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## 7. PARTICIPANT MANAGEMENT PROTOCOLS

Each participant is randomized to one of three treatment groups:

1. Intensive lifestyle intervention.
1. Metformin with standard lifestyle recommendations.
1. A metformin placebo with standard lifestyle recommendations.

### 7.1 Schedule of Follow-up Visits

Follow-up visits will be scheduled at 3 month intervals throughout the duration of the DPP. Participants assigned to the intensive lifestyle intervention will have more frequent scheduled follow-up visits to implement the program of weight reduction and increased calorie expenditure. Participants assigned to the two pharmacological treatments (metformin or placebo) will be scheduled for one visit one month after randomization for dose titration. All randomized participants will continue their scheduled follow-up visits for the duration of DPP regardless of their level of compliance with the assigned treatment. Outcome and safety assessments will be conducted according to the schedule in section 12.2.

#### 7.1.1 Interim Visits

An interim visit refers to all visits other than scheduled follow-up visits (i.e., standard or major 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.

#### 7.1.2 Suspension of Follow-up Visits

The occurrence or presence of the following will constitute inactive follow-up and suspension of the scheduled follow-up protocol:

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

Efforts to return participants to an active status will be made regularly, as appropriate.

### 7.2 Standard Lifestyle Recommendations

A. After randomization, all participants will receive the following standard lifestyle recommendations.

At the first visit, the staff will spend approximately 20 - 30 minutes with each participant individually, reviewing the importance of a healthy lifestyle for the prevention of NIDDM, and for prevention and treatment of other diseases (such as cardiovascular disease and hypertension). Materials, provided by the Lifestyle Resource Core, will be given to each participant and the staff will review the basic information in the materials with the participant. The materials will include information or recommendations on:

- **Healthy Eating** - The Food Pyramid is used as the basis of discussion. Participants are encouraged to consume the equivalent of a NCEP Step I diet.
- **Healthy Weight** - The materials include a weight chart, a description of how to measure their own waist, and guidelines for appropriate waist circumferences. The materials include discussion of the benefits of modest weight reduction (5-10% of initial weight) for those who are overweight and describe general behavior changes that can be made to produce weight loss. Changes in both dietary intake and exercise are recommended for weight loss and maintenance.
- **Physical Activity** - Participants are encouraged to adopt and maintain a more active lifestyle. The materials suggest ways to increase general activity (such as using stairs instead of elevators) and provide a chart with information regarding the number of calories used in 10 minutes of various forms of exercise. Participants are encouraged to increase their activity gradually and to try to reach the goal of at least 30 minutes of physical activity (such as walking or biking) on 5 days each week.
- **Smoking** - All participants who smoke are strongly encouraged to stop smoking. The materials include general information about the health risks associated with smoking, the benefits and specific strategies for stopping smoking, and a list of programs available to participants to help them stop smoking.

Participants are encouraged to read the materials carefully, to bring any questions they have to the next visit, and to try to gradually work toward a healthier lifestyle.

- Alcohol Intake - Participants, especially those in the pharmacological treatment groups due to the nature of the medication used in the DPP, are informed of the need to avoid excessive alcohol intake (see section 5.2.3) and binge drinking.
- B. At the end-month 3 follow-up visit, the staff briefly review the materials with the participant. The staff answer any questions regarding the information provided.
- C. At yearly intervals (soon after each annual assessment), the staff meet with each participant to review the information on diet, exercise, weight and smoking.

### 7.3 Intensive Lifestyle Intervention

The goals of therapy for participants randomly assigned to the intensive lifestyle intervention are two:

- Achieve a weight reduction of at least 7% of initial weight and maintain this weight reduction throughout the DPP.
- 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.

Recognizing that it is very difficult to produce long term changes in eating and exercise behaviors and in body weight, the intensive lifestyle intervention is designed to maximize the chances of achieving and maintaining these goals. The intensive lifestyle intervention is based on the premise that long-term changes in diet and exercise and sustained motivation to maintain behavior changes are most likely to occur in an intensive intervention that includes the following:

- Training in diet, exercise, and behavior modification skills
- On-going contact with participants, and continued, frequent (no less than monthly) support for behavior change
- Diet and exercise interventions that are flexible and sensitive to cultural differences and acceptable in the specific communities in which they are implemented
- A combination of individual and group intervention
- A combination of a structured protocol (in which all participants receive certain common information) and the flexibility to tailor strategies individually to help a specific participant achieve and maintain the study goals
- Emphasis on self-esteem, empowerment, and social support

#### 7.3.1 Description of Program

##### A. *Lifestyle Resource Core.*

The Lifestyle Resource Core, located at the University of Pittsburgh, developed the materials for the intensive lifestyle intervention and will provide on-going training and support for the case managers.

##### B. *Staff for Intensive Lifestyle Intervention.*

Case managers at each clinical center will carry out the intensive lifestyle intervention. Case managers will be individuals with experience in nutrition, exercise, and/or behavior modification and will receive further training from the Lifestyle Resource Core. The case managers are supported by staff at each center with additional expertise in nutrition, exercise, or behavior modification. Each participant randomized to the intensive lifestyle intervention is assigned a case manager who will work with him or her throughout the DPP (changing case managers for a specific participant may be necessary to help retain participants in the DPP or to help participants achieve the weight and exercise goals).

Other staff (e.g. peer counselors and exercise leaders) are employed as appropriate at each center.

##### C. *Format of Intervention.*

###### 1. 16-Session Core Curriculum.

Participants randomized to the intensive lifestyle intervention will participate in a 16-session core curriculum. This initial intervention will commence as soon as possible after randomization, and must begin within 2-3 months after randomization. These 16 sessions are to be held over 24 weeks. These initial 16 sessions will be individual sessions involving the participant and case manager; however, small groups may be formed if all members of a small group start and complete the 16 sessions together (closed group format). In addition, a spouse or other key family member may be invited to attend. The first 8 sessions and four of the following

8 sessions must be with the case manager; the other 4 or more sessions may be with the case manager, a peer-counselor, home visitor, or the equivalent. Topics and lesson materials to be utilized in this 16 session core curriculum have been developed by the Lifestyle Resource Core and are in the Lifestyle Intervention Manual. Topics included in this 16 sessions core curriculum include:

- a. Lifestyle change as a way to prevent diabetes: the importance of healthier eating and exercise behavior.
- b. Looking at what you eat - self-monitoring of eating behavior.
- c. Reducing fat intake - identifying high fat foods and appropriate lower fat alternatives.
- d. Looking at your physical activity - self-monitoring of activity.
- e. Increasing your physical activity - identifying activities that can be maintained long term.
- f. Changing the environment to promote lower fat and lower calorie intake (stimulus control techniques and shopping skills).
- g. Strategies for increasing exercise and reducing the barriers to exercise.
- h. Eating at home: food preparation and recipe modification skills to lower fat and calorie intake.
- i. Eating away from home: strategies for dieting in restaurants and other social eating situations.
- j. Problem solving.

The schedule of visits represents the minimum frequency of contact and can be adjusted for individual participants due to personal constraints such as illness, vacation, and travel. Participants will be taught to record their diet and exercise throughout the initial core curriculum phase of the program. The emphasis of the first 24 weeks will be on achieving the 7% weight loss goal and to achieve at least 150 min/week of moderate intensity exercise, and maintain this level of physical activity throughout the DPP. If participants are having difficulty achieving either or both of these goals, a “tool box” approach will be used to add new strategies to help individual participants achieve the weight and exercise goals. The Lifestyle Resource Core will be responsible for providing an initial list of tool box strategies, and individual case managers can propose additional strategies to the Core for their review. Tool box strategies to increase physical activity would include approaches such as provision of home exercise equipment to the participant or enrolling the participant in a local health club. Tool box strategies for weight loss would include strategies such as increased clinic visits, home visits, and provision of low calorie meals or frozen entrees to the participant.

## 2. Maintenance Phase.

Following the initial phase, all participants in the intensive lifestyle intervention will receive, at a minimum, monthly contacts for the remainder of the DPP. At least one contact every 2 months must be in person, and must be done by the case manager. The other contact can be by phone. In addition, starting in the second half of year 01 of intensive lifestyle intervention, “short courses” will be offered quarterly for those intensive lifestyle participants who wish to attend. Each course will last 4 - 6 weeks and will focus on a specific topic. Exercise courses will include such topics as resistance training or step aerobics. Nutrition topics might include recipe swap, holiday entertaining or stir fry cooking. Behavioral topics might include “keeping lapses from becoming relapses”, “emotions and eating” or “getting my family involved”. All participants who have completed the 16 session core curriculum will be invited to attend these classes and those participants having problems in specific areas (e.g. not getting enough exercise) will be strongly encouraged to join the appropriate class. The number of participants in these classes and the group make-up will thus differ for each topic. Individual centers will be able to propose ideas for “classes” and some flexibility will be given to centers in terms of which classes to offer (i.e. not all centers will have to offer the same classes), although all centers may need to offer one class related to diet, one to exercise, and one to a behavioral topic each year. Curricula for the 4 - 6 week classes will be developed by the Lifestyle Resource Core, with input from the individual centers. New classes will be introduced each year.

## 3. Exercise Sessions.

Each center will offer 2 supervised exercise sessions per week. These group exercise sessions may be held at churches, health centers, outdoors, etc. Any type of low intensity activity may be used (such as walking or aerobic dancing). These sessions are provided as an option for participants to increase their exercise. Centers can choose specific staff members to offer these sessions which will be offered throughout the DPP; however, if sufficient numbers of participants are not utilizing these sessions, this aspect of the protocol may be modified.

### 7.3.2 Indices of Adherence

Adherence to the intensive lifestyle intervention is assessed in the following manner:

- Data are recorded on all face to face contacts and phone contacts to ensure that all intensive lifestyle intervention participants receive the 16 core curriculum sessions and monthly contacts throughout the study. Attendance at supervised exercise sessions and group classes is documented (although these are not required of participants).
- Adherence to exercise protocol is determined from self-report questionnaires that assess physical activity, completed at screening step 3, end-months 6 and 12, and then annually, thereafter, in all DPP participants and with intensive lifestyle intervention diaries.
- Adherence to the weight loss goal is determined from the 6 month assessments of body weight.

## 7.4 Pharmacological Treatment

### 7.4.1 Description

In addition to the intensive lifestyle intervention, there is one pharmacological intervention and a placebo control group. Metformin 850 mg bid is the pharmacological intervention. A corresponding placebo is used to achieve a randomized, placebo controlled, double masked research design. The following codes are used in this section: MP-metformin placebo and MA-metformin active (850 mg). Metformin is an investigational drug for the treatment of IGT and will be used under an Investigative New Drug (IND) application with the Food and Drug Administration (FDA).

#### 7.4.1.1 Metformin

Metformin is an antihyperglycemic drug of the biguanide class used in the management of non insulin dependent diabetes (NIDDM) in over 90 countries for over 30 years. It was approved for use in the U.S. in 1995 and is distributed by Bristol Myers-Squibb under the trade name Glucophage and manufactured by Lipha, a French pharmaceutical firm.

Metformin reduces the excess hepatic glucose production that characterizes NIDDM without increasing insulin secretion (see section 3.7.1). With reduced hyperglycemia, glucose uptake by muscle and other insulin sensitive tissues is enhanced while insulin levels remain stable or decline. In addition to its antihyperglycemic action, metformin also has antihyperlipidemic effects, particularly the lowering of serum triglyceride levels and is sometimes associated with weight loss.

Metformin is related to phenformin, an agent used in the U.S. in the late 60's and early 70's but withdrawn from use because of the occurrence of severe, often fatal, lactic acidosis. Metformin has been found to cause lactic acidosis rarely (about 0.03 cases per 1,000 person years) and then only when used in persons with renal or hepatic insufficiency or during episodes of hypoxia or circulatory failure.

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

Metformin is not currently approved for use as a preventive for the development of NIDDM. However, some studies suggest that metformin may be effective in persons with impaired glucose tolerance, similar to those in the DPP, by reducing hepatic glucose release, enhancing insulin sensitivity, or through other mechanisms such as weight loss.

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

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

### 7.4.2 Dosing Schedule

The administration of coded medication, either active or placebo, takes 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. Thus, metformin will be administered with food and the dose (MP or MA) will be increased in two steps during the DPP.

#### 7.4.2.1 *Pre-randomization*

All DPP candidates participate in a three week run-in phase during eligibility screening in which participants take MP (metformin-placebo) twice daily, in the morning and evening with food (see section 6.2.3). Participants will be told that the pills are inactive during the run-in.

#### 7.4.2.2 *Post-Randomization - Steps I and II*

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

##### Step I

After randomization, pharmacological participants initially take one tablet with the morning meal. This is MP in the placebo control group and MA in the metformin 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 in the placebo control group and MA BID in the metformin group.

Table 7-1 Summary of Coded Medication Administration

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

\* 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, A - active, P – placebo

#### 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.

#### 7.4.3 **Restarts and Titration Due to Potential Non-Gastrointestinal Side Effects**

If non-gastrointestinal side effects considered likely to be due to coded medications occur and require cessation of coded medications during Step I, all coded medications will be stopped for four weeks. If the non-gastrointestinal symptoms disappear, a second attempt to introduce coded medications is made after four weeks. If symptoms re-occur, the coded medications will again be discontinued. A third try may be attempted after six months and a fourth try after another six months.

Potential non-gastrointestinal side effects include, but are not limited to: headache, mild edema, leg cramps, arthralgia, myalgia, dizziness, mild rashes, and dysmenorrhea. If non-gastrointestinal side effects occur that are considered likely due to coded medications during Step II, the participant will drop back to the Step I dosing schedule for four weeks. A second attempt to restart Step II is made after four weeks. If symptoms re-occur during

this second attempt to implement Step II, the participant is restarted at Step I for six months. A third attempt to restart Step II is made after six months. If this third attempt fails, the participant will be maintained at Step I for the remainder of the DPP. Gastrointestinal side effects are handled as indicated below.

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

##### *A. Laboratory Safety Monitoring*

During the DPP all participants assigned to one of the two pharmacological treatment groups will have periodic laboratory tests to assess possible toxic effects on the hepatic, hematopoietic and renal systems. These include:

- ALT and AST (liver enzymes) measured at end-months 3 and 6, and then every 6 months.
- A CBC with differential count at end-months 6 and 12, and then yearly.
- A serum creatinine every 6 months during the DPP.

In addition, women of childbearing age will have pregnancy tests when necessary based on symptoms and menstrual history.

##### *B. Discontinuation of Coded Medication Use During Hospitalizations*

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

##### *C. Gastrointestinal Symptoms*

These include diarrhea, abdominal pain, vomiting, nausea, a metallic taste, bloating, flatulence and anorexia. They are more likely to occur with metformin but may occur with placebo. If these symptoms are mild and tolerable, coded medications will be continued.

If they are moderate or difficult to tolerate, they will be presumed initially to be due to metformin and the protocol for reductions from Step II to Step I and Step I to temporary cessation will be implemented only for the coded metformin. If, after one week, these gastrointestinal symptoms are not alleviated by reducing or stopping MP or MA, all coded medications will be stopped. Coded medication may be restarted after 4 weeks at Step I. If coded medications cannot be tolerated on this second attempt, a third restart can be attempted at six months. A fourth and final restart can be implemented after another six months.

In the event that diarrhea, abdominal pain or vomiting becomes severe enough to cause dehydration or volume depletion, coded medication will be discontinued immediately and the participant will be evaluated and treated appropriately. Once dehydration or severe pain has resolved, coded medication can be restarted at the previous dose.

##### *D. Renal Insufficiency*

Serum creatinine safety measurements will be made every six months in all participants in the pharmacological treatment groups of the DPP. Metformin is not known to cause renal insufficiency. However, it is associated with an increased risk for lactic acidosis if used in persons whose glomerular filtration or creatinine clearance rates are below 60 mL/min (per 1.73 m<sup>2</sup> surface area). Thus, metformin use is contraindicated with serum creatinine  $\geq 1.5$  mg/dL [133  $\mu$ mol/L] in men and  $\geq 1.4$  mg/dL [124  $\mu$ mol/L] in women. If either condition occurs during the study, coded metformin (MP or MA) will be discontinued and serum creatinine rechecked in two weeks. Coded metformin will be restarted if the repeat serum creatinine is  $< 1.5$  mg/dL in men or  $< 1.4$  mg/dL in women. If the serum creatinine is again  $\geq 1.5$  mg/dL [133  $\mu$ mol/L] in men or  $\geq 1.4$  mg/dL [124  $\mu$ mol/L] in women, regardless of the cause, coded metformin will be stopped permanently and participants will be referred to their health care providers for an evaluation of potential causes of elevated creatinine. 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. For participants who are permanently off study medication, elevations in serum creatinine do not require confirmation, but will be reported to the health care provider. A creatinine clearance is

only performed post-randomization if the participant turns 80 years old during the DPP and did not receive a creatinine clearance for eligibility.

E. *Anemia*

A CBC will be determined for safety reasons at end-months 6 and 12, and at yearly intervals, thereafter, in all participants in the pharmacological treatment groups. 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. This evaluation will include measurement of serum B12 levels and exploration of other causes of anemia or macrocytosis, as indicated. Coded medication may be continued if the cause of the anemia is identified and treated. This includes the administration of vitamin B-12 when indicated.

F. *Hepatotoxicity*

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.

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.

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.

G. *Pregnancy and Nursing*

If a woman plans to become pregnant or becomes pregnant, coded medication will be discontinued. Following the pregnancy and nursing, the coded medication will be restarted at the Step I dosage level and then progressed to Step II as outlined above. See the Pregnancy Protocol, Section 7.5.4, for more details about coded medication unmasking and use following pregnancy.

H. *Radiological Studies Using Contrast Dyes*

Because of the potential danger of contrast induced renal insufficiency and lactic acidosis associated with metformin, under these conditions, the last dose of 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  $\mu$ mol/L) for men and < 1.4 mg/dL (124  $\mu$ mol/L) for women). A wallet ID will be given to all participants and a

warning letter will be sent to all primary care providers to alert them to the fact that participants may be taking metformin and that coded medication needs to be discontinued prior to any radiological studies involving contrast dyes.

*I. Lactic Acidosis*

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

*J. Hypoxic States - Congestive Heart Failure*

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

*K. Surgical Procedures*

Because of the risk of metabolic acidosis during general anesthesia and major surgical procedures, 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  $\mu$ mol/L) for men and  $< 1.4$  mg/dL (124  $\mu$ mol/L) for women). If an outpatient procedure is scheduled, a letter will be sent to surgeons to alert them to the fact that coded medication must be discontinued prior to surgery.

*L. Dermatological Reactions*

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

*M. Headaches*

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

#### **7.4.5 Indices of Adherence**

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

Adherence to the pharmacological treatment will be assessed by the following:

- By visual inspection of participant's returned pill containers, the case manager will estimate percent of prescribed coded medication taken.
- By conducting a brief, structured interview, the case manager will assist participants to (a) identify problems in adherence to the pharmacological treatment and (b) estimate adherence to the prescribed protocol since their previous visit.

Results of the case managers' adherence estimate and the interview with participant will guide the consideration of strategies to improve adherence.

#### **7.5 Definition and Management of Concomitant Conditions**

Clinical centers are neither sufficiently staffed nor funded to provide all primary care or ancillary care to participants involved in DPP. Whenever possible and acceptable to the referring primary care provider, conditions significantly affecting either the primary or secondary outcomes of the DPP should be cared for as specified by protocol within the context of the DPP in order to protect the integrity of the DPP research questions. In addition,

treatments for concomitant conditions which could potentially affect either the primary or secondary outcomes should be avoided. The following sections provide guidelines for therapy which should be vigorously pursued. However, investigators and staff must be sensitive and at times flexible with regard to the prerogative and needs of the primary care providers who have a participant enrolled in DPP. If the following conditions arise during the course of DPP, the investigator will contact the primary care provider by letter, informing him/her of the condition and provide a copy of the treatment options developed for DPP participants. Discussions with the primary care provider should be conducted in the spirit of negotiation and collegiality, with the intent of including the referring primary care provider in DPP operations. Treatment of all other conditions not directly related to DPP outcomes will be treated by referring primary care providers, community resources, or the clinical center as determined by referral patterns. Participants with concomitant conditions who otherwise meet eligibility criteria will remain on their pre-enrollment therapy.

### 7.5.1 Hypertension

There is a strong association between NIDDM and hypertension, apparently independent of age and obesity (Modan, et al., 1985; Yudkin, 1991). Based on available cross-sectional data, a cohort of participants in the likely age range for the DPP will include a high proportion (~35%) who will have hypertension. Following are recommendations for treatment:

#### A. Goals of Therapy:

1. Therapy should aim at maintaining BP <140/90 mm Hg. However, in participants over age 60, the initial goal of therapy should be to lower SBP to <160 mm Hg for those participants with SBP >180 mm Hg and to lower blood pressure by 20 mm Hg for those with SBP between 160 and 179 mm Hg. If this is well-tolerated, blood pressure should be lowered to target levels noted above.
2. At SBP levels of 140 to 160 mm Hg in participants with isolated systolic hypertension, life-style modifications may be sufficient to lower blood pressure. Antihypertensive drug therapy should be carried out more cautiously in older participants. Blood pressure measurements may be required in the standing as well as seated positions, and antihypertensive treatment should be initiated with smaller doses than usual.

#### B. Therapy:

1. Diet: Non-pharmacologic therapy should be employed initially, consisting of a prudent diet aimed at weight reduction if necessary and moderate sodium restriction (< 2.3 g of sodium), limitation of alcohol intake, and encouragement of physical activity. The participant and primary care provider will receive a standard printed set of instructions outlining the goals. Participants will be advised to lose weight if overweight, limit alcohol intake to < 1 oz per day of ethanol, to exercise aerobically regularly, to maintain adequate potassium, calcium and magnesium intake, to stop smoking, and to reduce dietary saturated fat and cholesterol intake. These guidelines will reinforce the standard lifestyle recommendations already in place for DPP. If the blood pressure does not fall into an acceptable range after 4-6 weeks, then pharmacologic therapy should be recommended.
2. Drug therapy should be based on specific needs of the participants, potential side effects of therapy, and consideration of other factors such as cost and availability. The following classes of agents can be employed as first-line agents; substitution and/or addition of drugs should be considered if blood pressure targets are not attained.
  - a. Angiotensin converting enzyme inhibitors.
  - b. Calcium channel antagonists.
  - c. Alpha adrenergic blockers.
  - d. Centrally-acting alpha<sub>2</sub>-agonists.
3. Because of their potential to worsen glucose intolerance, diuretic agents should be strongly discouraged for the treatment of hypertension in DPP participants (Bengtsson, et al., 1984; Skarfors, et al., 1989; MRC Working Party, 1981; Saxman, et al., 1994). When indicated for the treatment of edematous states or congestive heart failure, diuretics may be used with caution, and will be noted in the subsequent data analysis as a confounding variable. This applies to all diuretic therapy including thiazide and loop diuretics; there should be careful monitoring of serum potassium to maintain values above 4.0 mEq/L.
4. Beta-blockers should be strongly discouraged for the treatment of hypertension in DPP participants. When indicated for the treatment of CAD or tachyarrhythmias, beta-blockers should be used with

caution and will be noted in the subsequent data analysis as a confounding variable. This applies to labetalol (combined alpha-beta blocker) as well as both selective and nonselective beta-blockers.

## 7.5.2 Lipids

### 7.5.2.1 Dietary Treatment

Although the available data suggests that IGT is associated with an increased risk of atherosclerosis, IGT is not currently designated by the National Cholesterol Education Program (NCEP) report (National Cholesterol Education Program, 1993) as one of the cardiovascular risk factors; therefore, for the purposes of diagnosis and treatment of dyslipidemia in DPP, IGT will not be considered a cardiovascular risk factor.

The recommended initial dietary treatment for dyslipidemia (NCEP Step I) coincides exactly with the American Diabetes Association dietary recommendations for management of diabetes regarding the intake of saturated fat and cholesterol and the approach to excess body weight management (American Diabetes Association Consensus Statement, 1993). Thus the standard lifestyle recommendations for all DPP participants, independent of their lipid status, provides adequate initial dietary treatment for those with hyperlipidemia. Dietary treatment in DPP will be introduced at the time the DPP treatment is initiated and will be maintained by clinical centers. Primary care providers will be informed of these efforts. All participants will receive the same instruction by means of customized handouts that will contain dietary information based on the American Diabetes Association/NCEP Step I dietary recommendations. This will meet acceptable standards of care for both IGT and dyslipidemia while achieving a standardized level of dietary instruction.

Therefore in dyslipidemic participants:

- A. At 3 months, dietary recommendations will again be provided for dyslipidemic participants who were identified at baseline. A lipid profile will not be repeated at 3 months to assess dietary treatment, except in those participants with CVD.
- B. A lipid profile will be repeated at 6 months to identify participants who may qualify for lipid lowering drug therapy.

### 7.5.2.2 Drug Treatment

The cutpoints for initiating drug therapy for hypercholesterolemia have been recommended by the NCEP to be at an LDL-cholesterol of >220 mg/dL for premenopausal women (or men <35 years of age), at >190 mg/dL for low-risk diet-resistant participants, at >160 mg/dL for high risk participants and at >130 mg/dL (or less depending on the primary care provider's judgment) for participants with CVD. Participants with borderline-high (200-400 mg/dL) or high (400-1000 mg/dL) triglyceride levels are not routinely recommended for drug therapy unless there is concomitant CVD, a family history of premature CVD, concomitant hypercholesterolemia and low HDL-cholesterol, familial dysbetalipoproteinemia or familial combined hyperlipidemia, or a history of pancreatitis. Pharmacotherapy should be prescribed for participants with triglyceride levels in the region of 1000 mg/dL or greater. Lastly the NCEP recommends reducing LDL-cholesterol to <130 mg/dL in individuals with low HDL-cholesterol (35 mg/dL) and one other CVD risk factor. DPP participants will follow NCEP recommendations for drug treatment of dyslipidemia.

Dyslipidemia will be diagnosed according to the proposals discussed above and are summarized in the table below. IGT will not be considered to be a cardiovascular risk factor. As a secondary outcome, specific lipid levels measured during DPP will be masked (see section 5.6.3). However, hyperlipidemia participants will be unmasked to lipid results at 6 months if they qualify for drug therapy (at 3 months for CVD participants). Cardiovascular risk factor status will be updated whenever a lipid profile is repeated. Conversion to diabetes will add one risk factor.

Table 7-2

	Diagnosis	Diet therapy Cutpoint and Target for Therapy	Drug therapy Cutpoint
LDL-cholesterol with <2 risk factors	160 mg/dL (4.15 mmol/L)	160 mg/dL (4.15 mmol/L)	190 mg/dL (4.90 mmol/L)
LDL-cholesterol with $\geq 2$ risk factors	130 mg/dL (3.35 mmol/L)	130 mg/dL (3.35 mmol/L)	160 mg/dL (4.15 mmol/L)
LDL-cholesterol with CVD	100 mg/dL (2.60 mmol/L)	100 mg/dL (2.60 mmol/L)	130 mg/dL (3.35 mmol/L)
Triglyceride	400 mg/dL (4.52 mmol/L)	200 mg/dL (2.26 mmol/L)	(400 mg/dL (4.52 mmol/L))*

\* based on the primary care provider's judgment and according to NCEP guidelines

### 7.5.2.3 Treatment Protocols

#### A. Diet treatment

All participants independent of lipid status will be instructed in the equivalent of an NCEP Step I diet on entering DPP. The diet recommendations will be provided by the centers and primary care providers will be informed of this. Participants in the standard lifestyle recommendation groups will receive instruction by means of customized handouts and those in the intensive lifestyle intervention group will receive specific instructions according to the dietary design that has been developed for this group. Participants will receive repeat dietary instruction using the same methods described above.

#### B. Pharmacotherapy

Participants whose lipid levels qualify them for drug therapy at 6 months will have reached a secondary outcome and will be unmasked to lipid levels so that a decision can be made regarding hypolipidemic drug selection. Primary care providers will be informed. Thereafter actual lipid levels will be reported on these participants. Participants with CVD will have a 3-month lipid profile performed; if their levels qualify them for pharmacotherapy they will be unmasked to lipid levels for drug selection and early initiation of drug treatment.

#### C. Drug Treatment Options

1. Pure hypercholesterolemia:
  - HMG-CoA Reductase Inhibitor
  - Sequestrants
2. Pure hypertriglyceridemia:
  - Gemfibrozil (no alternative. Addition of sequestrant may be necessary if LDL cholesterol rises)
3. Combined hyperlipidemia:
  - Gemfibrozil plus a sequestrant
  - HMG-CoA Reductase Inhibitor
  - HMG-CoA Reductase Inhibitor plus gemfibrozil (in selected cases)

### 7.5.3 Psychological Diseases and Use of Psychoactive Agents

Severe psychiatric disorders can interfere with the compliance of participants with research protocols, and some psychoactive drugs are known to alter glucose tolerance and/or induce weight changes. Due to the high prevalence of psychiatric disorders in the general population, it is very likely that some participants will develop them after enrollment in the DPP.

Several psychoactive agents have been reported to interfere with appetite and/or glucose tolerance (Gray, et al., 1992; Levine, et al., 1989). The different selective serotonin reuptake inhibitors are considered to be a single class. The use of fluoxetine up to 20 mg/day (or equivalent doses of other SSRI) is permissible. The use of fluoxetine (or equivalent doses of other SSRI) at doses higher than 20 mg/day is an exclusionary criteria for the DPP and use subsequent to randomization will be noted in the data analysis as a confounding variable.

### 7.5.4 Pregnancy

Women with a history of gestational diabetes (GDM) are one of the potential groups of interest for the DPP. These women, together with many other participants in DPP, may be of childbearing potential during the course of

the DPP. Data from available cohorts suggest that about 6 percent of women of childbearing age may be expected to get pregnant in a given year.

#### **7.5.4.1 Indications During Pregnancy**

Metformin is contra-indicated in pregnancy although data on adverse effects on the fetus or the mother are scant. The embryotoxic effects of biguanides have recently been evaluated in the *in vitro* cultured mouse embryo model (Denno, et al., 1994). Because of the lack of teratogenicity of metformin in the few available studies, this drug is classified by the FDA as pregnancy category B (no evidence of risk in humans, animal findings negative).

There is no general contraindication for women continuing the exercise intervention during pregnancy (American Academy of Pediatrics, American College of Obstetricians and Gynecologists, 1988). The 150 min/wk target for women in the intensive lifestyle intervention should not require monitoring, but because of the lack of data on ketosis with vigorous exercising, regimens that exceed 1000 kcal per week may require monitoring of ketosis. Dieting for weight loss during pregnancy can be dangerous therefore guidelines for calorie intake (American Academy of Pediatrics, American College of Obstetricians and Gynecologists, 1988) will be recommended.

Women of childbearing age who are fertile, meet other eligibility requirements and wish to participate in the DPP will be informed of the potential risks to a pregnancy conceived while on any DPP pharmacological treatment. Women who consent to participate will be asked to practice reliable birth control including systemic hormones, intrauterine devices and barrier methods (diaphragm, male or female condom, cervical cap) with concomitant intravaginal spermicide.

#### **7.5.4.2 Safety Monitoring**

Women in the intensive lifestyle intervention group will be asked to obtain pregnancy tests if pregnancy is suspected. Women in the pharmacological treatment group will be asked to complete monthly menstrual diaries and to get immediate pregnancy testing if their menstrual cycles are more than one week overdue or they otherwise suspect they are pregnant.

#### **7.5.4.3 DPP Interventions During Pregnancy**

Women randomized to the pharmacological treatment who are found to be pregnant while taking coded medication will have their coded medication discontinued and be immediately unmasked to the pharmacological treatment assignment. Information on the potential teratogenicity of metformin will be provided to both the DPP participant as well as her provider(s) of obstetrical care in order to facilitate an informed decision on further handling of the pregnancy.

Recommendations that exercise should continue with a target of 150 min/wk per week will be forwarded to the providers of obstetrical care for DPP participants in the intensive lifestyle intervention who get pregnant during the course of the DPP. These principles will also apply to those women randomized to standard lifestyle recommendations.

Pregnancy will require modifying the diet intervention to accommodate the increase in calories recommended for a healthy pregnancy, and for lactation (American Academy of Pediatrics, American College of Obstetricians and Gynecologists, 1988). The recommended average daily caloric intake for pregnant women is 30-35 kcal/kg IBW. These recommendations should be forwarded to the provider(s) of obstetrical care for DPP participants who get pregnant during the course of the DPP, regardless of the DPP treatment group. DPP monitoring and visit schedules will be determined by the date of randomization.

#### **7.5.4.4 DPP Interventions During Breast Feeding**

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

#### **7.5.4.5 Outcome Assessment Following Pregnancy**

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

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

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

#### **7.5.5 Smoking**

The prevalence of smoking among people with impaired glucose tolerance is estimated to have declined in the past decade to about 20-25%, compared to the NHANES II data of 30-35%, and is consistent with U.S. smoking reduction overall (Harris, 1989). Thus, 800-1000 DPP participants are expected to be current smokers. DPP must follow the established public health policy to reduce the prevalence of smoking by discussing smoking as a compounding risk factor for CVD and emphasizing the overall benefits to health for those who quit.

Recommendations from the National Cancer Institute for practicing physicians include asking about smoking, advising smokers to quit, and assisting those who want to stop smoking by providing follow-up (Glynn, et al., 1989). These strategies will be employed by DPP personnel at the annual visits for participants, with distribution of educational materials to those expressing an interest in smoking cessation. Simultaneous referral back to their primary care providers and planned programs can also be offered.

#### **7.5.6 NIDDM**

##### **7.5.6.1 Diabetes Discovered At Screening**

Given the high risk characteristics of the volunteers undergoing screening for participation in DPP, it is anticipated that approximately 4000 individuals will be found to have previously unrecognized diabetes. Those individuals who have diabetes mellitus by ADA criteria will receive an informational letter indicating that they may have diabetes mellitus and should be seen by their primary care provider or available community resources for evaluation to confirm the diagnosis of diabetes and to initiate appropriate therapy. Participants will be given copies of their laboratory studies for their primary care providers, but DPP personnel will not participate in any further evaluation or treatment of these participants. Volunteers who do not have a primary care provider will be referred to local health care facilities.

##### **7.5.6.2 Interim Visits For Symptoms**

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

### 7.5.6.3 *Intervention and Follow-up for Participants with Diabetes and Fasting Glucose <140 mg/dL*

Assuming a 7.5% annual conversion rate in the control group and a 33% reduction in hazard rate in the intervention groups, 571 participants are anticipated to meet the DPP primary outcome during the course of the DPP. Participants, investigators, and primary care providers will be unmasked to the diagnosis of diabetes. In addition, all subsequent glucose and hemoglobin A<sub>1c</sub> determinations will be unmasked to participants and investigators. The pharmacological treatment group assignment will remain masked.

After informing the participant and the primary care provider of the diagnosis and explaining the significance, the investigator in conjunction with the primary care provider will endeavor to maintain the participant on their assigned treatment. Further DPP intervention will include intensification of any lifestyle intervention to which the participant has been randomized. For participants assigned to the intensive lifestyle intervention, intensification of diet and exercise with the aim of greater adherence and improved response will be implemented. For participants randomized to pharmacological treatment, the standard lifestyle recommendations (which are consistent with ADA Guidelines) will be reinforced as soon after the diagnosis as possible and the participant will be seen one month and three months later (ADA Clinic Practice Recommendations, 1998). Subsequent reinforcement of standard lifestyle recommendation will occur at the scheduled three month interval visits. In addition, all participants developing diabetes will be offered self monitoring of blood glucose (SMBG) with the option of monitoring fasting glucose levels two to three times weekly as well as during any acute illness or in the event of symptoms such as polydipsia, polyuria or polyphagia. SMBG results may be reviewed at quarterly visits and the participants will be instructed to inform the clinical sites if fasting glucose determinations exceed 140 mg/dL.

DPP participants will continue to be seen at quarterly intervals for clinical assessment. Secondary outcome measurements will continue to be performed. In addition, fasting glucose and hemoglobin A<sub>1c</sub> determinations will be obtained at quarterly visits.

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

In the event that participants progress to fasting glucose in excess of 140 mg/dL on two occasions, coded medication will be discontinued. Participants, investigators, and primary care providers will remain masked to the pharmacological treatment assignment until the end of the DPP. A stepped care protocol for treatment of diabetes mellitus as recommended by the American Diabetes Association will be recommended to the primary care provider. The protocol will include increased SMBG frequency and therapy with pharmacologic agents with the goal of achieving pre-prandial capillary glucose measurement 80 - 120 mg/dL (bedtime values of 100 - 140 mg/dL) and hemoglobin A<sub>1c</sub> determinations < 7%. Additionally, participants will be followed by their primary care providers for the development of any diabetes-related complications such as retinopathy or neuropathy. All DPP-related glucose tolerance testing for insulin secretion or insulin sensitivity studies will be terminated at this time and replaced with unmasked fasting plasma glucose and hemoglobin A<sub>1c</sub> values. However, participants will continue to be followed at scheduled intervals to collect other outcome data including measurements of cardiovascular outcomes.

### 7.5.7 **Cardiovascular Disease**

Cardiovascular events have been chosen to be one of the outcomes in DPP. The incidence of CVD is increased in participants with newly diagnosed NIDDM, and the risk of deaths in non-diabetic participants with impaired glucose tolerance is two times higher than in participants with normal glucose metabolism. The upper range of postload glucose distribution in a non-diabetic population is associated with a two- to three-fold increased mortality in middle-aged men and women (Stamler, et al. 1979; Fuller, et al. 1980; Eschwege, et al., 1985). On the other hand, many of the cardiovascular diseases themselves, or their treatments, have an effect on proposed treatments or outcomes of the DPP, or vice versa.

Cardiovascular diseases (CVD) in participants recruited to the DPP are significant for three reasons:

- CVD may have an effect on prognosis of the participants recruited,
- The symptoms of CVD may have an effect on the capability of participants to follow the guidelines of treatment especially in the intensive lifestyle intervention group, and
- The conversion rate from IGT to NIDDM may be higher in participants with CVD than in participants without CVD.

#### **Recommendations**

##### *A. Exercise Testing*

1. Participants randomized to the intensive lifestyle intervention 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:
  - previous hospital verified myocardial infarction; or
  - self reported history of “heart attack”; or
  - abnormal Q-waves in their ECG > 0.03 seconds in duration.
2. Sub-maximal exercise tolerance testing with simultaneous ECG and blood pressure monitoring will be performed for men older than 40 years and post-menopausal women not on hormone replacement therapy who have at least two of the following risk factors:
  - hypercholesterolemia, S-Chol > 240 mg/dL
  - hypertension, systolic BP > 160 and/or diastolic BP > 90 on two separate measurements or on medication for hypertension
  - current smoking
  - family history of CVD at the age less than 55 years

No exclusions will be made based on exercise test results, but participants who are classified by the results to have high risk of cardiovascular complications during the exercise should not be allowed to participate in the exercise program until receiving definitive therapy. High risk groups based on the results of exercise tests are those who have:

- angina pectoris at the low exercise level (< 6 METs); or
- ischemic ST segment depression > 2 mm at any level of exercise; or
- decline in systolic blood pressure > 15 mm Hg; or
- ventricular arrhythmia induced by exercise.

All other participants who have symptoms or signs of CVD during the exercise test are eligible to participate in the exercise program, but the level of the program must be individually adjusted. These participants must be taught to measure their heart rate during exercise and to keep exercise at a safe level (i.e. no symptoms of angina pectoris or dyspnea on exertion and maintenance of heart rate at least 10 BPM lower than that level at which symptoms appeared during the exercise tolerance test) (Fletcher, et al., 1990).

#### *B. Myocardial infarction or unstable angina during the DPP*

Participants who have myocardial infarction or unstable angina during the DPP should be treated according to the community standards. All participants in the pharmacological treatment groups will be eligible to continue to follow the DPP protocol after myocardial infarction without any major interruptions, unless specific contraindications arise. According to the American Heart Association Guidelines a submaximal exercise test should be performed within three weeks after an acute MI (Fletcher, et al., 1990). A maximal exercise test should be done more than 3 weeks after myocardial infarction, when the participant is ready to resume full activities. The participants in the intensive lifestyle intervention group should discontinue the exercise program after myocardial infarction until the risk stratification by exercise testing is done 6-8 weeks post-MI. The decision whether these participants are allowed to continue the exercise program or whether their exercise program should be modified is based on the exercise tolerance test.

#### *C. New angina pectoris*

Participants who have new symptoms suggesting angina pectoris during the DPP should be treated by their primary care providers according to the community standards and cardiological evaluation and exercise tolerance testing may be recommended to them. Participants in the intensive lifestyle intervention group will have their exercise program discontinued until the cardiological evaluation has been performed and their eligibility to continue the exercise protocol should be reconsidered after the results of the evaluation are available. Participants assigned to the pharmacological treatment can continue the DPP protocol without any major interruptions.

#### *D. PTCA or coronary by-pass (CABG)*

According to the American Heart Association Guidelines, exercise tolerance testing should be performed in the routine follow-up of participants who have undergone PTCA, and to every participant who complains of chest pain during exercise after these procedures. The participants of DPP who undergo PTCA or CABG during the DPP should be allowed to discontinue the exercise component of the DPP protocol for up to six months, if necessary. After this period their health status should be re-evaluated to determine their continuation in the exercise protocol with results of exercise tolerance testing playing a pivotal role. If these participants are in the intensive lifestyle intervention group, they will follow a modified exercise protocol for the rest of the DPP, if necessary.

#### *E. Medical treatment of CVD*

Beneficial effects of beta-blockers and ACE inhibitors on mortality and recurrent CVD events after myocardial infarctions are so clear that we cannot restrict their use after myocardial infarctions. The participants with heart failure should be treated according to the community standards and no restrictions on the use of any drugs will be made.

## **7.6 Retention Monitoring and Recovery of Inactive Participants**

Key to both the power and generalizability of findings of DPP is the retention of a large portion of participants throughout the entire DPP; however, recruitment, randomization, and retention of participants for DPP is likely to be difficult. Some of this is due to the fact that participants, although they will have IGT, are asymptomatic. Furthermore, IGT is not presently designated as a disease. In addition, participants who are interested in preventing diabetes will have no choice about the treatment group to which they are assigned. It is anticipated that persons who contemplate participation because of an interest in lifestyle modification may be quite different from those who are willing to take medications. Additional difficulty is imposed by the fact that some test results are masked. However, the greatest problem will probably be due to the demands placed upon participants in DPP with respect to time commitment, transportation, parking, and child or elder care, which vary considerably among the target populations. Steps to maximize retention of participants to the DPP are based upon these considerations.

Since a decision to discontinue follow-up visits is a clear loss to DPP, such decisions are considered not irrevocable and recovery efforts are required. Thus, enrolled participants who make a decision to discontinue follow-up are told they are welcome to return to DPP should they change their minds. Reasons for deciding to discontinue follow-up are explored with the participant. Participants continue to be contacted on a progressively less frequent schedule, starting monthly and decreasing to semi-annually to remind them of the opportunity to re-enter DPP and to maintain contact with them for possible recruitment for the final assessment at the end of DPP.

### **7.6.1 Steps to Maximize Adherence and Retention**

Adherence and retention in DPP is fostered by: a comprehensive array of participant education procedures which requires the interest, responsiveness, and continuous availability of professional staff; motivational programs, group activities, and rewards deployed according to the judgment of each participating center; plus removal of barriers to participation. Central training for the Program and Recruitment Coordinators in the techniques of “motivational interviewing” assists them in providing a framework based on this concept at each center. In addition to providing education regarding details of the interventions, much of staff contact with participants is of a general, supportive nature, addressing frustrations with DPP, problems in maintaining adherence, and even general life issues participants may face.

#### **7.6.1.1 Social Support**

The underlying philosophy of retention of participants is to encourage Program and Recruitment Coordinators, case managers, receptionists, and all other staff to interact with participants in a manner which enhances their sense of bonding to DPP. Additional tactics such as newsletters, outings, birthday and anniversary cards, and the like may be construed as facilitators of a sense of social connection with DPP, its staff, and fellow participants. It is likely that these connections and not the more tangible rewards themselves are the more important incentives to retention.

Because the kinds of activities and rewards that promote the social connections that bond participants to DPP will take very different shapes in different communities and groups, a high level of local development and design of these is desirable. This is facilitated by a menu of nationally available materials and strategies and frequent contact among centers to exchange suggestions such as:

- Quarterly newsletters, developed nationally but able to be tailored locally, including items of interest about participants and staff in different DPP sites to encourage a sense of community within DPP;
- Individual incentives that are less expensive when purchased in bulk and are ordered by Centers as desired from the Coordinating Center, such as mugs, T-shirts, and caps designed to raise a sense of identity with, and pride, in DPP;
- Locally purchased items such as movie tickets, bowling passes, sports tickets, anniversary cards, exercise video and audio tapes, and gift certificates to create a sense of identity with the local center;
- Refreshments (coffee, tea, sodas) for participants at clinic visits;
- Group social gatherings such as holiday parties, picnics, or sporting or cultural events;

- Additional inexpensive tokens such as key chains, pens, pencils, etc., that may be purchased in bulk if desired by several Centers.

#### **7.6.1.2      *Removal of Barriers to Participation***

In addition to these incentives, resources for removing barriers to participation such as child or elder care, transportation, and parking expenses are important considerations. These resources are considered separate from the incentives, as necessary support, to enable participants to adhere to treatment regimens (compliance) and to attend outcomes data collection visits (retention). These resources, given as cash, transportation vouchers, or parking passes, may vary greatly among the Centers.

#### **7.6.1.3      *Honoraria***

In addition, an honorarium will be paid to 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.

#### **7.6.2      *Monitoring Retention***

Recovery of patients on inactive follow-up uses protocols that are standardized according to each of the DPP treatment groups' attendance and adherence demands. These protocols include criteria for identifying participants whose level of adherence and/or attendance should trigger recovery efforts, as well as a graded hierarchy of recovery efforts. This hierarchy of efforts ranges from brief telephone discussion of missed meetings to an individualized counseling session with the case manager or other appropriate staff member in which the participant can review reasons for staying in DPP, concerns regarding DPP, and decisions about remaining a participant.

##### **7.6.2.1      *Visit Monitoring***

There is a computer-based monitoring system to record each visit with participants. One purpose of this system is to identify participants who are having problems with adherence to the protocol. Another purpose of the system is to identify participants who may be candidates for discontinuing follow-up of DPP and thus qualify for recovery efforts.

##### **7.6.2.2      *Measures of Stress and Social Support***

The following self-administered questionnaires will be completed during the DPP (see Section 12 for frequency of administration) for purposes of predicting adherence and retention, and determining the positive or negative impact of DPP treatments.

- **Retention and Treatment Monitoring Measures (Form Q06):**
  - - Life events index
  - - Social provisions scale
  - - Family household assessment
- **DPP-Specific Support Measures (Forms Q09 and Q10):**
  - - Baseline Visit (Form Q09)
  - - Follow-up Visits (Form Q10)