

PROTOCOL

for the

FOLLOW-UP OF DPP PARTICIPANTS RANDOMIZED TO TROGLITAZONE

Diabetes Prevention Program Research Group

November 6, 2001

Version 1.2

Distributed by the Coordinating Center

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SUMMARY

of

FOLLOW-UP OF DPP PARTICIPANTS RANDOMIZED TO TROGLITAZONE PROTOCOL MODIFICATIONS

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Diabetes Prevention Program Research Group

November 06, 2001

Version 1.2

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PREFACE

The substudy protocol for the Diabetes Prevention Program (DPP) cohort study of participants randomized to troglitazone therapy during the DPP randomized clinical trial, describes the background, design and organization of the cohort study. The protocol is maintained by the Coordinating Center (CoC) at the George Washington University Biostatistics Center through new release of the entire protocol or issuance of supplemental protocol memoranda. This preface contains a summary of the protocol modifications made during the cohort study. Comments or questions regarding aspects of the DPP substudy protocol, including distribution, should be directed to the staff of the CoC.

VERSION 1.0

Protocol Version 1.0, dated July 30, 1998, was developed by the Steering Committee of the DPP Research Group.

VERSION 1.1

1. Purpose

This protocol amendment describes: a) the early termination of the masked treatment phase and reporting of study results; b) changes to the study timeline; c) modifications to data collection; and d) addition of a consent form for this period. A template consent form (Ver. 1.1) for this amendment is added.

2. Data Monitoring Board (DMB) recommendations

On May 18th, 2001, the DMB for the DPP reviewed the accumulated data, and recommended unanimously to the NIDDK that the masked treatment phase of the three-arm study be terminated and major results presented. The Director of the NIDDK accepted this recommendation, and directed study leadership to accomplish these goals. This decision was based on the results of the interventions and not on safety issues or adverse events. The former Troglitazone participants were unmasked previously. Continued data collection for the evaluation of secondary outcomes was recommended.

3. Study timeline

This amendment changes the study timeline as follows. A Steering Committee meeting will be held on July 31-August 1, 2001 to unmask the results and formulate the consensus recommendations. Within seven (7) days following this, investigators will provide study participants with the major study results. A scientific meeting to present these results will be held in August. The final manuscript reporting major study results will be submitted for publication as soon as possible. This amendment will be valid from August 1, 2001 (or as soon as approved by IRBs) through February 28, 2002, or until amended. Regularly scheduled visits as planned will be continued.

4. Data Forms

Addition:

Section 9.1.2 Follow-up Period

- Home Visit (Form F06)

5. Data collection

Data collection will be modified as specified in the following addition:

Addition:

Section 12.1.1: Changes due to early termination of the masked treatment phase:

- a. A urine specimen to measure urine albumin and creatinine concentration will be collected at their next scheduled visit.
- b. Height will be measured
- c. Carotid ultrasound may be conducted at a visit to be scheduled.

6. Study timeline

Modification:

Section 13: The study timeline was changed as follows.

Phase II changed from “June 1998 – June 2002 Participant Follow-up – 23 months” to “June 1998 - December 2001 Participant Follow-up”

Phase III changed from “July 2002 – June 2003 Study Close-out and Data Analysis” to “June 2001 Initiate Study Close-out and Data Analysis”

7. Informed Consent Prototypes

Addition:

Section 15.2: “Information and Consent for Banking and Use of the Blood and Genetic Material” has been added to align with the current national scientific standards regarding the use of specimens for genetic studies.

Section 15.3: “Information and Amendment for the Completion of the Masked Treatment Phase for Former Troglitazone Participants” has been added to address specifics of completion of the masked treatment phase.

VERSION 1.2

Updates to Version 1.1 (i.e., Version 1.2, dated November 6, 2001) are activated by the Steering Committee's vote to accept a protocol to initiate the phase following termination of DPP masked interventions.

1. PURPOSE

This amendment covers the period of time between the termination of the DPP active intervention phase, washout study and individual debriefing (December 2001 - January, 2002) under Protocol version 1.1 and either: a) formal close-out of DPP; or b) initiation of a proposed long-term follow-up study. If the follow-up study is funded, it will be conducted under a new protocol and informed consent forms to be developed during 2002.

This protocol amendment will continue until the end of 2002, unless amended earlier.

Prior to the early termination of the masked phase of the DPP and knowledge of the final results, the Steering Committee voted to provide one or more effective therapies, if resources allowed, to the groups not previously receiving the therapy. This was based primarily on ethical concerns.

The purpose of this amendment is to modify DPP Troglitazone Protocol version 1.1 to provide all participants with a 16 session group implemented lifestyle training (Healthy Lifestyle Plan - HELP) with the same goals for weight-loss and activity as shown in DPP to be effective in reducing the risk of developing diabetes. Procedures and schedules provided in protocol version 1.1 remain in force, with small changes to the data collection schedules specified below. The goal of the "bridge" period is to ensure that all participants are offered the HELP program, and that data relevant to the proposed long-term follow-up study will be collected in an efficient manner.

Protocol version 1.2 makes the following changes to version 1.1:

- Adds the HELP program
- Removes masking of laboratory results
- Removes the requirement for masking of data collectors
- Initiates quarterly visits for participants enrolling in HELP, to be conducted in person or by telephone
- Incorporates HELP into guidelines for management of CVD and diabetes – see DPP Protocol version 4.5 section 7.5

2. STUDY DESIGN

Additions:

Section 5.1.1: Group lifestyle training

Following early termination of the masked treatment phase and debriefing of the DPP participants, all participants will be offered group implemented lifestyle training (Healthy Lifestyle Plan - HELP) with the same goals for weight-loss and activity as shown in DPP to be effective in reducing the risk of developing diabetes.

Section 5.4.2.1: Central laboratory outcomes

Outcome tests will not be masked during the bridge period, with the exception of temporary masking of oral glucose tolerance and fasting test results that require a repeat test for confirmation of diabetes, and a sample of normal tests to be repeated to minimize the amount of behavior change that occurs between tests.

Section 5.4.3.1.A: Data collectors – bridge period

Since the masked treatment phase of DPP is completed and all subjects and staff are unmasked, clinics may decide, based on staffing requirements, the proper certified person(s) to do outcome assessments.

3. PARTICIPANT MANAGEMENT PROTOCOLS

Additions:

Section 7.1.4: Schedule of follow-up visits during the “bridge” period

Mid-year and annual individual visits will take place in person. Quarterly follow-up visits will be initiated in those who enroll in HELP, and can be completed in person, or by phone. All participants are offered HELP group lifestyle sessions.

Section 7.2.2 Healthy Lifestyle Plan - HELP

Overview: Between January and June 2002, all participants (intensive lifestyle (ILS), metformin, placebo, and troglitazone, including those who have converted to diabetes) will be offered a 16-session group implemented lifestyle change program with the same goals used in DPP and similar in content to the core curriculum delivered to the original ILS participants. These will be offered in two eight-session blocks, with the opportunity to enroll for the second set of sessions given at the completion of the first block. The group sessions will also be offered to the former ILS participants as an opportunity for review and restart. The plan will be conducted in a group format, rather than individually. Centers may offer groups at different times of the day and the week, with the goal of completing all sessions by the end of June 2002. Local scheduling decisions may require that some centers extend beyond this date due to numbers of participants, staffing, etc.

Content: Participants will focus on weight loss first, rather than choosing between weight loss and physical activity, as done previously. The sessions will follow this order: 1) Welcome, Getting Started Losing Weight, 2) Be a Fat Detective, 3) Three Ways to Eat Less Fat, 4) Healthy Eating, 5) Move Those Muscles, 6) Being Active: A Way of Life, 7) Tip the Calorie Balance, and 8) Take Charge of What’s Around You. The remaining sessions will be: 9) Problem Solving, 10) Four Keys to Healthy Eating Out, 11) Talk Back to Negative Thoughts, 12) The Slippery Slope of Lifestyle Change, 13) Jump Start Your Activity Plan, 14) Make Social Cues Work for You, 15) You Can Manage Stress, and 16) Ways to Stay Motivated. Each of these sessions is described in the Lifestyle Manual of Operations. Supervised activity sessions, offered at or by a DPP Center, will be optional. Data will be collected to document attendance at each session, as well as weight and activity minutes throughout the sessions.

All participants who wish to take part in the group lifestyle training will be required to obtain approval from their primary care provider before beginning exercise, with the exception of those who were already participating in an exercise program as part of the ILS. If the primary care provider does not give approval, the participant will not be able to take part in the exercise component of the training.

Section 7.5.2: Retention monitoring and recovery of inactive participants for the bridge period

Participants who do not wish to participate in the HELP program will be encouraged to continue to participate in data collection visits until the bridge period is completed. Other aspects of retention monitoring will be maintained as resources allow.

4. DATA PROCESSING: DATA FORMS

Additions:

Section 9.1.3: Forms completion during the bridge period

Changes to forms completion during the bridge period are kept to a minimum, using versions of the data forms listed in the Protocol.

5. SCHEDULE OF PROCEDURES

Additions:

Section 12.1.2: Changes for the bridge period

Adverse events will be collected quarterly in addition to during mid-year and annual visits for those participants who take part in HELP.

6. STUDY TIMETABLE

Additions:

Section 13. Study Timetable

Phase IV:

January 1, 2002

No later than December 31, 2002

Bridge period start

Bridge period end

Study end:

December 31, 2002

June 30, 2003

Participant contact ends

End of final DPP funding cycle

7. CONSENT FORMS

Additions:

Section 15.4: "Information and addendum for the completion of the treatment phase of the Diabetes Prevention Program (DPP) for former troglitazone participants".

1. EXECUTIVE SUMMARY..... 1-1

1. EXECUTIVE SUMMARY

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

Cohort Background

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

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

Cohort Objective

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

Cohort Population

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

Cohort Intervention

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

Cohort Outcomes

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

Cohort Design

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

Analysis of the Cohort

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

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2. OBJECTIVES

2.1 Research Questions

Research questions of the troglitazone cohort include assessing differences over time within the troglitazone cohort and between the troglitazone cohort and the concurrent control group consisting of approximately 600 DPP participants randomized to double-placebo on or before May 27, 1998 with regard to the following:

- Time to confirmed diagnostic levels of diabetes, by ADA criteria (FPG \geq 126 mg/dL [7.8 mmol/L] or 2-hour plasma glucose \geq 200 mg/dL [11.1 mmol/L] after a 75 gram oral glucose tolerance test).
- Development of fasting hyperglycemia (FPG \geq 140 mg/dL [7.8 mmol/L]).
- Reversal of IGT to a state of normal glucose tolerance.
- Change in hyperglycemia as measured by glycohemoglobin and fasting and 2 hr. plasma glucose.
- Change in insulin secretion and sensitivity.
- Change in body weight.
- Occurrence and magnitude of risk factors for cardiovascular disease.
- Occurrence of cardiovascular morbidity and mortality.
- Occurrence and magnitude of major adverse events.

The troglitazone cohort will be offered lifestyle group sessions four times per year. Weight change within the troglitazone cohort will be determined. The troglitazone cohort and the approximately 600 DPP participants randomized to the DPP intensive lifestyle intervention on or before May 27, 1998, will be compared on weight change.

2.2 Subgroup Research Questions

Other research questions of the troglitazone cohort include assessing subgroups of troglitazone-treated participants with regard to the following:

- Consistency of the effects across the ethnic, age, and other selected subgroups.
- Baseline demographic, clinical, biochemical, and psychosocial parameters that predict outcome.

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3. BACKGROUND OF THE DPP

See the DPP Protocol Section 3 for the background of the DPP including the prevalence of type 2 diabetes and IGT, morbidity and mortality, risk factors for type 2 diabetes and IGT, progression of IGT to type 2 diabetes, etiology, IGT and macrovascular disease, interventions that may decrease progression from IGT to type 2 diabetes and the rationale for the study.

3.1 Discontinuation of the Troglitazone Pharmacological Intervention

Randomization to the troglitazone pharmacological intervention was suspended on May 27, 1998, and discontinued by the NIDDK on June 3, 1998. The NIDDK, with input from the DPP Data Monitoring Board, decided to discontinue use of troglitazone in the DPP based on the following: Associated with troglitazone use in the DPP, there is an increased risk of liver toxicity resulting in serum ALT levels greater than or equal to 8 times the upper limit of normal. In the DPP, there has been one case of hepatic failure requiring liver transplantation. Within the context of this research trial, safety monitoring, even if intensified, is not likely to eliminate the risk. It is also too early in the trial to estimate reliably and compare the absolute risk or benefit of continuing troglitazone in this study population. We are not willing to continue to study a drug for the purpose and benefit of preventing progression from impaired glucose tolerance to diabetes when the drug has demonstrated liver toxicity with hepatic failure.

Participants randomized to troglitazone prior to May 27, 1998, were unmasked to their intervention assignment and monitored to ensure that no liver toxicity developed after discontinuing the troglitazone medication. Pharmacological participants randomized to metformin or double-placebo, discontinued their troglitazone-placebo, continue their coded metformin medication and remained masked to their pharmacological assignment (metformin or metformin-placebo).

This protocol describes the continued follow-up of the cohort of participants randomized to the troglitazone intervention of the DPP.

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4. DEFINITION OF OUTCOMES

4.1 Diabetes

Diabetes is defined as progression of oral glucose tolerance test (OGTT) results from impaired glucose tolerance (IGT) at baseline to confirmed diabetes, by ADA criteria (FPG \geq 126 mg/dL [7.8 mmol/L] or 2-hour plasma glucose \geq 200 mg/dL [11.1 mmol/L] after a 75 gram OGTT). To assess progression to this outcome, an OGTT will be performed routinely on an annual basis under conditions described in the DPP Manual of Operations. If the OGTT result meets ADA criteria for diabetes, the participant will be called back for a repeat OGTT within 6 weeks. If two sequential OGTTs performed within 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 with the semi-annual follow-up visits.

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

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

4.2 Glucose and Insulin

- **HbA_{1c}:** Hemoglobin A_{1c} will be assessed to reflect recent average glycemia, to test its relationship to OGTT results and its utility as an indicator of glucose intolerance for the purposes of diabetes prevention. HbA_{1c} will be measured at end-month 6 and 12, and annually, thereafter.
- **Insulin and Glucose:** To assess insulin secretion, fasting and 30 minute plasma insulin and glucose and fasting plasma proinsulin will be collected during the annual OGTT. Fasting insulin will be used as surrogate for insulin sensitivity.

4.3 Cardiovascular

- **Arm Blood Pressure and Weight** Blood pressure and weight will be recorded during each semi-annual follow-up visit.
- **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, LDL-ApoB, LDL-cholesterol will be determined at end-month 6 and 12, and annually, thereafter.
- **Electrocardiogram:** A centrally-read ECG will be performed at each annual follow-up visit.

4.4 Safety Tests

- **Adverse Medical Events and Symptoms:** Queries for major adverse events and symptom histories will be conducted during each semi-annual follow-up visit. Serious adverse events, including death, will be reported immediately.
- **Physical Examination and Interval History** A physical and interval history will be performed during annual follow-up visits.

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5. STUDY DESIGN

See the DPP Protocol Section 5 for the design of the randomized clinical trial including participation inclusion and exclusion criteria, principles guiding selection of interventions, stratification and random assignment to treatment groups, timing and conditions of primary and secondary outcome assessment, and level of masking of treatment groups, central laboratory outcomes and clinical outcomes.

5.1 Overall Cohort Design

The study is a prospective observational cohort of the 585 participants originally randomized to troglitazone in a clinical trial to test the safety and efficacy of interventions designed to prevent NIDDM.

During the clinical trial, participants with IGT and FPG values of 95 - 125 mg/dL [5.3 - 6.9 mmol/L] were randomized; with an emphasis on recruitment of individuals with particularly high risk of development of NIDDM including those with obesity, the elderly, women with a history of gestational diabetes, and members of minority groups such as African Americans, Hispanic Americans, Asian and Pacific Island Americans, and Native Americans. Eligible volunteers for randomization were stratified according to center and assigned to one of the three intervention or control groups. The two pharmacological interventions were double blind and placebo controlled. After randomization, participants had quarterly clinical evaluations with a fasting plasma glucose at semi-annual visits and a 75 gm oral glucose tolerance test at annual visits.

Randomization to the troglitazone pharmacological intervention was suspended on May 27, 1998, and discontinued by the NIDDK on June 3, 1998. A total of 585 participants were randomized to troglitazone on or before May 27, 1998. The troglitazone cohort of 585 participants were unmasked to their intervention assignment and monitored to ensure that no liver toxicity developed after discontinuing the troglitazone medication. The cohort of 585 participants will continue to be followed with semi-annual visits for a duration of 4 years.

5.1.1 Group Lifestyle Training

Following early termination of the masked treatment phase and debriefing of the DPP participants, all participants will be offered group implemented lifestyle training (Healthy Lifestyle Plan - HELP) with the same goals for weight-loss and activity as shown in DPP to be effective in reducing the risk of developing diabetes.

5.2 Participation Criteria

5.2.1 Inclusion Criteria

1. Eligible for randomization in the DPP (see the DPP Protocol Sections 5.2.2 and 5.2.3 for the DPP inclusion and exclusion criteria, respectively).
2. One of the 585 participants randomized to troglitazone between July 1996 and May 1998.
3. Willing to give informed consent to continued follow-up with semi-annual visits

5.3 Timing and Conditions of Outcome Assessment

5.3.1 Diabetes Outcome

The diabetes outcome, progression from impaired glucose tolerance (IGT) to diabetes, is assessed by OGTT testing annually, by fasting plasma glucose (FPG) every six months, and at the time that symptoms consistent with hyperglycemia occur. Conditions for the OGTT are specified in the DPP Manual of Operations. The annual OGTT and 6 month FPG will be postponed for up to six weeks if a temporary concomitant condition exists that would affect glucose tolerance. An OGTT that is positive for diabetes, or a six-monthly FPG that is \geq 126 mg/dL [7.0 mmol/L], will be repeated for confirmation before the participant is considered to have reached the diabetes outcome. When a participant has been in a "time-out" (other than pregnancy), such as for a concomitant disease known to affect glucose tolerance, the diabetes outcome will be assessed at the time of the next regularly scheduled six-monthly FPG or annual OGTT after that time-out ends.

5.3.2 Glucose, Insulin, Cardiovascular and Safety Outcomes

Glucose, insulin, cardiovascular (weight, blood pressure, lipids and ECG) and safety (adverse events, physical and history) outcomes will be assessed according to the schedule in Section 12. Glucose and insulin will also be measured when a cohort participant reaches the diabetes outcome during a non-annual follow-up visit.

5.4 Level of Masking

5.4.1 Troglitazone Cohort

All participants in the cohort are unmasked to their original troglitazone assignment.

5.4.2 Central Laboratory Outcomes

Diabetes outcome data (OGTT and FPG results) measured centrally will remain masked to the investigators and to the participants until confirmed progression from IGT to diabetes. Plasma lipid levels and HbA_{1c} measured centrally will remain masked to the investigators and to the participants during the study. Two exceptions to this policy are: 1) if an individual result falls outside a pre-determined, clinically acceptable range representing a significant risk to the participant, it will be confirmed. If the result remains abnormal, the investigator and the participant will be notified and appropriate clinical steps will be taken. 2) If an individual participant insists on knowing specific outcome results, such as plasma lipid values, and their continued participation in the troglitazone cohort study is considered by the investigator to be in jeopardy, the investigator may request an exception from the Coordinating Center.

5.4.2.1 Central Laboratory Outcomes

Outcome tests will not be masked during the bridge period, with the exception of temporary masking of oral glucose tolerance and fasting test results that require a repeat test for confirmation of diabetes, and a sample of normal tests to be repeated to minimize the amount of behavior change that occurs between tests.

5.4.3 Clinical Outcomes

Some of the outcome data, such as blood pressure and weight will be measured at the clinical center. It is not feasible to keep these data masked from the participants, if they want to know their result. Therefore, participants will be unmasked to measurements of weight and blood pressure.

5.4.3.1 Data Collectors

In order to promote objectivity of data collection and to minimize the opportunity for bias, the intent is to separate outcome measurement from the case managers. This is particularly important for weight and blood pressure measures, where the potential exists for subjectivity. Case managers must not perform these outcome measures for participants with whom they are intervening.

5.4.3.1.A Data Collectors- Bridge Period

Since the masked treatment phase of DPP is completed and all subjects and staff are unmasked, clinics may decide, based on staffing requirements the proper certified person(s) to do outcome assessments.

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6. ENROLLMENT OF PARTICIPANTS

See the DPP Protocol Section 6 for the enrollment of participants in the randomized clinical trial including the recruitment goals and strategies, and the informed consent process and staged screening.

6.1 Troglitazone Cohort

6.1.1 Informed Consent

All participants eligible for the troglitazone cohort study must sign the informed consent contained in Section 15.

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7. PARTICIPANT MANAGEMENT PROTOCOLS

7.1 Schedule of Follow-up Visits for Data Collection

Follow-up visits after unmasking the participants randomized to troglitazone will be scheduled at 6 month intervals (i.e. mid-year and annual visits). After unmasking the troglitazone assignment, participants randomized to troglitazone were scheduled for an interim visit within 1 week and again 1 month and 2 months later to monitor liver function tests. After these interim visits, all troglitazone participants will continue their 6 month interval visits, based on the participant's date of randomization, for the duration of DPP (i.e., June 2002, or 4 years). Outcome and safety assessments will be conducted according to the schedule in Section 12.

7.1.1 Mid-Year Visits

During a mid-year visit, the "Participants Randomized to Troglitazone Follow-up Visit Inventory" is completed (DPP Form TR1). Form TR1 records weight, blood pressure, adverse events and prescription medications. At all mid-year visits, a fasting glucose specimen is collected and forwarded to the CBL using the "Mid-Year Follow-up Visits - Frozen Specimen" transmittal form (DPP Form C04). At the end-month 6 mid-year visit, a fasting specimen for lipids is also collected and forwarded to the CBL using Form C04 along with a HbA_{1c} specimen using the "Fresh Specimen" transmittal form (DPP Form C03).

7.1.2 Annual Visits

During an annual visit, the "Participants Randomized to Troglitazone Follow-up Visit Inventory" is completed (DPP Form TR1). Form TR1 records weight, blood pressure, adverse events and prescription medications. At all annual visits, a 2 hour OGTT is performed using the "OGTT Procedure - Follow-up Visits" form (DPP Form P01) with the glucose and insulin/proinsulin specimens forwarded to the CBL using the "Major Follow-up Visits - Frozen Specimens" transmittal form (DPP Form C05). A fasting specimen for lipids is also collected and forwarded to the CBL using Form C05 along with a HbA_{1c} specimen using the "Fresh Specimen" transmittal form (DPP Form C03). Also, at all annual visits, an ECG is performed and forwarded to the ECG Reading Center using the "ECG Procedure" form (DPP Form P02), and a physical and interval history is performed with the history information recorded on the "Interval History Questionnaire" (DPP Form Q08).

7.1.3 Interim Visits

An interim visit refers to all visits other than scheduled follow-up visits (i.e., mid-year or annual follow-up visits). Interim visits may be required for the monitoring or management of an emerging or existing condition, or to repeat procedures which, at a previous visit, were found to be deficient. Such visits may be held as frequently as deemed necessary and recorded on the "Interim Follow-up Visit Inventory" (DPP Form F03).

7.1.4 Schedule of Follow-up visits during the Bridge Period

Mid-year and annual individual visits will take place in person. Quarterly follow-up visits will be initiated in those who enroll in HELP, and can be completed in person, or by phone. All participants are offered HELP group lifestyle sessions.

7.1.5 Suspension of Semi-Annual Follow-up Visits

The occurrence or presence of the following will constitute inactive follow-up and suspension of the troglitazone cohort semi-annual follow-up visit protocol:

- Voluntary withdrawal by the participant, or condition which, in the opinion of the principal investigator, makes it unsafe for the participant to continue.

7.2 Quarterly Lifestyle Group Sessions

Lifestyle group sessions will be held quarterly starting September 1998. All participants randomized to troglitazone will be invited to attend these sessions. The purpose of these sessions is to provide basic information about losing weight through healthy eating and increasing physical activity. The educational information presented will be similar to that provided to the intensive lifestyle group.

The specific content of the group sessions will be based on intervention materials already developed for use in DPP. The Lifestyle Resource Core will provide guidelines and handouts for use in these sessions. Subsequent sessions will focus on topics such as rearranging the home environment to facilitate behavior change, healthy eating out, problem solving, stress and motivation. Sessions will be conducted as group classes with discussion of the information by participants. Participants who do not attend a session will be sent the session handouts.

7.2.1 Indices of Adherence

Adherence to the quarterly lifestyle group session is assessed in the following manner:

- Although not required of participants, attendance at the quarterly lifestyle group sessions is recorded on the DPP data form “Participants Randomized to Troglitazone Group Session Log” (Form TR2)

7.2.2 Healthy Lifestyle Plan - HELP

Overview: Between January and June 2002, all participants (intensive lifestyle (ILS), metformin, placebo, and troglitazone, including those who have converted to diabetes) will be offered a 16-session group implemented lifestyle change program with the same goals used in DPP and similar in content to the core curriculum delivered to the original ILS participants. These will be offered in two eight-session blocks, with the opportunity to enroll for the second set of sessions given at the completion of the first block. The group sessions will also be offered to the former ILS participants as an opportunity for review and restart. The plan will be conducted in a group format, rather than individually. Centers may offer groups at different times of the day and the week, with the goal of completing all sessions by the end of June 2002. Local scheduling decisions may require that some centers extend beyond this date due to numbers of participants, staffing, etc.

Content: Participants will focus on weight loss first, rather than choosing between weight loss and physical activity, as done previously. The sessions will follow this order: 1) Welcome, Getting Started Losing Weight; 2) Be a Fat Detective; 3) Three Ways to Eat Less Fat; 4) Healthy Eating; 5) Move those Muscles; 6) Being Active; 7) Tip the Calorie Balance; 8) Take Charge of What’s Around You; 9) Problem Solving; 10) Four Keys to Healthy Eating Out; 11) Talk Back to Negative Thoughts; 12) The Slippery Slope of Lifestyle Change; 13) Jump Start Your Activity Plan; 14) Make Social Cues Work for You; 15) You Can Manage Stress; and 16) Ways to Stay Motivated. Each of these sessions is described in the Lifestyle Manual of Operations. Supervised activity sessions, offered at or by a DPP Center, will be optional. Data will be collected to document attendance at each session, as well as weight and activity minutes throughout the sessions.

All participants who wish to take part in the group lifestyle training will be required to obtain approval from their primary care provider before beginning exercise, with the exception of those who were already participating in an exercise program as part of the ILS. If the primary care provider does not give approval, the participant will not be able to take part in the exercise component of the training.

7.3 Pharmacological Treatment

All participants randomized to troglitazone on or before May 27, 1998, were treated with active troglitazone and metformin-placebo until the participants were unmasked on June 5, 1998. Since unmasking, all troglitazone treated participants have discontinued the study medications.

7.3.1 Dosing Schedule

Prior to unmasking the troglitazone cohort, the administration of coded medications, either active or placebo, took place in three phases: run-in; and post-randomization steps I and II. The use of metformin at the dose of 850 mg twice daily is associated with gastrointestinal side effects at the onset of treatment. These side effects are reduced if the medication is taken with food and the dose titrated from once daily to twice daily over several weeks. Troglitazone bioavailability is enhanced when administered with food. Thus, both coded medications were administered with food and the dose of coded metformin (MP or MA) was increased in two steps during the DPP.

7.3.1.1 *Pre-randomization*

All DPP candidates participate in a three week run-in phase during eligibility screening in which participants take TP (troglitazone-placebo) once daily with the first food intake of the day and MP (metformin-placebo) twice daily, in the morning and evening with food. Participants are told that the pills are inactive during the run-in.

7.3.1.2 *Post-Randomization - Steps I and II*

Volunteers who successfully complete the run-in phase and are otherwise eligible are randomized to one of the four DPP treatments: intensive lifestyle intervention group, double-placebo control group, metformin group or troglitazone group. Volunteers randomized to one of the three pharmacological treatments then enter Step I of the pharmacological treatment regimen.

Step I

After randomization, pharmacological participants initially take two tablets with the morning meal. These are MP plus TP in the double-placebo control group, MA and TP in the metformin group, and MP and TA in the troglitazone group. This phase will last four weeks.

Step II

After four weeks in Step I (once daily dosage), participants are advanced to Step II (twice daily dosage). This is MP BID plus TP once daily in the double-placebo control group, MA BID and TP once daily in the metformin group, and MP BID plus TA once daily in the troglitazone group.

Table 7-1 Summary of Coded Medication Administration

Step	Week	Time*	Placebo**	Metformin**	Troglitazone**
Run-In	-3 to 0	AM	MP, TP	MP, TP	MP, TP
		PM	MP	MP	MP
Step - I	0 to 4	AM	MP, TP	MA, TP	MP, TA
		PM	None	None	None
Step - II	>4	AM	MP, TP	MA, TP	MP, TA
		PM	MP	MA	MP

* AM - Usually before breakfast; may be before first meal of the day
 PM - Usually before evening meal; may be taken before bedtime snack.

** M - metformin, T - troglitazone
 A - active, P - placebo

7.3.2 Prescription Medications

Prior to the troglitazone unmasking, all pharmacological participants had prescription medications recorded during each quarterly follow-up visit. After unmasking participants randomized to troglitazone, the troglitazone cohort will have prescription medications recorded on the "Participants Randomized to Troglitazone Follow-up Visit Inventory" (DPP Form TR1) during semi-annual follow-up visits.

7.4 Definition and Management of Concomitant Conditions

See the DPP Protocol Section 7.5 for the definition and management of concomitant conditions including hypertension, lipids, psychological diseases and use of psychoactive drugs, pregnancy, smoking, type 2 diabetes and cardiovascular disease.

7.5 Retention of the Troglitazone Cohort

7.5.1 Honoraria

An honorarium will be paid to troglitazone participants in recognition of the time and effort spent in the DPP. All participants receive this payment twice a year if participants have successfully completed scheduled visits and procedures.

7.5.2 Retention Monitoring and Recovery of Inactive Participants for the Bridge Period

Participants who do not wish to participate in the HELP program will be encouraged to continue to participate in data collection visits until the bridge period is completed. Other aspects of retention monitoring will be maintained as resources allow.

8. ADVERSE EVENT REPORTING..... 8-1

8. ADVERSE EVENT REPORTING

See the DPP Protocol Section 8 for the reporting of adverse events including the adverse event definition and procedures for eliciting and recording adverse events.

9. DATA PROCESSING	9-1
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9. DATA PROCESSING

See the DPP Protocol Section 9 for a description of the remote and centralized data management system, performance monitoring and interim statistical reports.

9.1 Data Forms

DPP data forms are completed to collect data relevant to the research questions regarding participants randomized to troglitazone. The sections that follow outline the data forms completed after unmasking the participants randomized to troglitazone. These data forms are contained in the DPP master data base maintained by the Coordinating Center (CoC).

9.1.1 Follow-up Period

The following data forms are completed after unmasking the participants randomized to troglitazone (i.e., after June 4, 1998):

- **Participants Randomized to Troglitazone Follow-up Visit Inventory (Form TR1):**
Completed at mid-year and annual follow-up visits: weight, arm blood pressure, adverse event assessment and current concomitant prescription medications.
- **Participants Randomized to Troglitazone Group Session Log (Form TR2):**
Completed for each troglitazone group session. Includes type of session and participants.
- **Interim Follow-up Visit Inventory (Form F03):**
Completed during follow-up visits when **Form TR1** is not required: reason for interim visit and adverse event assessment.
- **Missed Follow-up Visit Report (Form F04):**
Completed anytime a participant misses either a mid-year or annual scheduled follow-up visit: reason for missed visit and inactive follow-up status.
- **Home Visit (Form F06):**
Completed during mid-year or annual home visits for an inactive participants: adverse event assessment, current concomitant prescription medications.

9.1.2 Other Forms

The following questionnaire is completed during the annual follow-up visits:

- Interval History Questionnaire (Form Q08)

The following event data forms are completed as needed:

- Adverse Event Report (Form E01)
- Serious Adverse Event Report (Form E02)
- Diabetes Confirmation Report (Form E03)
- Pregnancy Confirmation Report (Form E04)
- Pregnancy Outcome Report (Form E05)
- Mortality Event Report (Form E06)

During the annual follow-up visits, the following worksheets are completed during the conduct of the respective procedure:

- OGTT Procedure - Follow-up Visits (Form P01)
- ECG Procedure (Form P02)

During the follow-up visits, the following report data form is completed whenever a lipid specimen is collected (see Section 12 for frequency of specimen collection):

- CHD Risk Status Report (Form R04)

The DPP data forms are created centrally at the CoC and sent to the clinics. The program coordinator reviews completed data forms prior to data entry. Completed forms are edited as they are entered into the microcomputer-based remote data management system.

9.1.3 Forms Completion During the Bridge Period

Changes to forms completion during the bridge period are kept to a minimum, using version of the data forms listed in the Protocol.

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10. STATISTICAL CONSIDERATIONS

10.1 Statistical Analysis Plan

Baseline Characteristics. Comparison of the baseline characteristics between the troglitazone cohort and the concurrent control group will use standard nonparametric statistical techniques, such as Fisher's exact test for categorical data (Agresti, 1990), and the Kruskal-Wallis test for ordinal or continuous data (Conover, 1980).

Outcomes. Analysis of the DPP cohort study will include a lifetable analysis of the time to confirmed development of diabetes. Separate product-limit life-table estimated cumulative incidence curves will be calculated for the troglitazone cohort and the concurrent control group and the groups compared using a logrank test (Kalbfleisch and Prentice, 1980). Within the troglitazone cohort, a proportional hazards regression model will be used to compare the impact of the duration of coded troglitazone therapy on the time to confirmed development of diabetes. For the diabetes outcome analysis, participants will be considered "administratively censored" if they complete the full duration of the DPP without confirmed development of diabetes. Participants who prematurely discontinue their follow-up visits prior to confirmed development of diabetes will be "censored" as of their last follow-up visit.

Other time to "event" outcomes (e.g., mortality, cardiovascular morbidity) will be analyzed using the same lifetable methods described above for the diabetes outcome. A proportional hazards regression model will be used to evaluate potential covariables that may modify the time to event outcomes (e.g., risk population defined by race/ethnicity and history of GDM, baseline fasting and 2 hour glucose, clinical site).

Longitudinal data analysis techniques will be used to analyze repeated measures data (e.g., glycemia, fasting lipids, weight, blood pressure) within the troglitazone cohort and between the troglitazone cohort and concurrent DPP treatment groups. These include analyses of the point prevalence of a discrete characteristic (e.g. hypertension) at successive repeated visits over time (Lachin and Wei, 1988); multivariate rank analyses of quantitative measures over successive visits (Wei and Lachin, 1984); the parametric linear random effects model of Laird and Ware (1982) to compare participant slopes over time (e.g., rate of change in fasting glucose) under a linearity and normality assumption; and techniques developed by Liang and Zeger (1986) to compare participant slopes under a generalized linear models framework.

11. STUDY ADMINISTRATION..... 11-1

11. STUDY ADMINISTRATION

See the DPP Protocol Section 11 for a description of the study administration including the organizational units, funding mechanisms/study resources, working committees and policies for publication and ancillary studies.

12. SCHEDULE OF PROCEDURES	12-1
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12.1.1 <i>Changes due to early termination of the masked treatment phase</i>	12-2

12. SCHEDULE OF PROCEDURES

12.1 Outcomes and Safety Testing

	Time Req. (min.)	Month												Primary Outcome*
		06	12	18	24	30	36	42	48	54	60	66	72	
Glycemia														
Fasting Glucose		X	X	X	X	X	X	X	X	X	X	X	X	M
30', 120' Glucose	120		X		X		X		X		X		X	M
HbA _{1c}		X	X		X		X		X		X		X	M
Insulin Secretion and Sensitivity														
Fasting, 30' Insulin			X		X		X		X		X		X	M
Fasting Proinsulin			X		X		X		X		X		X	M
Lipids (Fasting)														
Derived Beta Quant		X	X		X		X		X		X		X	
Full Beta Quant (If ↑ TG)		X	X		X		X		X		X		X	
LDL Particle Size		X	X		X		X		X		X		X	
LDL - ApoB		X	X		X		X		X		X		X	
LDL - CH		X	X		X		X		X		X		X	
Interval History, Physical and ECG														
Weight	5	X	X	X	X	X	X	X	X	X	X	X	X	
Arm BP	10	X	X	X	X	X	X	X	X	X	X	X	X	
Interval History Questionnaire	15		X		X		X		X		X		X	
ECG	15		X		X		X		X		X		X	
Safety Testing														
Adverse Event Report**		X	X	X	X	X	X	X	X	X	X	X	X	X

* For Primary Outcome Visit, items marked M need to be collected only if fasting plasma glucose (i.e., no OGTTs) were collected to determine diabetes.

** Adverse events will be collected at all follow-up visits (scheduled and interim)

Adverse events will be collected quarterly in those participants who take part in HELP

12.1.1 *Changes due to early termination of the masked treatment phase*

- a. A urine specimen to measure urine albumin and creatinine concentration will be collected at their next scheduled visit.
- b. Height will be measured
- c. Carotid ultrasound may be conducted at a visit to be scheduled.

12.1.2 *Changes for the Bridge Period*

Adverse events will be collected quarterly in addition to during mid-year and annual visits, in those participants who take part in HELP.

13. STUDY TIMETABLE..... 13-1

13. STUDY TIMETABLE

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 - May 1998	Recruitment and Follow-up - 23 months
	June 1998 – December 2001	Participant Follow-up
Phase III	June 2001	Initiate Study Close-out and Data Analysis
Phase IV	January 1, 2002	Bridge Period Start
	No later than December 31, 2002	Bridge Period End
Study End	December 31, 2001	Participant Contact Ends
	June 30, 2003	End of final DPP funding Cycle

14. BIBLIOGRAPHY..... 14-1

14. BIBLIOGRAPHY

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15. Consent Form

15.1 Information and Consent for Troglitazone Cohort Study

<p>NAME OF INSTITUTION</p> <p>INFORMATION AND CONSENT FOR FORMER TROGLITAZONE PARTICIPANTS DIABETES PREVENTION PROGRAM (DPP)</p>

INVESTIGATORS

Name of Principal Investigator

Title, Affiliation, Phone Number

Name of Co-Investigator(s)

Title, Affiliation, Phone Number

Name of Program Coordinator

Title, Affiliation, Phone Number

Name of Recruitment Coordinator

Title, Affiliation, Phone Number

<p>24-Hour Emergency Telephone Number</p>
--

<p>(List phone number(s) here)</p>

INVESTIGATOR'S STATEMENT:

PURPOSE AND BACKGROUND

This research study is called the Diabetes Prevention Program (DPP). You have been given the details concerning the Purpose and Background of this study in the previous Consent Form.

This study will test several ways to prevent the common form of diabetes (type 2 Diabetes, also called Non-Insulin-Dependent Diabetes Mellitus or NIDDM). One of these was the medicine troglitazone. You were in the group taking this medicine. Because of serious liver damage in a few individuals taking this medicine, including a participant in the DPP who died with liver damage that may have been due to this medicine, the DPP has stopped this treatment. You are being asked to continue to be followed in the DPP for the next 4 years.

BENEFITS

You have already received an extensive medical examination. We will tell you if we find any problems and if you permit it, we will tell you doctor. Your health will be closely watched during this study, and problems such as diabetes might be found and treated sooner than if you were not in the study. This might improve your health.

Tests have shown you do not have liver damage. We want to continue to follow you in the DPP, even if you are not on any assigned medicine. We can still learn more about type 2 diabetes if everyone who formerly was taking troglitazone continues in the DPP.

PROCEDURES

You will take part in the study for 4 more years. You will continue to follow healthy eating and exercise habits (“standard care”). “Standard care” is the type of treatment you expect from your own doctor if you are thought to be at high risk for getting diabetes, if you are overweight, or if you are physically inactive. You will also be invited to attend quarterly lifestyle group sessions. Your health will be closely watched, making it likely that problems will be found sooner than if you were not in the study. Any problems found will be told to you. Visits will be every 6 months.

Procedures to be carried out while you are in the study include the following:

1. A history and physical examination, including an electrocardiogram (ECG), will be done every 12 months. This will take about 1 hour.
2. Blood pressure will be measured in your arm every 6 months. This will take about 10 minutes.
3. Body measurements: Your weight will be measured every 6 months.
4. A blood sample will be taken from your arm (about 2 tablespoons). This will be done every 6 months. You will be asked not to eat or drink anything, except water for 12 hours before your appointment. A repeat blood sample (about 1 tablespoon) might be taken in some persons.
5. Oral glucose test: You had this test during screening for the study. This test will take about 2 and ½ hours. It will be done every 12 months. You will be asked to not eat or drink anything, except water, for 12 hours before your appointment. A blood sample, about 1 tablespoon, will be taken from your arm. You will then be asked to drink a glassful of flavored sugar water over 5 minutes. Another blood sample (about 1 tablespoon) will be taken from your arm at 30 and again at 120 minutes later.

Taking part in this study will require our knowing about any other medicines that you might be using or might wish to use. Some medicines are not preferred, but many others are all right. Should you need to start taking medicine, the study doctors will work closely with your own doctor to tell you which you may take. If you do not have your own doctor, the study doctors will direct you to medical care.

RISKS, STRESS, AND DISCOMFORT

There are several possible risks of the study that were described to you in detail in the previous Consent Form.

OTHER INFORMATION

Some of the test results will not be made known to you or the clinic staff or your own doctor. This is known as “masking”. Blood tests will be masked whereas weight and blood pressure will not be masked. If any of the test results are abnormal you will be notified.

(Institutional language as suggested by your IRB should be substituted for the following sections.)

Participation in this study is completely voluntary. You are free to take back your consent and stop taking part in this study at any time. You may ask any questions about the study at any time. Your current or future care will not be affected by your stopping the study. All study procedures will be free of charge. You will receive money (\$150 a year) and gifts for your time and effort.

Information that we get from you will be kept confidential to the extent allowed by law.

We will ask you to give us personal information such as address, phone numbers, and social security number, to help us reach you if we lose touch.

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

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

This study can be stopped or modified at any time.

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

Investigator's Signature

Date

PARTICIPANT'S STATEMENT:

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

Participant's Signature

Date

cc: Investigator

15.2 Information and Consent for Banking and Use of the Blood and Genetic Material (DNA)

<p>NAME OF INSTITUTION</p> <p>INFORMATION AND CONSENT FOR BANKING AND USE OF BLOOD AND GENETIC MATERIAL (DNA) OBTAINED IN THE DIABETES PREVENTION PROGRAM (DPP)</p>
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INVESTIGATORS

Name of Principal Investigator
Title, Affiliation, Phone Number

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

Name of Program Coordinator
Title, Affiliation, Phone Number

<p>24-Hour Emergency Telephone Number (List phone number(s) here)</p>
--

INVESTIGATOR'S STATEMENT:

PURPOSE AND BACKGROUND

You have been given the details concerning the Purpose and Background of the Diabetes Prevention Program (DPP) in the DPP Treatment Phase Consent Form. **This consent form is to provide you with additional information concerning storage (banking) and use of your blood and genetic material (DNA) for future studies. You gave consent previously for blood samples to be drawn for DNA and other testing. These samples were obtained during the DPP and currently are in storage. If the blood sample you already provided for DNA during the DPP was insufficient, you will be asked to provide another sample (about 1 tablespoon) for future genetic testing.**

We are studying the development of Type 2 diabetes, and heart and blood vessel (cardiovascular) diseases in the DPP. New blood factors, and new relationships between blood factors and diabetes or heart disease, may be found in the future. Likewise, we know diabetes and heart disease run in families, but we don't know what genes are involved in the development of these diseases. Laboratory methods are available that allow tests of inherited factors called genes. By studying the DNA in your blood sample, researchers might be able to identify the gene(s) that carry the trait(s) or risk factors for problems such as Type 2 diabetes, heart disease and related conditions (high cholesterol, etc). If we do identify the specific genes, in the future we may be able to develop better diagnostic tools and treatments for these diseases.

You are being asked to participate in a blood and genetic material bank and for permission to use your blood and genetic material in future studies because you are a participant in the Diabetes Prevention

Program, and are at high risk of developing diabetes or you have developed diabetes. Approximately 3800 DPP participants nationwide will be asked to participate in the blood and genetic bank and in future blood factor and genetic studies.

BENEFITS

There will be no direct benefit to you as a result of the research performed with your blood or genetic material. The tests that will be done will not be diagnostic (useful for finding medical problems). Therefore, at this time we do not plan to provide results of any blood or genetic testing to you.

The specific test(s) to be done on the blood samples has not been established at this time, and the laboratory that will perform the testing has not yet been identified. We expect that our studies of blood and genetic factors involved in diabetes, cardiovascular disease, and related conditions (such as high cholesterol) will take many years to complete. We may never, in fact, identify the specific factors or genetic material responsible for these conditions.

You will not receive any money for permission to use your blood samples and genetic material. All study procedures are free of charge.

PROCEDURES

In addition to the DPP procedures about which you have already been told and to which you have already agreed, we are asking you to review the information in this consent form concerning use of your blood and genetic material in future studies.

If the blood sample you already provided for DNA during the DPP was not sufficient, you will be asked to provide another sample. About 2 tablespoons of blood will be drawn from a vein in your arm. The blood will be stored for future blood and genetic testing. If your previous sample was adequate, you will not have more blood drawn, but you are asked to tell us about how to use these samples.

Your samples would be used only for obtaining information about blood factors and genes for diabetes, cardiovascular disease and related conditions.

RISKS, STRESS, AND DISCOMFORT

This research will not affect your medical care. Therefore, you, your family, or your doctor will not receive results of these studies, and the results will not become a part of your medical record. The study investigators will make every effort to maintain confidentiality by labeling your samples with a number rather than with your name or other personal information. However, in the unusual circumstance that your test results are unintentionally made known to a third party, or revealed to you because they are important to your medical care, this information could affect your ability to be insured and employed, and your future plans for children or your family relationships. Additionally, having information about your genes may reveal information regarding health risks to other members of your family who are now living or not yet born. If this should occur, the study will assist you in identifying genetic counseling resources but will not pay for genetic counseling if it is necessary.

Risks associated with drawing blood from your arm include pain, bruising, lightheadedness and, on rare occasion, infection. Whenever possible, blood for the research discussed above will be drawn at the same time as samples for other DPP tests. If it is not possible, an additional needle stick will be required.

By agreeing to donate your blood to the DPP researchers, you may forfeit sharing in any financial gain, which may be obtained in the event that your donated material results in the development of a product with commercial application.

(Institutional language as suggested by your IRB should be substituted for the following sections.)

CONFIDENTIALITY

Information that we receive from you will be kept confidential to the extent allowed by law. Your blood and genetic material will be kept in storage indefinitely or until the sample is no longer viable (living). A code number identifies samples and the link between the code and your personal information is stored in a secure location at the insert your institution name. Thus, your blood and DNA will not be directly identified with your name. Your samples would be released to a DPP investigator (or other investigator authorized by the DPP) only after determination of the scientific usefulness of a proposed study.

OTHER

Participation in the blood and genetic material bank and future blood and genetic studies is entirely voluntary. You are free to take back your consent at any time and you may request that your sample be permanently removed from the blood and DNA bank. If you decide that you do not want to participate in the banking part of the DPP, you may still continue participation in the DPP. You may ask any questions about the study at any time. Your stopping the study will not affect your current or future care.

To request that your sample be permanently removed from the blood and DNA bank, contact: (insert PI name, address, phone and fax numbers).

We will ask you to give us personal information such as address, phone numbers, and social security number, to help us reach you if we lose touch.

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

This study can be stopped or modified at any time.

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

Investigator's Signature

Date

PARTICIPANT'S STATEMENT:

The study described above has been explained to me. I understand that I am consenting to the blood and genetic storage part of DPP only as checked below. If I have any questions, I know that I can contact one of the investigators listed on the first page.

_____ Participant's Signature

_____ Date

I agree to have my blood drawn (about 2 tablespoons) if determined to be necessary by the investigators:

_____ YES

_____ NO

_____ INITIALS

I give permission for my blood to be stored in a central bank, at a banking site to be determined, for future use by the study investigators in studies of diabetes:

_____ YES

_____ NO

_____ INITIALS

I give permission for my blood to be examined for inherited factors (genes) in the development of diabetes:

_____ YES

_____ NO

_____ INITIALS

I give permission for the results of studies on my blood to be used to develop improved methods for diagnosis, prevention, and treatment of diabetes:

_____ YES

_____ NO

_____ INITIALS

I give permission for the results of studies on my blood to be used for research about other health problems (for example, heart disease or related conditions such as high cholesterol):

_____ YES

_____ NO

_____ INITIALS

I give permission for my blood to be examined for inherited factors (genes) in the development of non-diabetic health problems (for example, heart disease or related conditions such as high cholesterol):

_____ YES

_____ NO

_____ INITIALS

A representative of the investigators associated with this study may contact me in the future to take part in more research.

_____ YES

_____ NO

_____ INITIALS

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

_____ YES

_____ NO My specimens MUST be destroyed once you have been notified of my death.

_____ INITIALS

At the present time, we think that the tests for inherited factors (genes) will be for research purposes only, that is, they will not be useful to you or your health care provider. However, it is possible in the future that the DNA tests will find some results that will be useful to you, your family, and your health care provider. One result could be that there is a gene or genes in you and some members of your family that raises or lowers the risk for diabetes or heart disease. Such a result might take many years to be found. You may want to know the result. The study will assist you in identifying genetic counseling resources but will not pay for genetic counseling if it is necessary.

In the event that a useful result is found, I would like you to:

Tell me of the results Initials: _____

If I am not alive, tell the results to the relative(s) below: Initials: _____

Name of relative: _____ Relationship _____

Name of relative: _____ Relationship _____

Name of relative: _____ Relationship _____

Do not notify me or my family of the results Initials: _____

Other: Initials: _____

15.3 Information and Amendment for the Completion of the Masked Treatment Phase for Former Troglitazone Participants

<p>NAME OF INSTITUTION</p> <p>INFORMATION AND AMENDMENT FOR THE COMPLETION OF THE MASKED TREATMENT PHASE FOR FORMER TROGLITAZONE PARTICIPANTS DIABETES PREVENTION PROGRAM (DPP)</p>
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INVESTIGATORS

Name of Principal Investigator
Title, Affiliation, Phone Number

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

Name of Program Coordinator
Title, Affiliation, Phone Number

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

<p>24-Hour Emergency Telephone Number (List phone number(s) here)</p>
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INVESTIGATOR'S STATEMENT:

PURPOSE AND BACKGROUND

This research study is called the Diabetes Prevention Program (DPP). You have been given the details concerning the Purpose, Background, Procedures, Risks and Benefits, and Costs of this study in a previous Consent Form. **This amendment is to provide you with information regarding the completion of the treatment phase of the DPP.**

The masked treatment phase of DPP will be completed earlier than planned. Masked treatment is when volunteers in the study don't know which medication they were taking. You already know that you were treated with troglitazone for a relatively brief period of time in the DPP before it was discontinued in June, 1998.

We have reported the main study results to you. This consent form will explain what we will ask you to do in the next few months.

You will be asked to schedule your individual debriefing visit from August through October. At your debriefing visit, you will be given your individual results collected during your participation in DPP.

PROCEDURES

You will be asked to continue to visit your case manager every six months as before, until all study participants have completed their individual debriefing visit, anticipated to be sometime in late 2001.

Procedures to be carried out at one of your next visits include the following:

1. Blood flow and blood vessel wall thickness may be measured by ultrasound in your neck (carotid vessels). This will take about 30 minutes. If you did not have this test at the start of the study, you may not be asked to repeat it.
2. Body measurements: Your height will be measured. This will take about 2 minutes.
3. A urine sample will be collected.

BENEFITS

During your participation in the DPP, you have received extensive medical examinations. We will continue to tell you if we find any problem. If you have not done so already, you will be asked to sign a written permission to release medical information to your doctor. As in the past, your health will be closely monitored during this final phase of the study. Problems such as diabetes might be found and treated sooner than if you were not in the study. This might improve your health.

At your debriefing visit, you will be given a summary of the results obtained during the time you participated in the study. These results may be beneficial to you in planning for your future health care.

RISKS, STRESS, AND DISCOMFORT

There are several possible risks of the study that were described to you previously in the Treatment Consent Form. There are no additional risks during this period. The carotid ultrasound study uses sound waves to measure the thickness of blood vessel walls. It is a commonly used diagnostic test that is non-invasive and painless.

OTHER INFORMATION

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

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

Information that we get from you will be kept confidential to the extent allowed by law.

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

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

This study can be stopped or modified at any time.

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

PARTICIPANT'S STATEMENT:

The study described above has been explained to me. I understand that I am consenting to continue to participate in DPP during the end of the treatment phase. If I have any questions, I know that I can contact one of the investigators listed on the first page. I have been given a copy of this consent form.

Participant's Signature Date

Person obtaining consent Date

Investigator's Signature Date

cc: Investigator
Participant

15.4 Consent Forms for Bridge Period

<p>NAME OF INSTITUTION</p> <p>INFORMATION AND ADDENDUM FOR THE COMPLETION OF THE TREATMENT PHASE OF THE DIABETES PREVENTION PROGRAM (DPP) FOR FORMER TROGLITAZONE PARTICIPANTS</p>
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INVESTIGATORS

Name of Principal Investigator

Title, Affiliation, Phone Number

Name of Co-Investigator(s)

Title, Affiliation, Phone Number

Name of Program Coordinator

Title, Affiliation, Phone Number

Name of Other Staff (optional as per IRB)

Title, Affiliation, Phone Number

<p>24-Hour Emergency Telephone Number</p>
--

<p>(List phone number(s) here)</p>

INVESTIGATOR'S STATEMENT:

PURPOSE AND BACKGROUND

This research study is called the Diabetes Prevention Program (DPP). You have been given the details concerning the Purpose and Background of this study in a previous Consent Form. **This addendum is to provide you with information regarding the completion of the treatment phase of the DPP and the start of Group Lifestyle Sessions.**

Because of positive results, the masked phase of the DPP ended early. In August 2001, the results were announced, showing that the risk of Type 2 diabetes was reduced by 58% in the lifestyle arm of the study, 31% in the metformin arm and 24% in the troglitazone arm. We are now approaching the completion of the treatment phase of the DPP. This period will begin in January 2002. Group Lifestyle Sessions will be offered to all DPP participants during this time. You are being invited to take part in these sessions as well as to continue your participation in the DPP.

BENEFITS

During your participation in the DPP, you will continue to receive medical testing.. We will continue to tell you if we find any problem. If you have not done so already, you will be asked to sign a written permission to release medical information to your doctor. As in the past, your health will be closely monitored during this final phase of the study. Problems such as diabetes might be found and treated sooner than if you were not in the study. This might improve your health.

Intensive lifestyle intervention was shown to be very effective in reducing the onset of diabetes. Participation in a group lifestyle intervention may help to reduce your risk of developing diabetes.

PROCEDURES

All study participants will be invited to participate in a 16-lesson lifestyle change program similar in content to the curriculum that was included in the DPP intensive lifestyle intervention. The program will be offered in two parts consisting of 8 lessons each and will occur in a group class rather than an individual format. A trained professional will lead the group meetings. Each lesson will be offered several different times per week in order to allow you to attend at a time that is convenient for you. Classes will begin in January and be completed by mid-2002 and will last 1-2 hours per session.

The exercise and diet goals of the program are walking 2 1/2 hours (150 minutes) per week (or similar activity) and using healthy eating habits to lose 7% of your body weight. You will be weighed at the classes. You will also be given materials to help track your fat and calorie intake and your activity. After completion of the first 8 lessons, you will be invited to sign up for the second half of the program (the last 8 lessons). The classes will help you learn more about making healthy food choices and increasing activity. They will also allow you to talk about concerns you have in changing your lifestyle habits. If you do not attend a lifestyle class, handouts from that lesson will be mailed to you.

Although the group lifestyle sessions will be offered to ALL DPP participants, you may choose not to take part in these sessions and still remain a participant in the DPP. In addition to the group lifestyle sessions, you will be asked to continue to attend mid-year and annual assessments. In addition, participants who have developed diabetes during the study will be asked to attend an interim visit for a blood glucose check between the annual and mid-year visits.

Procedures to be carried out at the clinic visits:

Mid-year visit: (Approximately 45 Minutes)

1. Blood pressure will be measured in your arm. This will take about 10 minutes
2. Body Measurement: Your weight will be measured.
3. A blood sample (about 1 tablespoon) for fasting glucose will be taken from your arm. You will be asked not to eat or drink anything, except water for 12 hours before your appointment. A repeat blood sample (about 1 tablespoon) may be necessary for some persons.

Annual Visit: (Approximately 1.5-3.5 hours)

1. **[Clinics should insert whether they will do a physical examination - it is now optional]**

[if yes - insert: A physical examination will be completed. This will take about ½ hour.]

2. Electrocardiogram (ECG) will be performed. This will take about ½ hour.
3. Blood pressure will be measured in your arm. This will take about 10 minutes.
4. Body measurements: Your weight will be measured.
5. You may be asked to complete some questionnaires regarding your health.
6. Oral glucose test: This test will take about 2 and ½ hours. You will be asked to not eat or drink anything, except water, for 12 hours before your appointment. A blood sample will be taken from your arm. You will then be asked to drink a glassful of flavored sugar water over 5 minutes. Another blood sample) will be taken from your arm at 30 and again at 120 minutes. The total amount of blood drawn for this test is approximately 1 tablespoon. A repeat oral glucose test may be necessary for some persons. People with diabetes will not be asked to complete the oral glucose test, but will have a fasting blood glucose drawn.
7. Additional blood samples will be taken from your arm at the same time that you are having blood drawn for the oral glucose test, for lipids (blood fats), clotting factors, and other blood tests related to diabetes and heart disease. The total blood drawn for all these tests will be 3-4 tablespoons. A repeat blood sample (about 1 tablespoon) might be necessary in some persons.

Interim Blood Glucose Check for Participants with Diabetes (Approximately 30 minutes)

1. A blood sample (about 1 tablespoon) for fasting glucose will be taken from your arm. You will be asked not to eat or drink anything, except water for 12 hours before your appointment.

RISKS, STRESS, AND DISCOMFORT

There are several possible risks of the study that were described to you previously in the Treatment Consent Form. There are no additional risks during this end of study period.

Risks associated with exercise include fatigue, muscle soreness, and injury such as sprained ankles or pulled muscles. Risks are reduced by proper warm-up and cool-down periods. There may be additional risk of heart problems for those who have a chronic disease or experience symptoms with exercise, although this risk is extremely minimal considering the intensity of the recommended exercise, i.e., walking. You will need to contact your primary care provider for his/her permission for you to take part in the physical activity segment of the healthy lifestyle program. If you do not receive signed permission from your primary care provider, you will not be able to take part in the exercise segment of the program.

Risks associated with drawing blood from your arm include pain, bruising, lightheadedness and on rare occasion, infection.

CONFIDENTIALITY

Information that we receive from you will be kept confidential to the extent allowed by law. Information we collect about you will be put into a research record that will be sent to a central data site. A code number and initials identify your records. The link between the code and your name is stored in a secure location at the insert your institution name. Thus, your central research record will not be directly identified with your name. Anonymous information may be released to a DPP investigator (or other investigator authorized by the DPP) only after determination of the scientific usefulness of a proposed study.

OTHER INFORMATION

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

(Institutional language as suggested by your IRB should be substituted for the following sections.)

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

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

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

This study can be stopped or modified at any time.

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

PARTICIPANT'S STATEMENT:

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

Participant's Signature	Time	Date
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Investigator's Signature	Date
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Person obtaining consent	Date
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cc: Investigator
Participant