

**PROTOCOL**  
for the  
**DIABETES PREVENTION PROGRAM**  
**(DPP)**

IND # 49,782

Diabetes Prevention Program Research Group

May 18, 2001

Version 4.4

Distributed by the Coordinating Center

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**SUMMARY**  
**of**  
**DIABETES PREVENTION PROGRAM**  
**PROTOCOL MODIFICATIONS**

IND # 49,782

Diabetes Prevention Program Research Group

May 18, 2001

Version 4.4

Version 1.0 December 5, 1995

Version 2.0 April 15, 1996

Version 2.1 July 31, 1996

Version 2.2 November 21, 1996

Version 3.0 June 24, 1997

Version 3.1 November 7, 1997

Version 3.2 January 22, 1998

Version 4.0 June 3, 1998

Version 4.1 July 20, 2000

Version 4.2 May 9, 2001

Version 4.3 May 18, 2001

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# PREFACE

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

## VERSION 1.0

Protocol Version 1.0 (dated December 5, 1995) was developed by the Steering Committee of the DPP Research Group.

## VERSION 2.0

The release of Protocol Version 2.0 (dated April 15, 1996) followed modifications by the Steering Committee of the DPP Research Group prior to initiation of participant recruitment. Version 2.0 includes the following major changes to Version 1.0:

### **1. Data Monitoring Board (DMB) Recommendations**

a. *Rechallenge Following Lactic Acidosis:* Considering the potential clinical severity of lactic acidosis, the DPP-DMB recommended that participants assigned to pharmacological treatment who develop lactic acidosis have their coded medication permanently discontinued. The DPP Steering Committee approved the recommendation.

Modifications:

Section 7.4.4; Paragraph I: Eliminated the sentence “Reinstitution of MP or MA may be considered if another cause of lactic acidosis is identified and resolved”. Changed the prior sentence to “...coded metformin (MP or MA) will be discontinued immediately and not restarted.”

b. *Participant Burden:* Concerned about participant burden and potential retention problems with DPP participants, the DPP-DMB recommended decreasing the amount of information collected at the annual follow-up visits.

Modifications:

Section 7.6.2.2: The availability of social support section of the self-administered Retention and Treatment Monitoring Measures (Form Q06) has been eliminated. The DPP-Specific Support Measure has been split into two self-administered questionnaires: a baseline measure (Form Q09) and follow-up visit measures (Form Q10).

Section 12: The Retention and Treatment Monitoring Measures (Form Q06) will be administered at the mid-year standard follow-up visit (end-months 6, 18, 30, ...). The DPP-Specific Support Measure - Follow-up Visits (Form Q10) will be administered at major follow-up visits (end-months 12, 24, ...).

### **2. Screening Procedures**

Modifications:

Section 5.2.3; Paragraph A.4.a: Added the Central Biochemistry Laboratory (CBL) upper limit for serum AST and ALT eligibility.

Section 5.2.3, Paragraph A.7.a-c: Added the CBL ranges for electrolyte or acid-base abnormality determination.

Section 5.2.3; Paragraph A.8.b: Added “/mL” to “Granulocytes < 1500”.

Section 5.2.3; Paragraph A.3: TSH will not be assessed in the setting of uncontrolled hypercholesterolemia. The text “(3) uncontrolled hypercholesterolemia. (Potential participants who are optimally treated are eligible to restart the screening process).” was eliminated.

Sections 6.2.3, 9.1.1 and 12: Screening step 3, step 4 and step 5 have been renamed to screening step 3-Start, step 3-End and step 4, respectively.

Section 6.2.3 and Section 12.1: Carotid ultrasound will be performed prior to randomization. The sentence “Participants will be scheduled for carotid ultrasound evaluation before or at the randomization visit (Step 4) prior to actual randomization” was added to the paragraph “Run-In Follow-up”. The sentence “Participants will be scheduled for carotid ultrasound evaluation within four weeks of the randomization visit.” was eliminated from the last paragraph. Appropriate changes have been made to the Section 12.1 table.

### **3. Intensive Lifestyle Intervention**

All participants randomized to the intensive lifestyle intervention group must have a symptom-limited maximal exercise tolerance test (ETT) if they have specific characteristics (see Section 7.5.7; Paragraph A.1). A symptom-limited maximal ETT performed prior to enrollment in the DPP is acceptable if performed within 6 months of initiating the exercise program. The DPP clinic must conduct a symptom-limited maximal ETT prior to initiating the exercise program, otherwise.

#### **Modifications:**

Section 7.5.7; Paragraph A.1: Changed the first sentence “Participants randomized to the Lifestyle Intervention Group will have a symptom-limited maximal exercise tolerance test within 6 months prior to initiation of any exercise program, if they have:” to “Participants randomized to the intensive lifestyle group must have had a symptom-limited maximal exercise tolerance test within 6 months prior to initiation of any exercise program, or will have a symptom-limited maximal exercise tolerance test prior to initiation of any exercise program, if they have:”.

### **4. Pharmacological Treatment**

#### **Modifications:**

Section 3.7.1: Changed “Metformin” in the fifth sentence to “Phenformin”.

Section 5.3: Added a final sentence: “Sulfonylureas, even in the relatively low doses that have been used in past studies of prevention, are associated with hypoglycemia. Because of this potential side-effect, sulfonylureas were not considered further for use in the DPP.”

Section 7.4.1.1: Paragraph F: Deleted last sentence and replaced with “This study will complete two years of treatment in April 1996.”

Paragraph G was replaced: Original paragraph “During ongoing preliminary evaluation of microscopic histopathology of a two year toxicology study in B6C3F1 mice, a higher than expected number of vascular tumors, initially diagnosed as hemangiosarcomas, was identified. This increase occurred at blood levels which were 10-15 times higher than those observed in patients treated with 400 mg/day, the proposed dose of troglitazone in the DPP. These tumors were identified late in the second year of a two-year mouse bioassay. Hemangiosarcomas were also observed spontaneously in control mice. No increased incidence of tumors compared to controls have been observed in animals treated with lower doses (blood levels 5 times those proposed for the DPP). A long-term study in rats which is also in progress has not shown similar findings. No sarcomas, or vascular tumors have been reported in any human study to date.

Paragraph G: New paragraph: “During ongoing preliminary evaluation of microscopic histopathology of a two year toxicology study in B6C3F1 mice, a higher than expected number of vascular tumors, initially diagnosed as hemangiosarcomas, was identified. This increase occurred at blood levels which were 13 times higher than those observed in patients treated with 400 mg/day, the proposed dose of troglitazone in the DPP. These tumors were identified late in the two-year rodent bioassay. Spontaneous hemangiosarcomas were also observed in control mice. No increased incidence of tumors compared to controls has been observed in mice treated with lower doses (blood levels 3-5 times those proposed for the DPP). A two year study of troglitazone in rats has not shown an increase in vascular tumors compared with placebo. No sarcomas, or vascular tumors have been reported in any human study to date.

Paragraph H: was eliminated

Section 7.4.1.2: Changed “(0.03 cases per 100,000 person years)” in the third paragraph to “(0.03 cases per 1,000 person years)”.

Section 7.4.4: Paragraph F: Changed “regress to <3.0 times normal.” in the second paragraph to “regress to <1.8 times normal.”

## 5. Outcomes

### Modifications:

Global Change: The DPP primary outcome is the development of diabetes according to World Health Organization criteria. These criteria do not distinguish between IDDM and NIDDM. Therefore, “NIDDM” was changed to “diabetes” whenever discussing the DPP primary outcome.

Section 4.2.2 and Section 12: C-reactive protein has been added as a CBL determination at screening step 4, end-months 6 and 12 and end of study. PAI-1 has been eliminated.

Section 5.4.2: To help maintain masking of outcome assessors to treatment group assignment in this partially masked design, the “Y” in the randomization number (i.e., participant number) was changed from the letter “P” for pharmacological treatment and “L” for intensive lifestyle intervention to a number.

Section 5.5.1: Section 7.5.4.5 ‘Outcome Assessment Following Pregnancy’ indicates that “Women who become pregnant during the DPP will have outcome assessment suspended until 6-8 weeks following delivery. This outcome measure following pregnancy will always be an OGTT.” To emphasize this point, the fifth sentence in Section 5.5.1 was changed from “When a participant has been in a ‘time-out’, such as for a concomitant disease...” to “When a participant has been in a ‘time-out’ (other than pregnancy), such as for a concomitant disease...”.

Section 12.2; Outcomes, Safety Testing, and Measures for Adherence: Steering Committee Priority 2 has been eliminated. The following priority 1 CBL measurements have been augmented with an end-month 6 determination: HbA<sub>1c</sub>, LDL-ApoB, LDL-CH and saved specimens.

Section 12.2; Physical Activity: The Low Level Physical Activity Recall (Form Q04) has been changed from administration every 6 months (end-months 6, 12, 18, ...) to end-months 6 and 12 and annually, thereafter.

## 6. Adverse Events

The data forms for DPP include two adverse event forms: Adverse Event Report (Form E01) and Serious Adverse Event Report (Form E02). If a serious adverse event occurs, both Forms E01 and E02 must be faxed to the CoC. In addition, unmasking the pharmacological treatment group assignment for a serious adverse event will be accomplished by contacting the drug distribution center.

Modifications:

Section 8.2: Changed the end of the last sentence to "...DPP Adverse Event Report (Form E01)."

Section 8.2.1: Changed the sentence in the second paragraph from "...fax the completed DPP Adverse Event Report (302-881-8752)" to "fax (301-881-8752) the completed Adverse Event Report (E01) and the 'initial' Serious Adverse Event Report (E02)"

Section 8.2.1: Changed the sentence in the third paragraph from "...will open the medication assignment code..." to "...will contact the drug distribution center for pharmacological treatment assignment unmasking..."

**7. Data Forms**

The DPP data forms have been modified since Protocol Version 1.0. Section 9.1 has been changed to reflect these modifications. Data forms added, eliminated, separated or combined since Version 1.0 are summarized below:

Data Forms Added:

Interval History Questionnaire (Form Q08)  
Mortality Event Report (Form E06)

Data Forms Eliminated:

Availability of Social Support  
Intercurrent Illness

Data Forms Separated:

Lifestyle Contact - Telephone (Form L02)  
Lifestyle Contact - In Person (Form L03)  
  
DPP-Specific Support Measure - Baseline Visit (Form Q09)  
DPP-Specific Support Measure - Follow-up Visit (Form Q10)  
  
Pregnancy Confirmation Report (Form E04)  
Pregnancy Outcome Report (Form E05)

Data Forms Combined:

Retention and Treatment Monitoring (Form Q06) combined:  
- Life Events Index  
- Social Provisions Scale  
- Family Household Assessment

**8. Timeline**

The DPP timeline was modified to reflect the current scheduling plan (see Section 13 outline).

**9. Informed Consent Prototypes**

Step 3 Consent Form, Page 5, #9 AND Treatment Consent Form, Page 4, #9:

Changed: "genes that might be related to Type 2 Diabetes" to "genes that might be related to Type 2 Diabetes and related conditions."

Step 3 Consent Form, Page 8, line 5 AND Treatment Consent Form, Page 6, line 7:

Changed: "genes that are important in Type 2 Diabetes" to "genes that are important in Type 2 Diabetes and related conditions."

Step 3 Consent Form, Page 3, Group A, line 4 AND Treatment Consent Form, Page 2, Group A, line 4:

Changed: "every week for 8 weeks, then every other week for 16 weeks" to "16 sessions over a 24 week period."

Step 3 Consent Form, Page 7, first paragraph, add “Similarly, although blood vessel tumors (angiosarcomas) have been seen in long-term mouse toxicity studies, similar findings have not been confirmed in rat studies, nor have blood vessel tumors been seen in human studies, and the significance of this to humans is uncertain.”

Step 3 Consent Form, Page 8, paragraph 6 AND Treatment Consent Form, Page 6, paragraph 6:  
Delete: “If you are hurt as a direct result of the study, medical treatment will be done at no cost within the limits of our compensation plan. Beyond this, treatment will be at your expense or that of your insurance carrier.” and replace with the statement “[Each center should incorporate a statement to address medical liability.]”

## 10. Editorial Changes

Global Changes:

The following terminology was used in Protocol Version 2.0:

- 4 treatments (intensive lifestyle intervention, metformin, troglitazone, double-placebo)
- 3 interventions (intensive lifestyle intervention, metformin, troglitazone)
- 3 pharmacological treatments (metformin, troglitazone, double-placebo)

Changed “arm” to “group”; “basic care” to “standard lifestyle recommendations”; “endpoint” to “outcome”; “patient” or “subject” to “participant”; “Study Group” to “DPP Research Group”

Specific Changes:

Section 4.2.2: Changed “Ankle Blood Pressure” to “Ankle/Arm Systolic Blood Pressure”

Section 7.4.4: Changed “febril” to “febrile”

## VERSION 2.1

Updates to Version 2.0 (i.e., Version 2.1, dated July 31, 1996) followed modifications by the Steering Committee of the DPP Research Group soon after the initiation of participant recruitment. Version 2.1 includes the following major changes to Version 2.0:

### 1. Participation Criteria

Modifications:

Section 5.2.3; paragraph A.7.a-c: Changed the item from “Electrolyte or acid-base abnormality” to “Electrolyte abnormality”. Eliminated letters a. “Serum sodium <136 or >145 mmol/L”, and c. “Serum bicarbonate <24 or >31 mmol/L”. Changed serum potassium exclusionary ranges from “<3.7 or >5.2 mmol/L” to “<3.2 or >5.5 mmol/L”. Added a final sentence: *Serum sodium and bicarbonate levels are reported to the clinical centers during screening to alert investigators to participants with electrolyte or acid-base levels outside expected ranges.*

### 2. Level of Masking

Modifications:

Section 5.6.2; second sentence: Changed “Secondary outcome data measured centrally will remain masked to the investigators and to the participants during the study.” to “Plasma lipid levels and HbA1c results measured centrally will remain masked to the investigators and to the participants during the study.”

### 3. Outcomes

Modifications:

Section 12.1; Eligibility Screening and Baseline Measurements: The requirement for serum pregnancy test (HCG, determined locally) has been moved from Screening Step 2, OGTT to Step 4, Baseline/Randomization, to be determined before randomization (for eligibility).

#### **4. Data Processing**

Modifications:

Section 9.1.3; Other Forms: Form P04 - Adiposity Substudy Worksheet and Form P05 - Re-screening OGTT Procedure were added to the list of procedure forms after Form P03 - Carotid Ultrasound Worksheet.

#### **5. Informed Consent Prototypes**

Modifications:

Step 2 Consent Form, Page 2, number 2.: Added “You will also be asked to give a urine sample.”

Step 3 Consent Form, Page 2, Next to last paragraph: Eliminated the last sentence “You will be asked to give a urine sample.”

Treatment Consent Form, Page 6: Added a new 6th paragraph “We will ask you to give us personal information such as address, phone numbers, and social security number, to help us to reach you if we lose touch.”

#### **6. Editorial Change**

Modifications:

Page 7-5, 4th paragraph, 2nd sentence: Changed “...the proposed of dose of troglitazone...” to “... the proposed dose of troglitazone.”

The following change was made to Protocol Version 2.0, but not noted in the Preface at that time:

Section 12.2; Outcomes, Safety Testing, and Measures for Adherence: The following priority 1 CBL measurements were augmented with annual determinations: LDL particle size; LDL - ApoB; LDL - CH. LDL Particle size and CRP were also augmented with an end-month 6 determination.

### **VERSION 2.2**

Updates to Version 2.1 (i.e., Version 2.2, dated November 21, 1996) followed modifications by the Steering Committee of the DPP Research Group. Version 2.2 includes the following major changes to Version 2.1:

#### **1. Participation Criteria**

Modifications:

Section 5.2.3; paragraph A.8.a: Changed hematocrit exclusionary ranges from “<39% in men or <35% in women” to “<36.0% in men or <33.0% in women.”

Section 7.4.4; paragraph E; second sentence: Changed “If anemia (defined as a hematocrit <39% in men and <35% in women). . .” to “If anemia (defined as a hematocrit <36.0% in men and <33.0% in women). . .” Added “or if the hematocrit decreases by 4 or more points from the level at study entry (e.g., from 44% to 40%)” after the comma after “develop.” The updated second sentence reads as “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 CBC and differential will be repeated within one month.”

#### **2. Baseline Tests**

Modifications:

Section 12.1; Eligibility Screening and Baseline Measurements: The requirement for “plasma glucose” has been removed from Step 4, Baseline/Randomization. The fasting plasma glucose measured at Step 2 is now the baseline measure of fasting plasma glucose.

## VERSION 2.3

Updates to Version 2.2 (i.e., Version 2.3, dated March 27, 1997) followed modifications by the Steering Committee of the DPP Research Group. Version 2.3 includes the following major changes to Version 2.2:

### **1. Participation Criteria**

Modifications:

Section 5.2.2; paragraph E.1: Added a sentence: Because Asian-Americans develop diabetes and IGT at a BMI that is lower than the BMI of the general U.S. population with IGT and NIDDM, the BMI criteria for eligibility for Asian Americans will be 22 kg/m<sup>2</sup> or greater.

### **2. Pharmacological Treatments**

Modifications:

Section 7.4.1.1, first sentence: Changed “Troglitazone is an orally active insulin sensitizer of the thiazolidinedione class currently being co-developed by Parke-Davis...” to “Troglitazone is an orally **administered** insulin sensitizer of the thiazolidinedione class that was developed by Parke-Davis...”.

Section 7.4.1.1, third paragraph, first sentence: Changed “...and is currently under study in the United States (Parke-Davis) and Europe (Glaxo).” to “... and was approved for use in the United States in 1997 in selected subgroups of patients with NIDDM.”

Section 7.4.1.1, Table 7-1 was replaced.

### **3. Outcomes**

Modifications

Section 12.2; Lipids: The Derived Beta Quant, and Full Beta Quant in the case of elevated triglyceride, have been added at month-6.

Section 12.2; Safety Testing: A footnote has been added to refer to CBC: “In the pharmacological treatment groups.”

### **4. Bibliography**

Addition to list of Publications:

Wei LJ, Lachin JM. Properties of Urn Randomization in Clinical Trials. Controlled Clinical Trials, 9:345-364, 1988.

Modification:

Citation: Edelstein, et.al: updated.

### **5. Informed Consent Prototypes**

Modifications:

Treatment Consent Form, Page 3, number 4; first and second sentences: Changed “troglitazone, a medicine that is now being studied in people with diabetes. It has not yet had final approval for use in treating patients by the Food and Drug Administration (FDA).” to “troglitazone, a medicine used for lowering blood sugar.”

## VERSION 3.0

Updates to Version 2.3 (i.e., Version 3.0, dated June 24, 1997) followed modifications based on the ADA change to the criteria for diabetes that affected the definitions of the DPP eligibility and primary outcome criteria. The eligibility criteria for DPP will change to fasting glucose levels of 95 to 125 mg/dL. Similarly, the fasting glucose outcome will change to 126 mg/dL and greater as opposed to 140 mg/dL and greater. The 2

hour values for both eligibility and the primary outcome will remain the same. Version 3.0 includes the following major changes to Version 2.3.

### **1. Glucose Eligibility Criteria**

Modifications:

The following sections have been updated with the new glucose eligibility criteria:

- Executive Summary, fifth paragraph.
- Section 5.1, first paragraph.
- Section 5.2.2, paragraph D.1 and D.2.
- Section 6.2.3, fourth paragraph.
- Section 10.1, second paragraph

### **2. Primary Outcome Criteria**

Modifications:

The following sections have been updated with the new ADA definition of diabetes:

- Executive Summary, seventh paragraph.
- Section 4.1, second and third paragraph.
- Section 5.2.3, paragraph C.1a and C.1c.
- Section 5.5.1, first paragraph.
- Section 7.5.6.2, first paragraph.

### **3. Changed WHO criteria to ADA criteria**

Modifications:

The following sections have been modified:

- Executive Summary, seventh paragraph.
- Section 4.1, first paragraph.
- Section 6.2.3, fourth paragraph.
- Section 7.5.4.5, first paragraph.
- Section 7.5.6.1, first paragraph.

Deletion:

Section 10.1: Deleted "...as defined by WHO criteria." from the first sentence.

### **4. Bibliography**

Addition to list of Publications:

American Diabetes Association. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care, 20 (7), 1997.

### **5. Informed Consent Prototypes**

Modifications:

Section 15.3: Step 3 Consent Form, page 15-9, number 4: Changed "troglitazone, a medicine that is now being studied in people with diabetes. It has not yet had final approval for use in treating patients by the Food and Drug Administration (FDA)." to "troglitazone, a medicine used for lowering blood sugar."

Section 15.3: Step 3 Consent Form, Page 15-13, first paragraph: Changed "Troglitazone: This medicine is being studied in the U.S., Canada, Europe, and Japan." to "Troglitazone: This medicine is used for lowering blood sugar."

The four consent forms are now included in the protocol as Chapter 15 instead of as attachments.

### **5. Data Forms**

Additions:

The following data forms have been added. Section 9.1 has been modified to reflect these additions.

Medication Adherence Interview (F05)  
CHD Risk Status Report (R04)  
Oral Contraceptive Pill Report (R05)

## **6. Study Administration**

Addition:

Section 11.1.2: Coordinating Center; first sentence of second paragraph. Carotid Ultrasound Reading Center (CURC) was added to the list of central resources.

## **7. Video Presentation**

There is only one DPP video and it is shown during Screening Step 2. The following sections have been modified.

Modification:

Section 6.2.1: Informed Consent Policy; fourth sentence of third paragraph: Changed “At two points, the participant views a slide/video presentation during which DPP investigators are present to answer questions.” to “The participant views a video presentation during which DPP investigators are present to answer any questions.”

Section 6.2.3: Initial Contact (Step 1); last sentence of second paragraph: Changed “Persons with results in the target range are given more information about the DPP, including a slide/video presentation, and those who give informed consent will continue through the screening process and are scheduled for an oral glucose tolerance test (OGTT).” to “Persons with results in the target range are given more information about the DPP and those who give informed consent will continue through the screening process and are scheduled for an oral glucose tolerance test (OGTT).”

Section 6.2.3: Initiate Run-in (Step 3 - Start); second to last sentence: Changed “During this time, additional information about the DPP is provided, including a slide/video presentation, and a volunteer understanding questionnaire confirms understanding.” to “During this time, additional information about the DPP is provided and a volunteer understanding questionnaire is administered to confirm understanding.”

Addition:

Section 6.2.3: Oral Glucose Tolerance Test - OGTT (Step 2); first paragraph: Add “A video presentation provides additional information about the study.”

## **8. Volunteer Understanding Questionnaire**

There is only one Volunteer Understanding Questionnaire administered during Screening Step 3. The following section has been modified.

Deletion:

Section 6.2.3: Run-in Follow-up (Step 3 - End); second paragraph: Deleted “A second volunteer understanding questionnaire is administered to confirm understanding.”

## **9. Editorial Change**

Deletion:

Section 7.5.6.2: Interim Visits For Symptoms; second to last sentence of first paragraph: Deleted “... similarly to the 6 month visits.”

## **VERSION 3.1**

Updates to version 3.0 (i.e., Version 3.1, dated November 7, 1997) include two major modifications. The first set of modifications, based on data presented in the troglitazone package insert following FDA approval,

involves the blood hormone level of estrogen in women taking oral contraceptive pills. The second set of modifications, based on the October 1997 change to the troglitazone package insert, increases the collection and monitoring of liver function tests. Version 3.1 includes the following major changes to Version 3.0:

### **1. Exclusion Criteria**

Modification:

Section 5.2.3, paragraph 4a, first sentence: Changed from “Self-reported chronic hepatitis or cirrhosis, or serum AST or ALT elevated by the following criteria:” to “Self-reported idiosyncratic drug reactions, chronic hepatitis or cirrhosis, or serum AST or ALT elevated by the following criteria:”

### **2. Troglitazone**

Addition:

Section 7.4.1.1: Inserted new fifth and sixth paragraphs: “During the first 8 months of post-marketing surveillance of troglitazone use, 35 world-wide cases of liver function abnormalities, 32 of which were mild and reversible, were reported. Two cases of liver failure occurred among 650,000 patients using troglitazone for variable periods. The two cases occurred in patients who developed severe liver function test abnormalities but were continued on troglitazone therapy. The cases with liver abnormalities were thought to be idiosyncratic in nature. On the basis of the potential for troglitazone to be associated with severe liver function abnormalities, the labeling for troglitazone (Rezulin) was changed on October 31, 1997, to recommend periodic liver function testing (within the first one to two months of therapy, then every three months during the first year of therapy, and periodically thereafter.)

Monitoring for liver toxicity during the DPP included measurement of ALT and AST levels at 3 months, 6 months and every 6 months thereafter for all medication treated subjects (to preserve masking) from the outset of the study. The first 14 months of experience in the DPP revealed fewer than 2% of drug treated patients with liver function test abnormalities > 3 times the upper limit of normal. All of these abnormal levels returned to normal. Nevertheless, in view of the potentially severe, albeit very rare, idiosyncratic liver abnormalities with troglitazone, increased monitoring of liver function tests was instituted with the addition of monitoring at 1 month and 9 months of therapy to the initial monitoring schedule for all medication treated volunteers.”

Section 7.4.1.1: Inserted a new ninth paragraph “Troglitazone therapy has been noted to decrease the blood hormone level of estrogen in women taking oral contraceptive pills (birth control pills). Although the decrease in hormone levels might decrease the potency of the pill as a contraceptive (decrease its protective effect against pregnancy), unexpected pregnancies have not been observed in clinical studies. However, in order to be as safe as possible, birth control pills with a slightly higher hormone content are recommended. If a female participant is randomly assigned to one of the medication groups and chooses an oral contraceptive to provide effective birth control, a pill with at least 35 µg of estrogen and 0.5 mg of norethindrone is recommended. If a female participant randomly assigned to medication therapy is already treated with a “low estrogen” oral contraceptive with less than 35 µg ethinyl estradiol (or its equivalent) and/or less than 0.5 mg norethindrone (or its equivalent), she should consult her gynecologist to consider changing to an oral contraceptive with at least 35 µg ethinyl estradiol and 0.5 mg norethindrone, or their equivalents.”

### **3. Safety Monitoring and Measures to Reduce and Manage Potentially Drug Related Side Effects**

Modification:

Section 7.4.4, paragraph A, first bullet: Changed “ALT and AST (liver enzymes) measured at end-months 3 and 6, and then again every 6 months.” to “ALT and AST (liver enzymes) measured at end-months 1, 3, 6, 9 and 12, and then every 6 months.”

Section 7.4.4, paragraph F, first paragraph: Changed “Hepatic enzymes (ALT and AST) will be measured at end months 3 and 6 and every 6 months, thereafter, in all participants in the

pharmacological treatment groups of the DPP. Hepatic enzyme elevations are rare with metformin or troglitazone and may be no more frequent than with placebo. Nevertheless, metformin should not be used in persons with known active liver disease or hepatic insufficiency” to “Hepatic enzymes (ALT and AST) will be measured at end-months 1, 3, 6, 9 and 12, and every 6 months, thereafter, in all participants in the pharmacological treatment groups of the DPP. Hepatic enzyme elevations are rare (< 2%) with metformin or troglitazone, but rare cases of liver failure have been reported with troglitazone. Metformin should not be used in persons with known active liver disease or hepatic insufficiency.”

Section 7.4.4, paragraph F: Deleted the second, third and fourth paragraphs: “If ALT and AST levels are < 1.8 times the upper limits of normal, all coded medications will be continued. If ALT or AST is 1.8 to 3.0 times the upper limit of normal, coded medications will be continued and a search for other causes of elevated liver enzymes initiated. This will include taking a history to determine alcohol intake and other medications or hepatic toxins and testing for hepatitis A, B and C. Repeat blood tests will be performed at two week intervals for six weeks until the abnormalities resolve or ALT and AST levels regress to < 1.8 times normal.

If enzymes > 1.8 times normal persist on repeat testing, all coded medications will be stopped and enzyme levels and liver tests monitored at two week intervals until liver enzymes return to <1.8 times normal.

If the likely cause of the abnormal liver enzymes is found and the abnormalities are corrected (e.g. excess alcohol, other drugs, hepatitis, etc.) coded medications may be resumed one time after liver enzymes return to < 1.8 times normal.”

Addition:

Section 7.4.4, paragraph F: Inserted the following information after the first paragraph:

- “1. If either ALT or AST level is 1.8 - 3.0 times the upper limit of normal.
  - a. Continue coded medication and within 2 weeks:
    - i. Search for other causes (history, physical, and local laboratory tests including direct and total bilirubin, albumin, prothrombin time, and serologies for hepatitis A, B and C, which should be performed locally).
    - ii. Repeat liver function tests at CBL every two weeks for 6 weeks or until level returns to less than 1.8 times the upper limit of normal.
  - b. If another cause(s) for elevated LFTs is identified, or if ALT or AST remains 1.8 - 3.0 the upper limit of normal, continue medication at discretion of investigator with continued monitoring of ALT and AST levels at the CBL at scheduled quarterly follow-up visits for the next year, and every 6 months thereafter.
2. If either ALT or AST is > 3-fold above the upper limit of normal:
  - a. Stop medication immediately and
  - b. Repeat liver function tests at CBL as soon as possible (within 1 week) and
  - c. Search for other causes of liver damage (see 1.a.i. above)
  - d. If repeat levels are > 3 and no other cause identified, drugs are not to be restarted.
  - e. If cause other than drug toxicity is identified and subsequent AST and ALT levels, tested every two weeks in CBL, decrease to < 1.8, medication can be restarted. After restarting medications, ALT and AST should be tested every two weeks for 1 month, and then at scheduled quarterly visits for one year, followed by the usual 6 monthly tests. If retest results are > 1.8, medications will be discontinued permanently.”

#### **4. Intervention and Follow-up for Participants with Diabetes and Fasting Glucose $\geq$ 140 mg/dL**

Modification:

Section 7.5.6.4; fourth sentence: Changed “. . . pre-prandial capillary glucose measurement less than 140 mg/dL . . .” to “. . .pre-prandial capillary glucose measurement 80 - 120 mg/dL . . .”

#### **5. Outcomes, Safety Testing, and Measures for Adherence**

Modification:

Table 12.2; page 12-4, second footnote, first sentence: Changed “. . . for liver function, fasting liver enzymes (ALT-SGPT, AST-SGOT) . . .” to “. . . for liver function, liver enzymes (ALT-SGPT, AST-SGOT) . . .”

Table 12.2; page 12-4, second footnote, last sentence: Changed “In addition, liver enzymes will be collected at the end-month 3 visit.” to “In addition, liver enzymes will be collected at end-month 1, 3, and 9.”

## **6. Informed Consent Prototypes**

### **Modification:**

Section 15.3: Step 3 Consent Form; page 15-10, number 8: Changed “A urine sample will be collected every 12 months.” to “A urine sample will be collected at baseline and at the end of the study.”

Section 15.3: Step 3 Consent Form; page 15-10, number 10: Changed “If you are in a medication group a blood sample (about 1 tablespoon) will be taken from your arm after your first 3 months in the study” to “If you are in a medication group a blood sample (about 1 tablespoon) will be taken from your arm at months 1, 3, 6, 9 and 12, and then every 6 months.”

Section 15.3: Step 3 Consent Form; page 15-13, first paragraph, fifth sentence: Changed “We know that at doses higher than will be used in this study, troglitazone has been associated with liver test abnormalities” to “We know that troglitazone has been associated with liver test abnormalities in approximately 2% of treated individuals.”

### **Addition:**

Section 15.3: Step 3 Consent Form; page 15-13: Inserted a new second paragraph “Troglitazone lowers blood levels of oral contraceptives (birth control pills) in women who take birth control pills. Although this may weaken the ability of birth control pills to prevent pregnancy, unexpected pregnancies have not occurred in studies with troglitazone. However, in order to be careful, any woman who is put in the medicine treatment group and is taking birth control pills will be asked to discuss the dose of her birth control pill with her doctor.”

Section 15.3: Step 3 Consent Form, page 15-13: Inserted after fifth sentence: “In general, the abnormalities are mild and reversible. Although, two cases of severe liver disease have been reported (out of 650,000 troglitazone treated patients), these two patients continued the treatment with troglitazone after very severe liver function abnormalities had developed. In the DPP, your liver function tests will carefully monitored and medication will be stopped if clinically significant abnormalities develop.”

### **Modification:**

Section 15.4: Treatment Consent Form; page 15-18, number 4 Group D, first sentence: Changed “. . . troglitazone, medicine that is now being studied in people with diabetes. It has no yet had final approval for use in treating patients by the Food and Drug Administration (FDA).” to “. . . troglitazone, a medicine used for lowering blood sugar.”

Section 15.4: Treatment Consent Form; page 15-19, number 8: Changed “A urine sample will be collected every 12 months.” to “A urine sample will be collected at baseline and at the end of the study.”

Section 15.4: Treatment Consent Form; page 15-19, number 10: Changed “If you are in a medication group a blood sample (about 1 tablespoon) will be taken from your arm after your first 3 months in the study” to “If you are in a medication group a blood sample (about 1 tablespoon) will be taken from your arm at months 1, 3, 6, 9 and 12, and then every 6 months.”

## **VERSION 3.2**

Updates to version 3.1 (i.e., Version 3.2, dated January 22, 1998) include two major modifications made by the Steering Committee of the DPP Research Group. One set of modifications addresses changes made to the metformin package insert to limit the use of metformin in persons who might be at risk for lactic acidosis. Another set of modifications addresses changes to the troglitazone package insert that requires additional liver function testing. Version 3.2 includes the following major changes to 3.1:

### **1. Exclusion Criteria**

Additions:

Section 5.2.3, paragraph A.3.g. “New York Heart Association Functional Class 2 in persons who are currently treated with a loop diuretic or digitalis preparation”

Section 5.2.3, paragraph A.5.c. “In individuals who are or will become 80 years of age during the study, a direct measure of creatinine clearance, based on a 24 hour urine collection, will be required. Creatinine clearance levels  $\geq 75$  mL/min will be required in order for these individuals to be eligible.” Note that for participants who are already randomized and are 80 years old, or will become 80 during the DPP, a direct measure of creatinine clearance, based on a 24 hour urine collection, will be required at their next clinic visit following their 80th birthday.

### **2. Intensive Lifestyle Intervention**

Modification:

Section 7.3, second bullet: Changed “Achieve an increase in calorie expenditure of at least 700 kcal/week through moderate intensity exercise (such as walking and bicycling), and maintain this increased level of physical activity throughout the DPP” to “Achieve at least 150 min/week of moderate intensity exercise (such as walking and bicycling), and maintain this level of physical activity throughout the DPP.”

### **3. Safety Monitoring and Measures to Reduce and Manage Potentially Drug Related Side Effects**

Modifications:

Section 7.4.4., paragraph A, first bullet: Changed “ALT and AST (liver enzymes) measured at end-months 1, 3, 6, 9, and 12, and then every 6 months.” to “ALT and AST (liver enzymes) measured at end-months 1 through 7, 9, 12, and then every 6 months.”

Section 7.4.4, paragraph F, first sentence: Changed “Hepatic enzymes (ALT and AST) will be measured at end-months 1, 3, 6, 9 and 12, and every 6 months, there after, in all participants in the pharmacological treatment groups of the DPP.” to “Hepatic enzymes (ALT and AST) will be measured at end-months 1 through 7, 9, 12, and then every 6 months, in all participants in the pharmacological treatment groups of the DPP.”

Section 7.4.4, paragraph J: Changed “Hypoxic States” to “Hypoxic States - Congestive Heart Failure”

Section 7.4.4, paragraph J, second sentence: Changed “If the underlying hypoxic state is corrected, reinstatement of coded metformin may be considered.” to “If the underlying hypoxic state is corrected or CHF is transient (for example, after an acute MI), reinstatement of coded metformin may be considered. Medication arm participants who develop CHF (NYHA Functional Class  $> 2$ ) during the study should have their coded metformin stopped. Medication arm participants who develop NYHA Functional Class 2 and require a loop diuretic or digitalis preparation should have their coded metformin stopped.”

### **4. Adverse Event Reporting**

Modifications: To create consistency with the International Conference on Harmonisation, the FDA has revised definitions of serious adverse events:

Section 8.1, second paragraph: Changed “Serious adverse event refers to :

- Any fatal event
- Any life-threatening event
- Any event that is permanently disabling
- Any event which requires in-patient hospitalization or prolongs hospitalization
- Any event that is a congenital anomaly or cancer
- Any overdose which results in an adverse event regardless of severity” to

“Serious adverse events have been defined to include any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity; or
- A congenital anomaly/birth defect”

Section 8.2, first paragraph, first sentence: Changed “. . . collecting information on adverse experiences during the staged screening process and at scheduled quarterly follow-up visits.” to “. . . collecting information on adverse experiences during the staged screening process and at Standard (Form F01), Major (Form F02), and Interim (Form F03) follow-up visits.”

## **5. Study Administration**

Modification:

Section 11.1.1; first paragraph, first sentence: Changed “Each of the 25 participating clinical centers . . .” to “Each of the participating clinical centers . . .”

## **6. Schedule of Procedures**

Addition:

Table 12.1; Step 3 - Run-in start: Added “Creatinine Clearance. Only for participants who are or will become 80 years of age during the DPP.”

## **7. Outcomes, Safety Testing, and Measures for Adherence**

Modifications:

Table 12.2; page 12-4, second footnote, last sentence: Changed “In addition, liver enzymes will be collected at end-month 1, 3, and 9.” to “In addition, liver enzymes will be collected at end-months 1 through 7, and 9.”

Table 12.2; page 12-4, third footnote: Changed “Adverse events will be collected every 3 months.” to “Adverse events will be collected at Standard (Form F01), Major (Form F02) and Interim (Form F03) follow-up visits.”

## **8. Informed Consent Prototypes**

Modifications:

Section 15.3: Step 3 Consent Form; page 15-10, number 10: Changed “If you are in a medication group a blood sample (about 1 tablespoon) will be taken from your arm at months 1, 3, 6, 9 and 12, and then every 6 months.” to “If you are in a medication group a blood sample (about 1 tablespoon) will be taken from your arm at months 1 through 7, 9, 12, and then every 6 months.”

Section 15.3: Step 3 Consent Form; page 15-12, sixth paragraph, seventh sentence: Changed “Very few persons (less than one in 10,000 and usually persons with poor kidney function or with liver disease) . . .” to “Very few persons (3 in 100,000 and usually persons with poor kidney function or with liver disease) . . .”

Section 15.3: Step 3 Consent Form: page 15-13, first paragraph, fourth sentence: Changed “Side effects might include: loss of appetite, upset stomach, vomiting, stomach pain, diarrhea, bloating or gas, headache, anemia, or low white blood cell count.” to “Side effects might include: loss of appetite, fatigue, dark urine or jaundice (yellow eyes or skin), upset stomach, vomiting, stomach pain, diarrhea, bloating or gas, headache, anemia, or low white blood cell count. You will be asked to contact your DPP clinic as soon as possible if you develop loss of appetite, fatigue, dark urine or jaundice (yellow eyes or skin), which occur with liver disease.”

Section 15.4: Treatment Consent Form; page 15-19, number 10: Changed “If you are in a medication group a blood sample (about 1 tablespoon) will be taken from your arm at months 1, 3, 6, 9 and 12, and then every 6 months.” to “If you are in a medication group a blood sample (about 1 tablespoon) will be taken from your arm at month 1 through 7, 9, 12, and then every 6 months.”

#### **VERSION 4.0**

Version 4.0 of the DPP Protocol, dated June 3, 1998, includes a major modification; the discontinuation of troglitazone in the DPP (see section 5.3.1). The following changes have been made to version 3.2:

##### **1. Discontinuation of the Troglitazone Arm**

Information regarding the discontinuation of the troglitazone arm can be found in the Executive Summary and section 5.3.1. All references made to the troglitazone intervention protocol have been deleted. All occurrences are not noted. Participants randomized to troglitazone continue follow-up by the DPP Research Group (see the DPP protocol “Follow-up of DPP Participants Randomized to Troglitazone”).

##### **2. The LFT Testing Schedule**

Changed schedule from months 1 through 7, 9, 12 and then every 6 months to months 3 and 6 and then every 6 months. Each occurrence is not noted.

##### **3. Sample Size and Statistical Analysis**

This section has been modified for the 3 arm study.

##### **4. Granulocytes**

Deletions:

Section 5.2.3, number 8b: Deleted “Granulocytes < 1500/mL”

Section 7.4.4, paragraph N: Deleted “*Granulocytopenia*: Troglitazone has been rarely associated with granulocytopenia. CBCs will be checked at end- months 6 and 12, and annually, thereafter. If granulocyte counts are < 1,500, coded troglitazone (TA & TP) should be discontinued and not resumed until the counts are > 1,500. CBC's should be rechecked at two week intervals until the problem is resolved. Other causes for granulocytopenia will be investigated.”

##### **5. Renal Insufficiency**

Addition:

Section 7.4.4, paragraph D, after last sentence: Added “Coded metformin will also be discontinued in individuals who have a post-randomization creatinine clearance (based on a 24 hour urine collection) level < 75 mL/min. A creatinine clearance is only performed post-randomization if the participant turns 80 years old during the DPP and did not receive a creatinine clearance for eligibility.”

##### **6. Secondary Outcomes**

Addition:

Section 4.2.6:

**Quality of Well-Being Scale:** A preference-based measure for overall health that may be used for quality-adjusted life years computations.

## 7. Safety Monitoring and Measures to Reduce and Manage Potentially Drug Related Side Effects

Modification:

Section 7.4.4., paragraph F: Deleted:

“Hepatic enzymes (ALT and AST) will be measured at end-months 1 through 7, 9, 12, and then every 6 months, in all participants in the pharmacological treatment groups of the DPP. Hepatic enzyme elevations are rare (< 2%) with metformin or troglitazone, but rare cases of liver failure have been reported with troglitazone. Metformin should not be used in persons with known active liver disease or hepatic insufficiency.

1. If either ALT or AST level is 1.8 - 3.0 times the upper limit of normal.
  - a. Continue coded medication and within 2 weeks:
    - i. Search for other causes (history, physical, and local laboratory tests including direct and total bilirubin, albumin, prothrombin time, and serologies for hepatitis A, B and C, which should be performed locally).
    - ii. Repeat liver function tests at CBL every two weeks for 6 weeks or until level returns to less than 1.8 times the upper limit of normal.
  - b. If another cause(s) for elevated LFTs is identified, or if ALT or AST remains 1.8 - 3.0 the upper limit of normal, continue medication at discretion of investigator with continued monitoring of ALT and AST levels at the CBL at scheduled quarterly follow-up visits for the next year, and every 6 months thereafter.
2. If either ALT or AST is > 3-fold above the upper limit of normal:
  - a. Stop medication immediately and
  - b. Repeat liver function tests at CBL as soon as possible (within 1 week) and
  - c. Search for other causes of liver damage (see 1.a.i. above)
  - d. If repeat levels are > 3 and no other cause identified, drugs are not to be restarted.
  - e. If cause other than drug toxicity is identified and subsequent AST and ALT levels, tested every two weeks in CBL, decrease to < 1.8, medication can be restarted. After restarting medications, ALT and AST should be tested every two weeks for 1 month, and then at scheduled quarterly visits for one year, followed by the usual 6 monthly tests. If retest results are > 1.8, medications will be discontinued permanently.”

Inserted the following section:

Hepatic enzymes (ALT and AST) will be measured at end-months 3 and 6, and then every 6 months, in all participants in the pharmacological treatment groups of the DPP. Hepatic enzyme elevations are rare with metformin and may be no more frequent than with placebo. Nevertheless, metformin should not be used in persons with known active liver disease or hepatic insufficiency.

If either ALT or AST level is 1.8 times the upper limit of normal or higher, search for other causes (history, physical, and local laboratory tests including direct and total bilirubin, albumin, prothrombin time, and serologies for hepatitis A, B and C, which should be performed locally) and proceed as follows:

1. If either ALT or AST level is 1.8 - 3.0 times the upper limit of normal:
  - a. Continue coded medication and
  - b. Repeat liver function tests at CBL every two weeks for 6 weeks or until level returns to less than 1.8 times the upper limit of normal.
  - c. If ALT or AST remains 1.8 - 3.0 times the upper limit of normal, continue coded medication at discretion of investigator with continued monitoring of ALT and AST levels at the CBL at scheduled quarterly follow-up visits for the next year followed by the protocol schedule of liver function testing.
  - d. If ALT or AST is < 1.8 times the upper limit of normal, continue coded medication and the protocol schedule of liver function testing.
2. If either ALT or AST is > 3.0 times the upper limit of normal:
  - a. Stop coded medication immediately and

- b. Repeat liver function tests at CBL every week for 6 weeks or until level returns to less than 1.8 times the upper limit of normal.
- c. If ALT or AST remains 1.8 - 3.0 times the upper limit of normal, re-challenge the coded medication at discretion of investigator (since metformin is not associated with liver disease) with continued monitoring of ALT and AST levels at the CBL at scheduled quarterly follow-up visits for the next year followed by the protocol schedule of liver function testing.
- d. If ALT or AST is < 1.8 times the upper limit of normal, re-challenge coded medication and the protocol schedule of liver function testing.

Participants are instructed that in the event they develop malaise, nausea, vomiting, dark urine, jaundice or right upper quadrant abdominal discomfort, they should stop coded medication and report the symptoms immediately to their DPP clinical center. Upon notification, the clinical center staff must obtain a blood sample as soon as possible (within 1 week) for liver function tests at the CBL. If both ALT and AST are less than 1.8 times the upper limit of normal, the participant may be re-challenged with the coded medication. If either value is > 1.8 times the upper limit of normal then follow testing procedures outlined above.

## **8. Dropout**

Modification:

Section 7.6: An editorial change was made to reduce confusion. The term dropout has been replaced with inactive or discontinue follow-up visits.

## **9. Adverse Event Reporting**

Addition:

In accordance with the FDA Guidelines effective April 6, 1998, the following additional category has been added to the definitions of a serious adverse event:

Section 8.1, first paragraph, sixth bullet:

- “Important medical events that may not result in death, be life-threatening or require hospitalization if, based on appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent a serious adverse event.”

## **10. Data Processing**

Deletion:

Section 9.1.3, fourth paragraph, second bullet:

- Oral Contraceptive Pill Report (Form R05)

Addition:

Section 9.1.3, first paragraph, eleventh bullet:

- Quality of Well-Being Scale (Form Q11)

## **11. Outcomes, Safety Testing, and Measures for Adherence**

Addition:

Section 12.2, Quality of Life: Added Quality of Well-Being Scale

Section 12.2, Adherence Measures: Added Medication Adherence Interview

Section 12.2, inserted after first bullet: Added “• The Medication Adherence Interview will be completed at the month 1 visit and then at Standard (Form F01) and Major (Form F02) follow-up visits.”

Modification:

Section 12.2, Primary Outcome Visit: The items completed at the Primary Outcome Visit have been reduced.

## **VERSION 4.1**

Version 4.1 of the DPP Protocol, dated July 20, 2000, includes major modifications made by the Steering Committee of the DPP Research Group. The following changes have been made to version 4.0:

## **7. Safety Monitoring and Measures to Reduce and Manage Potentially Drug Related Side Effects**

### **Modification:**

Section 7.4.4, paragraph D: Changed from “If the serum creatinine is again  $\geq 1.5$  mg/dL [133  $\mu\text{mol/L}$ ] in men or  $\geq 1.4$  mg/dL [124  $\mu\text{mol/L}$ ] in women, an evaluation of potential causes of renal insufficiency will be made” to “If the serum creatinine is again  $\geq 1.5$  mg/dL [133  $\mu\text{mol/L}$ ] in men or  $\geq 1.4$  mg/dL [124  $\mu\text{mol/L}$ ] in women, regardless of cause, coded metformin will be stopped permanently and participant will be referred to their health care providers for an evaluation of potential causes of elevated creatinine.”

### **Addition:**

Section 7.4.4, paragraph D: Added “For participants who are permanently off study medication, elevations in serum creatinine do not require confirmation, but will be reported to the health care provider.”

### **Modification:**

Section 7.4.4, paragraph F: Deleted:

“If either ALT or AST level is 1.8 times the upper limit of normal or higher, search for other causes (history, physical, and local laboratory tests including direct and total bilirubin, albumin, prothrombin time, and serologies for hepatitis A, B and C, which should be performed locally) and proceed as follows:

1. If either ALT or AST level is 1.8 - 3.0 times the upper limit of normal:
  - a. Continue coded medication and
  - b. Repeat liver function tests at CBL every two weeks for 6 weeks or until level returns to less than 1.8 time the upper limit of normal.
  - c. If ALT or AST remains 1.8 - 3.0 times the upper limit of normal, continue coded medication at discretion of investigator with continued monitoring of ALT and AST levels at the CBL at scheduled quarterly follow-up visits for the next year followed by the protocol schedule of liver function testing.
  - d. If ALT or AST is  $< 1.8$  times the upper limit of normal, continue coded medication and the protocol schedule of liver function testing.
2. If either ALT or AST is  $> 3.0$  times the upper limit of normal:
  - a. Stop coded medication immediately and
  - b. Repeat liver function tests at CBL every week for 6 weeks or until level returns to less than 1.8 times the upper limit or normal.
  - c. If ALT or AST remains 1.8 – 3.0 time the upper limit or normal, re-challenge the coded medication at discretion of investigator (since metformin is not associated with liver disease) with continued monitoring of ALT and AST levels at the CBL at scheduled quarterly follow-up visits for the next year followed by the protocol schedule of liver function testing.
  - d. If repeat ALT or AST is  $< 1.8$  times the upper limit of normal, re-challenge coded medication and protocol schedule of liver function testing.”

Inserted the following section:

- “1. If either ALT or AST level is 1.8 - 3.0 times the upper limit of normal:
  - a. Continue coded medication and
  - b. Repeat liver function tests at CBL within two weeks.
  - c. If repeat ALT or AST remains 1.8 - 3.0 times the upper limit of normal (ULN), continue coded medication at discretion of investigator, with continued monitoring of ALT and AST levels at the CBL monthly until the level is  $< 1.8$  ULN, at which time continue the protocol schedule of liver function testing every 6 months.
  - d. If medication is stopped, monthly monitoring is not required; resume the usual schedule of monitoring every 6 months.

- e. If repeat ALT and AST are < 1.8 times ULN, continue coded medication and the protocol schedule of liver function testing every 6 months.
- 2. If either ALT or AST is > 3.0 times the upper limit of normal:
  - a. Stop coded medication immediately and
  - b. Repeat liver function tests at CBL within 2 weeks.
  - c. If repeat ALT or AST decreases to 1.8 to 3.0 times ULN, re-challenge with the coded medication at discretion of the investigator (since metformin is not associated with liver disease) and continue monitoring as in 1.c., above.
  - d. If repeat ALT or AST is > 3.0 times ULN, refer participant to his or her local health care provider for evaluation. LFTs will be repeated in 6 months.
  - e. If repeat ALT and AST are < 1.8 times ULN, continue coded medication and the protocol schedule of liver function testing every 6 months.”

Section 7.4.4, paragraph H: Changed from “... coded medication will be discontinued 48 hours before of administration of contrast dyes and then restarted 48 hours after the dye administration, assuming that the serum creatinine levels are in an acceptable range (< 1.5 mg/dL (133 µmol/L) for men and < 1.4 mg/dL (124 µmol/L) for women)” to “... the last dose of coded 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. Coded medication will be re-started if the serum creatinine levels are in the acceptable range (< 1.5 mg/dL (133 µmol/L) for men and < 1.4 mg/dL (124 µmol/L) for women).”

Section 7.4.4, paragraph K: Changed from “... coded medication will be discontinued at least for 48 hours prior to any anticipated surgical procedures. Coded medication will obviously be held while participants are NPO for outpatient procedures. The most recent dose of the coded medication can be reinstated after the procedure when oral medications are allowed” to “... coded medication will be suspended prior to such anticipated surgical procedures, with the last dose administered on the day prior to surgery. Coded medication will obviously be held while participants are NPO for procedures. Serum creatinine should be checked after such procedures and coded medication will be restarted if the serum creatinine levels are in the acceptable range (< 1.5 mg/dL (133 µmol/L) for men and < 1.4 mg/dL (124 µmol/L) for women).”

## **VERSION 4.2**

Updates to Version 4.1 (i.e., Version 4.2, dated May 9, 2001) followed study group discussion of the need to align consent forms with the current national scientific standards regarding the use of specimens for genetic studies. Version 4.2 contains the following major additions to Version 4.1:

### **Informed Consent Prototypes**

#### **Addition:**

A new consent form, “Information and consent for banking and use of blood and genetic material (DNA) obtained in the Diabetes Prevention Program” has been added to align with the current national scientific standards regarding the use of specimens for genetic studies.

#### **Addition:**

A new consent form, “Information and Addendum for the end of study period of the treatment phase of the Diabetes Prevention Program” has been added to address specifics of end-of-study visit scheduling.

## **VERSION 4.3**

Updates to Version 4.2 (i.e., Version 4.3, dated May 18, 2001) followed NIDDK’s acceptance of the recommendation by the Data Monitoring Board to terminate the masked treatment phase early.

## **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) unmasking of the drug assignments and stopping placebo; d) use of metformin as an open-label extension; e) modifications to data collection following removal of the end of study visit; and f) addition of a consent form for this period that includes consent for carotid ultrasound, measurement of height, questions concerning urinary incontinence (Q13), and questions concerning barriers, support and medication assignment (Q14). A template consent form (Ver. 4.3) for this amendment is added.

## **2. Data Monitoring Board (DMB) recommendations**

The DMB for the DPP reviewed the accumulated data, and recommended unanimously to the NIDDK that the masked treatment phase be terminated, drug assignments be unmasked, and major results presented. The Director of the NIDDK accepted this recommendation on May 18<sup>th</sup>, 2001, 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. 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. Unmasking of medication assignment and stopping of placebo**

Participants who were assigned to the medication arm of the DPP will be unmasked to their treatment assignments beginning in August, 2001. This will occur at the individual debriefing sessions when participants are informed of their individual results and treatment assignment during the DPP. Persons assigned placebo will be told to stop taking their placebo medication.

Version 4.3 contains the following major additions to Version 4.2:

Addition:

Section 5.6.1.1: Unmasking due to early termination of the masked treatment phase; Pharmacologic treatment assignment, previously double masked, will be unmasked starting in August 2001. Participants previously assigned to placebo will discontinue their study medications.

## **5. Open label extension of metformin**

Participants who were assigned to metformin will be so informed. If participants tolerated metformin, and do not have other possible contraindications noted in the protocol (renal insufficiency, excessive alcohol intake, etc.), continued metformin will be recommended in an unmasked (open label) format. The NIDDK has applied to the FDA for an amendment under IND #49,782. Safety monitoring of metformin will continue on a three-monthly basis without change from protocol version 4.2.

Addition:

Section 7.4.2.3: Unmasking and open-label follow-up  
Participants who were randomized to DPP study medications will be unmasked starting in August, 2001. Those persons without contraindications, who are willing to continue to take it, will be offered Metformin unmasked, in open label format, following amendment of the study IND #49,782 from the FDA. Safety monitoring described below will continue without revision.

## **6. Data collection**

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

Addition:

Section 12.2.1: Changes due to early termination of the masked treatment phase

- a. Scheduled “End of study visits” (as noted in Table 12.2) will not be conducted due to early termination of DPP.
- b. A urine specimen to measure urine albumin and creatinine concentration will be collected.
- c. Carotid ultrasound may be conducted at a visit to be scheduled.
- d. Questions concerning urinary incontinence (Q13), and questions concerning barriers, support and medication assignment (Q14) in the DPP will be asked.

## 7. Data Forms

Addition:

Section 9.1.2 Follow-up Period

- Home Visit (Form F06)

Section 9.1.3 Other Forms:

- Economic Evaluation Questionnaire (Form Q12)
- Urinary Incontinence Questionnaire (Form Q13)
- End of Study Questionnaire (Form Q14)

## 8. Study timeline

Modification:

Section 13 The study timeline was changed as follows.

Phase II changed from “July 1996 - February 1999 Recruitment and Follow-up – 2 and 2/3 years” to “July 1996 – June 1999 Recruitment and Follow-up”

Phase II changed from “March 1999 – June 2002 Participant Follow-up – 3 and 1/3 years” to “July 1999 – 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”

## 9. Informed Consent Prototypes

Deletion:

Section 15.6: “Information and Addendum for the End of Study Period of the Treatment Phase”.

Addition:

Section 15.6: “Information and Amendment for the completion of the Masked Treatment Phase” has been added to address specifics of completion of the masked treatment phase.

## VERSION 4.4

Updates to Version 4.3 (i.e., Version 4.4, dated May 18, 2001) followed NIDDK’s acceptance of the recommendation by the Data Monitoring Board to terminate the masked treatment phase early.

This protocol amendment describes the washout study of metformin to examine the contribution of acute pharmacologic effects to DPP results.

### 1. Specific Aim

Addition:

Section 2.3.1 Mechanism of Metformin: To clarify the mechanism of metformin’s salutary effect on diabetes development during the DPP (acute pharmacological vs. long-term effect on metabolism) by performing a short-term washout study during which medications will be held and subsequent development of diabetes assessed.

### 2. Background/Rationale

Addition:

Section 3.9: Rationale for Medication Washout. The primary outcome of the DPP is the development of diabetes, diagnosed by annual oral glucose tolerance tests (OGTTs) (Diabetes Prevention Program Research Group, 1999). Study treatments are only suspended briefly for outcome assessments. Specifically, the life-style intervention is not interrupted and medications are only held on the morning of the OGTT (usually for 12-15 hours from the dose taken the evening before). Since metformin proved to be effective in delaying the onset of diabetes, it is important to determine if the effects of metformin on the primary outcome were due simply to its acute pharmacologic actions.

The choice of metformin as one of the DPP interventions was predicated on its proven antihyperglycemic effect in both diabetic and non-diabetic individuals (Bailey, 1992; Strumvoll, et. al., 1995). Metformin is known to inhibit hepatic glucose production, predominantly by inhibiting gluconeogenesis (Bailey, et. al., 1996). There is also evidence that metformin may improve insulin action in muscle. (Bailey, et. al., 1996) A positive effect of metformin on the primary outcome in DPP, namely to decrease the number of participants who converted to diabetes, would presumably be interpreted to result from these biological actions. The possibility exists that the positive effect of metformin in DPP might, at least in part, have resulted from an acute effect of metformin to lower blood glucose, and hence would to that extent be acutely reversible. (No previous studies examining acute vs. chronic effects of metformin have been performed.) This possibility was discussed during the planning stage of DPP in relation to whether OGTT testing in DPP should be conducted on or off metformin treatment. However, since the participants receiving medications were randomly assigned to metformin, troglitazone or placebo, any decision to hold medications before the annual OGTT (or 6 monthly fasting glucose test) would have had to take into account the long half-life of troglitazone. Stopping medications for as long as two to four weeks was felt to be impractical and, therefore, medications were not formally “washed out” prior to OGTTs during the DPP.

During the closeout of the DPP, we will have the opportunity to test whether the acute withdrawal of metformin is associated with a rapid deterioration in glucose tolerance significant enough to abrogate the positive effect of the drug during DPP. Such a result would imply the presence of a cohort of participants receiving metformin treatment whose dysmetabolism is adequately controlled by this agent, but who rapidly deteriorate when treatment is abruptly withdrawn. Such a group might be found among those with IGT who are most susceptible to conversion to diabetes, and whose eventual conversion is delayed by metformin. Presumably, they have severe enough defects in insulin secretion and action such that they would express diabetic hyperglycemia in the absence of metformin administration. Withdrawal of metformin treatment would then lead those who are most susceptible to convert to diabetes acutely, and in a manner that potentially could be reversed by reinstating metformin treatment. On the other hand, the persistence of a significant difference in the proportion of converters in the metformin group versus the placebo group after a metformin “washout” would imply that the efficacy of metformin in DPP extends beyond its acute antihyperglycemic action. In the latter case, there would be substantial interest in learning more about the durability and possible mechanisms of a chronic effect of metformin and clearly this would be an important topic for future studies.

### **3. Subjects**

Addition:

Section 5.2.1.1: Principles Guiding Selection for the Washout Study

All DPP participants who have not developed diabetes and who are randomly assigned to medication therapy (placebo or metformin) will be eligible and invited to join the washout study. Medication treated subjects will be eligible regardless of their level of compliance. The only exclusion criteria will be if potential volunteers have some condition that precludes performance of an OGTT according to the original DPP protocol, e.g. treatment with glucocorticoids.

### **4. Method**

**Addition:**

Section 5.5.3 Washout Study Assessment: With the announcement of the DPP results in August, 2001, each DPP site will communicate with their participants at a general meeting, and by telephone and through the mail in order to initiate the debriefing process. Medication participants who agree to participate in the washout study will be asked to continue their medications until approximately 7 days prior to a post-washout OGTT to be performed within approximately the next 6 weeks. The nature and purpose of the washout study will be explained to them and informed consent will be obtained. DPP medication group subjects who agree to participate in the washout project will agree not to be told of their previous DPP assignment (metformin vs. placebo) until after completion of the washout OGTTs. Participants found to have converted to diabetes will require a confirmatory OGTT (still off study medication), as was performed during the DPP.

**5. Analysis**

**Addition:**

Section 10.3.1 Washout Analysis: The washout OGTT will be performed under different conditions than the other OGTTs in DPP, i.e. with study drug withheld. Furthermore, its timing relative to randomization will differ among participants (ranging from approximately 2-5 years after randomization). Thus, it will not be possible to analyze the washout as simply one additional data point in the same time-to-event (survival) analysis to be used for the main study. Instead, the washout OGTT (combined with a repeat test to confirm a new diagnosis) will be used in an analysis of prevalence of diabetes from randomization to the time of washout. The prevalence of diabetes will thus be determined by counting as cases all those diagnosed under the usual DPP follow-up procedure plus those diagnosed by the washout OGTT. The prevalence will be expressed as a simple percentage of all subjects enrolled and will be compared between metformin and placebo treatment groups. The analysis will be stratified by DPP study year of randomization, and the significance and homogeneity of the treatment effect over these strata will be assessed by standard statistical methods for stratified proportions data, such as the Mantel-Haenszel summary statistic and the Breslow-Day test for homogeneity over strata.

As a supplement to this analysis, we will also conduct the same analysis on the last OGTT results prior to washout. This is the appropriate analysis for comparative purposes rather than the time-to-event analysis of the DPP primary outcome, diabetes conversion without metformin “washout”.

**6. Bibliography**

**Addition:**

Section 14.1 Bibliography for Background to the Washout Study

1. Diabetes Prevention Program Research Group. The Diabetes Prevention Program: Design and methods for a clinical trial in the prevention of type 2 diabetes mellitus. *Diabetes Care* 1999, 22:623-34.
2. Bailey CJ. Biguanides and NIDDM. *Diabetes Care* 1992;15:755-72.
3. Strumvoll M, Nurgham N, Perriello G, et al. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. *N Engl J Med* 1995;333:550-54.
4. Bailey CJ, Turner RC. Metformin. *N Engl J Med* 1996;334:574-79.

**7. Informed Consent Prototypes**

**Addition:**

Section 15.7: “Information and Consent for a ‘Washout’ Study of Metformin and Placebo” has been added to address specifics of the washout study phase.