	Mid	Ann	Mid	Ann	Mid	Ann	Mid	Ann	Mid	Ann	Mid	Ann
Saved Specimens												
Fasting EDTA Plasma (no serum is stored)		X		X		X		X		X		X
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
Other Chemistries												
Relevant biological markers related to the pathogenesis of diabetes and its complications										X		
Economic Evaluation												
Resource Utilization								X				
QWB		X	X				X				X	

EOS = end of study
# 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.
** 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
+++ DXA scans will be completed on a sample of participants during DPPOS Year 12

Outcomes Schedule, DPPOS Phase 3: Visit Years 13-18

Participant DPPOS visit year	Year 13		Year 14		Year 15		Year 16		Year 17		Year 18	
Visit calendar year	7/1/14-10/31/15		7/1/15-10/31/16		7/1/16-10/31/17		7/1/17-10/31/18		7/1/18-10/31/19		7/1/19-10/31/20	
DPPOS funding calendar year	2/1/15-1/31/16		2/1/16-1/31/17		2/1/17-1/31/18		2/1/18-1/31/19		2/1/19-1/31/20		2/1/20-1/31/21	
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
120' glucose+				X				X				X
HbA1c		X		X		X		X		X		X
Insulin Secretion and Sensitivity												
Fasting insulin		X		X				X				X
Lipids												
Lipid profile				X				X				X
Kidney Function												
Urine Albumin & Creatinine		X		X		X		X		X		X
Serum Creatinine		X		X		X		X		X		X
History												
Symptoms and Events (including CVD and Cancer)	X	X	X	X	X	X	X	X	X	X	X	X
Cancer Risk Factors		X		X		X		X		X		X
Physical												
Weight		X		X		X		X		X		X
Height						X						X
Waist Circumference		X		X				X				
DXA (bone and body composition measures)++										X		
Blood Pressure												
Arm BP		X		X		X		X		X		X
Quality of Life												
Beck						X						
SF-36						X						
Urinary Incontinence						X						

Outcomes Schedule, DPPOS Phase 3: Visit Years 13-18, Continued

Participant DPPOS visit year	Year 13		Year 14		Year 15		Year 16		Year 17		Year 18	
Visit calendar year	7/1/14-10/31/15		7/1/15-10/31/16		7/1/16-10/31/17		7/1/17-10/31/18		7/1/18-10/31/19		7/1/19-10/31/20	
DPPOS funding calendar year	2/1/15-1/31/16		2/1/16-1/31/17		2/1/17-1/31/18		2/1/18-1/31/19		2/1/19-1/31/20		2/1/20-1/31/21	
Mid-year or Annual visit	Mid	Ann	Mid	Ann	Mid	Ann	Mid	Ann	Mid	Ann	Mid	Ann
Physical Activity, Nutrition, Behavior, Functional												
ADL/IADL		X				X				X		
Sexual Function						X						
Physical Function including the 6-minute walk test						X						X
Spirometry						X						X
MAQ												X
Cognition												
Cognitive Function						X					X	X
Cardiovascular												
ECG				X				X				
Eye												
Retinal Photography and OCT								X				
Neurologic												
Monofilament		X		X		X		X		X		X
MNSI		X										
MNSI questionnaire only										X		X
Sensory exam (vibration and pinprick)										X		X
Heart rate variability				X				X				
Saved Specimens												
Fasting Serum and EDTA Plasma		X		X		X		X		X		X
Spot Urine		X		X		X		X		X		X
Additional Safety Measures												
Serum Creatinine				X				X				
CBC*		X										
Vitamin B12*				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

Economic Evaluation												
Resource Utilization								X				X
QWB								X				

+ For diabetic participants: The OGTT with 120' glucose collection is discontinued

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

* CBC and/or B12 for participants actively taking study metformin

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

++ DXA scans will be completed on a sample of participants during DPPOS Year 17

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 – August 31, 2002	Protocol development
Phase 1	September 1, 2002 – January 31, 2009	Participant follow-up
	July 2006 – October, 2007	Year 5 major visit
	February 1, 2008 – January 31, 2009	Phase 1 Analysis
	June 2008	Submit funding renewal
Phase 2	February 1, 2009 – October 2015	Participant follow-up
	July 2012 – October 2013	Year 11 major visit
	October 2013	Begin Phase 2 Analysis
	May 2014	Submit funding renewal
	March 2015	Re-submit funding renewal

Phase 3	February 1, 2015 – October 2020	Participant follow-up
	February 1, 2015 – January 2016	Bridge period funding awarded
	July 2017 – October 2018	Year 16 major visit
	February 1, 2019 – January 31, 2021	DPPOS Phase 3 (first 5 years) analysis
	May 2020	Submit funding renewal

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