DIABETES PREVENTION TRIAL - TYPE 1 DIABETES (DPT-1)

1. SUMMARY

Type 1 Diabetes Mellitus (Type 1 DM) arises in genetically predisposed individuals as a consequence of immune-mediated destruction of the pancreatic islet insulin secreting β-cells. The onset of clinical symptoms of diabetes represents the end point of a chronic progressive decline in β-cell function, and it appears only when the majority of β-cells have been lost. Since Type 1 DM develops insidiously, often years after the induction of the pathogenic immune-mediated destructive process, it can be predicted using immunological markers and tests of insulin secretion. The ***Diabetes Prevention Trial of Type 1 Diabetes*** **(DPT-1)** has been designed to test whether intervention during the prodromal period of the disease can delay its clinical onset.

It is possible to identify impending clinical Type 1 DM through the detection of autoantibodies directed against self-antigens of the pancreatic β-cells. Since first degree relatives of probands with Type 1 DM have more than ten-fold the risk of Type 1 DM in the general population, the DPT-1 will focus on such relatives. Their initial blood (serum) screening will be for islet cell autoantibodies (ICA) detectable by the indirect immunofluorescence of cytoplasmic islet cell antigens in sections of normal human pancreas. Those individuals found to have ICA will then be staged into one of four different categories of risk of Type 1 DM, dependent upon their point of progression to the clinical disease. Type 1 DM risk assessment in non-diabetic relatives is based on a number of factors, including: genetic susceptibility, age, the presence of ICA especially if found together with insulin autoantibodies (IAA), and the degree of loss of first phase (1 + 3 minute) plasma insulin response (FPIR) during an intravenous glucose tolerance test (IVGTT). In the DPT-1, "High Risk" relatives will be those that have been predicted to have at least a 50% probability of developing Type 1 DM within the next five years on the basis of positive ICA and low FPIR to IVGTT. Moderate risk relatives are those with positive ICA, but normal FPIR to IVGTT. This group is further divisible into those with an "Intermediate Risk" on account of positive IAA and those with only a "Modest Risk" who are IAA negative. The "Low Risk" relatives lack ICA.

The purpose of dividing subjects into these four predictive risk groups is that different intervention strategies are best applied to them because of their stage of natural history, while the invasiveness of the therapeutic approaches to be tested needs to be appropriately reconciled with the estimated risk of Type 1 DM in the different risk groups.

In the "High Risk" group, the protocol is designed to determine whether parenteral insulin therapy, consisting of periodic courses of continuous intravenous insulin, with

accompanying chronic subcutaneous insulin, will delay their expected development of clinical Type 1 DM. The trial is a randomized, controlled, multicenter clinical trial, in which subjects randomized to an *Experimental Group* which will have the active intervention, while subjects randomized to the *Closely Monitored (Control) Group* will be closely monitored and offered treatment at the earliest sign of clinical Type 1 DM. The DPT-1 investigators acknowledge that a placebo-controlled, double-masked, multicenter clinical trial would be most desirable scientifically. Yet, the practicalities of administering chronic subcutaneous placebo injections of a cloudy suspension and of admitting subjects for four days of periodic courses of continuous intravenous placebo infusions create numerous burdens for research subjects and place them at increased risk. This has led the investigators to select for the *Closely Monitored (Control) Group* a protocol that is randomized, unmasked and without use of placebo, but one that involves close monitoring. The investigators recognize that this is a compromise, but appreciate it is in the best interest of those research subjects committing to this research alliance. Moreover, close observation and potential early intervention offers subjects randomized to the *Closely Monitored (Control) Group* the benefit of early diagnosis and the potential of early intervention for treatment of clinical Type 1 DM. This is more than the standard of care in the general medical community for non-diabetic relatives.

The intervention protocol for the “Intermediate Risk” group is designed to determine whether presentation of an islet cell autoantigen (i.e. orally ingested insulin) to the immune system via the intestinal mucosa could induce disease relevant immunological tolerance, thereby delaying the development of Type 1 DM. This latter trial is designed to be a randomized, placebo-controlled, double-masked, multicenter clinical trial, which will be staggered after the initiation of randomization for the parenteral insulin trial.

These two studies are envisioned to be the first in a series of studies designed to test the potential to prevent or delay the development of Type 1 DM.

2. RATIONALE

Parenteral insulin has been successfully used to prevent diabetes in two animal models of spontaneous diabetes, and has undergone trial in newly diagnosed and prediabetic human beings. Repeated injections of insulin in young, prediabetic BB rats (1-5) or NOD mice (6-7) from early life has been demonstrated to inhibit the development of diabetes and reduce the severity of islet inflammation (insulitis) seen in their pancreases. In humans, intensive insulin therapy in newly diagnosed patients, involving two weeks treatment with intravenous insulin delivered via an artificial pancreas, preserved β-cell function for at least one year (8-9). A pilot study of a small group of subjects with prediabetes has suggested that prophylactic parenteral insulin therapy combining 5 days of insulin by intravenous infusion every 9 months and daily subcutaneous insulin injections preserves β-cell function and may prevent diabetes (10). A similar randomized pilot study combining yearly infusions of intravenous insulin and subcutaneous insulin for six months, also suggests potential benefit of the intervention (11). Another randomized small pilot study comparing intravenous insulin, subcutaneous insulin, and the combination of the two, with a control group, also suggests that these interventions have potential benefit (12). Another randomized pilot study has treated a larger group of relatives, some already with onset of glucose intolerance, with daily subcutaneous insulin injections, and report the approach safe and the preliminary results encouraging (13). In these circumstances, insulin may be either serving as an immune modulator or through resting the β-cells thereby making them less susceptible to immune attack because of decreased expression of secretory granule associated antigens. The intervention protocol for the "High Risk" relatives will extend these observations by testing parenteral insulin therapy in a full scale controlled clinical trial, with a sensitivity to detect diabetes protection in one out of three relatives so treated.

In the NOD mouse model of Type 1 DM, it has been demonstrated that the oral administration of islet autoantigens is effective in delaying the onset of Type 1 DM (14-19). Repeated ingestion of insulin by young, prediabetic NOD mice has been shown to inhibit their development of diabetes. It also has been shown that ingestion of glutamic acid decarboxylase (GAD), another putative β-cell antigen, by prediabetic NOD mice inhibits the development of diabetes (19). The results suggest that tolerance provoked by oral insulin or GAD administration can attenuate pancreatic islet autoimmunity, leading to a delay in the onset of the disease. The intervention protocol given as part of a randomized placebo controlled clinical trial in "Intermediate Risk" relatives, will test the protective potential of repeated oral islet cell antigen (insulin) presentation (oral tolerance induction) to prevent or delay Type 1 DM when given early

in the natural history of the pathogenic events. This protocol has a sensitivity to detect diabetes protection in one out of two relatives so treated.

There is the theoretical possibility that, instead of delaying or preventing the development of disease, antigen specific therapy (parenteral or oral insulin) may have the potential of accelerating the immune process which leads to β-cell destruction and the development of diabetes.

2.1 Long Term Follow-Up of Subjects Developing Diabetes - Rationale

The diagnosis of diabetes is only one point on a continuum of the disease process that begins before and continues after diagnosis. Immunologic and β-cell function aspects of the type 1 diabetes disease process are closely monitored on all subjects enrolled in the DPT-1 by measuring ICA and IAA yearly, mixed meal tolerance tests (MMTT) and intravenous glucose tolerance tests (IVGTT) every other year, and oral glucose tolerance tests (OGTT) with c-peptide measurements every six months. In addition to potentially altering the development of diabetes, parenteral and/or oral insulin treatment may alter the rate of decline in β-cell function and/or islet autoantibody titers. In fact, a treatment effect on β-cell function may be more significant than the development of overt diabetes. The DPT-1 Study Group wants to investigate whether any treatment effects are seen after the diagnosis of overt diabetes. Moreover, subjects enrolled in the control arms of both the oral and parenteral insulin protocols constitute one of the largest and most intensively evaluated cohorts of subjects at increased risk of diabetes followed prospectively. Such a large scale prospective investigation requires the organizational structure of the DPT-1. This well-characterized cohort constitutes an ideal group to better characterize the natural history of the type 1 diabetes process and the rate of decline in β-cell function. In addition, because of the careful prospective evaluation of DPT-1 subjects, many individuals are diagnosed with diabetes while still asymptomatic, often with elevated post-prandial glucose but normal fasting glucose levels. Since they are asymptomatic, diabetes in these individuals is diagnosed at an earlier stage than in the general population and community at large where the diagnosis is usually made because the patient seeks medical attention for symptoms due to more severe hyperglycemia. Since type 1 diabetes is not usually been diagnosed at this stage, the natural history from this stage of type 1 diabetes is unknown. Finally, many studies have shown that preservation of β-cell function after diagnosis of type 1 diabetes is strongly correlated with easier and better glycemic control, less microvascular complications, and less hypoglycemia. Long-term follow-up of DPT-1 subjects diagnosed with diabetes will allow the study group to

investigate whether intervention results in improved glycemic control, less hypoglycemia and ultimately less microvascular complications and how long such beneficial effects persist.

3. OBJECTIVES

The major objective of the DPT-1 is to determine whether early intervention by antigen based therapies in non-diabetic relatives of persons with Type 1 DM can delay their development of Type 1 DM as a clinical disease. Since insulin is a well characterized antigen specifically produced by β-cells, it will be used for this purpose in the initial DPT-1 studies. Two protocols, with the following characteristics, will be undertaken.

3.1. Principal Objectives:

1. Parenteral Antigen Protocol: To determine whether early intervention with parenteral insulin therapy, consisting of periodic courses of intravenous insulin with accompanying chronic daily subcutaneous injections of long acting (ultralente) recombinant human insulin, will delay or prevent the development of clinical Type 1 DM in "high risk" (i.e. $\geq$ 50% risk over 5 years) non-diabetic relatives of patients with Type 1 DM. This intervention in the *Experimental Group* will be compared with a *Closely Monitored (Control) Group* who will have close observation and early initiation of treatment at the first evidence of clinical Type 1 DM.

2. Oral Antigen Protocol: To determine whether intervention with repeated oral administration of a potential autoantigen- (i.e. recombinant human insulin), given extremely early in the course of development of Type 1 DM, will prevent or delay the development of clinical Type 1 DM in "intermediate risk" (i.e. 25-50% risk over 5 years) non-diabetic relatives of patients with Type 1 DM. This intervention will be compared with placebo given in a double-masked fashion.

3.2. Other Objectives in Both Protocols:

1. To determine the influence of these interventions on β-cell function.
2. To determine the influence of these interventions on humoral and cellular immune responses directed at pancreatic β-cells and their antigens.
3. To improve predictability of Type 1 DM among relatives.
4. To identify factors that influence rate of progression of the disease process to clinical Type 1 DM and beyond.
5. To better characterize the natural history of the Type 1 DM disease process.

3.3. Operational Objectives in Both Protocols:

1. To recruit, screen, stage, and randomize sufficient numbers of subjects to provide adequate statistical power for both protocols to determine whether Type 1 DM can be delayed in 1 of 3 subjects in the parenteral antigen protocol and 1 of 2 subjects in the oral antigen protocol.

2. To maintain acceptable levels of adherence to the randomly assigned therapies over time, including the completeness of follow-up and outcome measures.

3. To monitor and maintain the precision and accuracy of the laboratory assessments used in the screening, staging, and follow up of the study subjects.

3.4. Natural History Objectives:

1. To describe the natural history of the evolution of diabetes in the control subjects, and thereby the influence of intervention in the experimentally treated subjects.

3.5. Administrative Objectives:

1. To establish an administrative structure to coordinate studies, assimilate and implement new studies, monitor clinical centers, provide statistical support, provide oversight, interact with sponsors, and otherwise conduct multicenter clinical trials for prevention and stabilization of Type 1 DM.

2. To establish the communication network for effective interaction, collaboration, and pooling of data between centers.

3. To establish a network of collaborating clinical centers for screening, recruiting, and follow-up of subjects for participation in intervention trials both to prevent or delay development of clinical Type 1 DM and to preserve β-cell function in recently diagnosed clinical Type 1 DM.

3.6. Principal Study Outcome:

1. In both the parenteral antigen protocol and the oral antigen protocol, the principal study outcome is the development of diabetes (originally by criteria modified from the "adult" criteria established by the National Diabetes Data Group (NDDG) in 1979, and by the 1997 American Diabetes Association (ADA) subsequent to their adoption). The original modified NDDG criteria, which must be met on <u>two occasions</u>, were:

- [i] abnormal glucose tolerance based on a 75 gm oral glucose tolerance test, i.e. 2 hour plasma glucose $\geq$ 200 mg/dL AND one intervening value (between ½ hour and 1½ hours) $\geq$ 200 mg/dL -- on two separate oral glucose tolerance tests [if the diagnosis is by this criteria, the two occasions for performance of the test should be one to two months apart].

OR

- [ii] fasting plasma glucose $\geq$ 140 mg/dL (core laboratory) -- on two separate days

OR

- [iii] unequivocal symptoms AND plasma glucose $\geq$ 200 mg/dL -- on two separate days

OR

- [iv] the combination of [ii] and [iii] on two separate days; or the combination of [i] on one day with either [ii] or [iii] on a separate day.

The ADA Criteria, which must be met on two occasions (unless criteria [iv] is present) are:

[i] casual (any time of day without regard to time since last meal) plasma glucose $\geq$ 200 mg/dL, if accompanied by unequivocal symptoms (i.e. polyuria, polydipsia, polyphagia, and/or weight loss),

OR

[ii] fasting (no caloric intake for at least 8 hours) plasma glucose $\geq$ 126 mg/dL (core laboratory),

OR

[iii] 2-hour plasma glucose $\geq$ 200 mg/dL during a 75 gram oral glucose tolerance test (OGTT),

OR

[iv] unequivocal hyperglycemia with acute metabolic decompensation (e.g. ketoacidosis).

In DPT-1, unless criteria [iv] is present or the fasting glucose is $\geq$ 250 mg/dl (at the bedside or in the local laboratory on the day of testing), it is preferred that at least one of the two testing occasions involve an oral glucose tolerance test (OGTT). If the first criterion met is [iii], i.e. by the 2-hour OGTT value, the OGTT should be repeated within 60 days. It is essential that every effort be made to obtain the necessary tests to establish the diagnosis of diabetes.

3.6.1. Categories of Glycemia Established by the American Diabetes Association in 1997:

The critical values are the fasting (no caloric intake for at least 8 hours) plasma glucose and the plasma glucose 2 hours after consumption of oral glucose, administered in less than 5 minutes in a dose of 75 grams (in adults) or 1.75 g/kg body weight to a maximum of 75 grams (in children), as a solution in flavored water.

Normal Glycemia:

- fasting plasma glucose < 110 mg/dL AND
- 2 hour plasma glucose < 140 mg/dL

Impaired Glucose Tolerance (IGT):

- fasting plasma glucose < 110 mg/dL AND
- 2 hour plasma glucose 140-199 mg/dL

Impaired Fasting Glucose (IFG):

- fasting plasma glucose 110-125 mg/dL AND
- 2 hour plasma glucose < 140 mg/dL

Diabetes Mellitus (DM) *[see Section 3.6 for details]*:

- fasting plasma glucose $\geq$ 126 mg/dL OR
- 2 hour plasma glucose $\geq$ 200 mg/dL

[It is possible to have both IGT and IFT].

3.7. Subsidiary Outcomes:

1. Preservation of β-cell function, as determined by plasma C-peptide and/or plasma insulin response to oral glucose, to a mixed formula meal, and to intravenous glucose.

2. Humoral and cellular immune responses directed at pancreatic β-cells and their antigens.

4. OPERATIONAL STRATEGY

Operationally, implementation of the DPT-1 will involve three steps:

STEP 1. **SCREENING** - Initial eligibility screening of relatives for Type 1 DM risk by determination of islet cell autoantibodies (ICA).

STEP 2. **STAGING** - Definition of risk category by staging of ICA-positive relatives as to their degree of risk of clinical Type 1 DM.

STEP 3. **INTERVENTION** - Implementation of the appropriate intervention protocol based on risk category.

Separate informed consents (A; B; and C or D for Steps 1, 2, and 3 respectively) will be obtained for each of these steps. Consent forms are available in English and Spanish.

Screening will identify subjects with evidence of ongoing pancreatic islet cell autoimmunity. Screening will be confined to relatives of persons with Type 1 DM, who are at increased risk of Type 1 DM compared to the general population. (Definition of "Type 1 DM" in proband: proband's diabetes onset prior to age 40 and receiving insulin therapy within one year of diagnosis. This definition is used to limit inadvertent screening of relatives of probands with Type 2 DM, and is not intended to exclude relatives of persons who have Type 1 DM but in whom onset was after age 40. If there is ambiguity as to eligibility, such as whether a proband has Type 1 DM, this will be resolved by an Eligibility and Events Committee.) Whereas first degree relatives - up to 45 years of age - will be targeted, other relatives, e.g. nieces, nephews, aunts, uncles, cousins, grandchildren - up to 20 years of age - will be accepted. However, such other relatives will not be actively sought, because the frequency of positive ICA is substantially less than in first degree relatives.

The initial screening for determination of islet cell autoantibodies (ICA) may be conducted at Centers, Affiliates, and Satellites, or by individual arrangements of appropriate families through regional laboratories. In addition, individuals or physicians who learn of the DPT-1 may send samples directly to the ICA Core Laboratory. All ICA analyses will be determined by the ICA Core Laboratory.

Staging to define risk category will be conducted only for those non-diabetic relatives who screen positive for ICA and consent to undergo further evaluation. The staging will include measurement of insulin autoantibodies (IAA) (and possibly other islet related immune markers) and intravenous glucose tolerance testing (IVGTT) to assess first phase insulin response (FPIR), using the sum of the plasma insulin values of the 1 minute and 3 minute samples, noted as "Insulin Σ (1'+3')". Samples will also be obtained for molecular HLA-DQ typing. For relatives

meeting initial eligibility criteria, oral glucose tolerance testing (OGTT) will be performed to characterize state of carbohydrate tolerance, both to exclude diabetes and enable the stratification of relatives with impaired or indeterminate glucose tolerance. Staging of ICA positive relatives may be conducted at Centers and Affiliates, with samples sent to the Core Laboratories for determination of staging parameters and assessment of eligibility for enrollment in one of the intervention protocols.

Intervention will be conducted only amongst those who consent to participate. The assignment of the intervention protocol will be based solely on the risk category defined during staging. Two intervention protocols will be used: one, the parenteral antigen protocol, amongst "high risk" subjects; and the other, the oral antigen protocol, amongst "intermediate risk" subjects (although it should be noted that when enrollment is completed for the parenteral antigen protocol, which will be initiated first, the eligibility criteria for the oral antigen protocol may be modified to permit higher risk subjects to be enrolled in that protocol). The primary outcome of both protocols is the development of clinical Type 1 DM. Therefore, subjects will be followed until their development of Type 1 DM or the time period planned for the conclusion of the study. The intervention protocols will be conducted at Centers and approved Affiliates with a General Clinical Research Center (GCRC) or equivalent facility. All blood and serum samples for outcome determinations will be sent to the Core Laboratories for analysis.

Masking. It is intended that DPT-1 be a double masked, controlled clinical trial. The oral antigen protocol in intermediate risk subjects will be double masked as to both treatment assignment and outcome. The parenteral antigen protocol in high risk subjects will be double masked as to outcome, but not as to treatment assignment.

In order to assure that masking is maintained, investigators, clinical staff, and subjects will be masked to outcome measures, including all screening, staging, and follow-up data results. All principle and subsidiary outcome measures will be determined ***only*** in the Core Laboratories and results revealed only as dictated by DPT-1 Study Procedures, except as mandated by protocol.

Because local measurements may result in unmasking, DPT-1 Policy precludes local measurement of any eligibility or outcome measure in any subject actively enrolled in DPT-1 except:

- fasting glucose values on the day of performance of any tolerance test (and on a confirmatory day if local value equals or exceeds 160 mg/dL),

- glucose values obtained during intravenous insulin infusions,
- emergency samples essential for patient care,
- parameters approved for measurement in an ancillary study.

Lack of conformity to this policy will be considered a breach of scientific integrity and be subject to NIH review and action.

To assess quality control, DPT-1 has a program involving split duplicates of a subset of samples selected by the Data Management Unit. These samples will be sent to the Core Laboratories in a masked manner. The potential involvement of a subject in this system will increase the total volume of blood to be obtained at the time of performance of a quality control test.

5. RISK CATEGORIES

Risk categories amongst non-diabetic relatives of probands with Type 1 DM are defined below. The risk categories apply to subjects who have "Normal" status confirmed by oral glucose tolerance test (OGTT). Other individuals who also are non-diabetic relatives of Type 1 DM probands, but who have either "Impaired Glucose Tolerance" (IGT) or "Impaired Fasting Glucose" (IFG) status of glucose, are considered "High Risk". Criteria for inclusion of subjects in intervention protocols are summarized. Staging procedures are outlined more completely in later sections. The risk categories determining eligibility for the intervention protocols are as follows:

HIGH RISK - Eligible for Parenteral Antigen Protocol

- Age - 4-45 years

Siblings or Offspring of Type 1 DM Proband

(& Second and Third Degree Relatives, i.e. Nieces, Nephews, Aunts, Uncles, Grandchildren, Cousins Age 4-20 Years)

- Age 8-45 yrs (Siblings or Offspring) or Age 8-20 yrs (Other Relatives)
  - ICA Positive $\geq$ 10 JDF Units in Two Separate Serum Samples
  - IVGTT-Insulin Σ (1'+3') < 10th %ile of age matched normal controls (i.e. < 100 μU/ml) in 2 (of up to 3) IVGTTs
  - Not HLA-DQA1*0102,DQB1*0602
- Age 4-7 years
  - ICA Positive $\geq$ 10 JDF Units in Two Separate Serum Samples
  - IVGTT-Insulin Σ (1'+3') < 10th %ile of age matched normal controls (i.e. < 60 μU/ml) in 2 (of up to 3) IVGTTs
  - Not HLA-DQA1*0102,DQB1*0602

Parents of Type 1 DM Proband

- Age $\leq$ 45 years
- ICA Positive $\geq$ 10 JDF Units in Two Separate Serum Samples
- IVGTT-Insulin Σ (1'+3') < 1st %ile of age matched normal controls (i.e. < 60 μU/ml) in 2 (of up to 3) IVGTTs
- Not HLA-DQA1*0102,DQB1*0602

INTERMEDIATE RISK - Eligible for Oral Antigen Protocol

- Age - 3-45 years

Siblings or Offspring of Type 1 DM Proband

(& Second and Third Degree Relatives, i.e. Nieces, Nephews, Aunts, Uncles, Grandchildren, Cousins Age 3-20 Years)

- Age 3-45 yrs (Sibs or Offspring) or Age 3-20 yrs (Other Relatives)
- ICA Positive $\geq$ 10 JDF Units in Two Separate Serum Samples
- IAA Positive $\geq$ 39 nU/ml (i.e. > 3 Standard deviations above the mean of normal controls) in Two Separate Serum Samples
- Failure to Meet HIGH RISK Criteria for IVGTT-Insulin Σ (1'+3')
- Not HLA-DQA1*0102,DQB1*0602
- Normal OGTT

Parents of Type 1 DM Proband

- Age $\leq$ 45 years
- ICA Positive $\geq$ 10 JDF Units in Two Separate Serum Samples
- IAA Positive $\geq$ 39 nU/ml (i.e. > 3 Standard deviations above the mean of normal controls) in Two Separate Serum Samples
- Failure to Meet HIGH RISK Criteria for IVGTT-Insulin Σ (1'+3')
- Not HLA-DQA1*0102,DQB1*0602
- Normal OGTT

6. DESIGN

In accordance with these objectives and the above strategy, the DPT-1 has the following design features:

6.1. Parenteral Antigen Protocol:

1. Screening will be conducted over four years; some 15,000 non-diabetic relatives of persons with Type 1 DM will be screened each year (60,000 – 100,000 individuals overall).

2. Approximately 3.6% of non-diabetic relatives screened are expected to be ICA positive (20), so that approximately 540 relatives per year will be eligible for staging.

3. Approximately 35% of ICA positive non-diabetic relatives staged are expected to meet the "High Risk" criteria (20), and thus be eligible for the parenteral antigen protocol, or approximately 180 individuals per year.

4. Approximately 50% of eligible subjects are expected to consent to be randomized for the parenteral antigen protocol, or approximately 90 individuals per year.

5. The sample size projection for the parenteral antigen protocol is 340 subjects, assigned approximately in equal numbers to the experimental group and the control group. This sample size provides a power of 80% to detect a 35% difference in the annual hazard rate for the onset of Type 1 DM, expected to be 21% per year in the control group, assuming $\alpha = 0.05$ (two tail test), 4 year accrual, 6 year total study, and allowing for a 10% drop-out rate.

6. In the parenteral antigen ("High Risk") protocol, the experimental therapy is parenteral recombinant human insulin, consisting of periodic courses of intravenous regular insulin with accompanying chronic subcutaneous long acting (ultralente) insulin given twice daily, before breakfast and at bedtime.

7. Of necessity, treatment assignment will be unmasked. However, treatment outcome will be double masked for outcome measures. An unmasked Data Safety and Quality Monitoring Group (DSQ) will review emerging outcome data to protect the well-being of study participants.

6.2. Oral Antigen Protocol:

1. Screening will be conducted over four years; some 15,000 non-diabetic relatives of persons with Type 1 DM will be screened each year (60,000 –100,000 individuals overall).

2. Approximately 3.6% of non-diabetic relatives screened are expected to be ICA positive (20), so that approximately 540 relatives per year will be eligible for staging.

3. Approximately 40% of ICA positive non-diabetic relatives staged are expected to meet the "Intermediate Risk" criteria (20), and thus be eligible for the oral antigen protocol, or approximately 216 individuals per year

4. Approximately 65% of eligible subjects are expected to consent to be randomized in the oral antigen protocol, or approximately 140 individuals per year.

5. The sample size projection for the oral antigen protocol is 490 subjects, assigned approximately in equal numbers to experimental therapy and placebo control therapy. This sample size provides a power of 80% to detect a 50% difference in the annual hazard rate for the onset of Type 1 DM, expected to be 6% per year in the control group, assuming $\alpha = 0.05$ (two tail test), 4 year accrual, 6 year total study, and allowing for a 10% drop-out rate.

6. In the oral antigen ("Intermediate Risk") protocol, the experimental therapy will be the oral administration of recombinant human insulin given as daily capsules (or, if the subject cannot swallow capsules, the contents dissolved in juice or sprinkled on food), to induce immunological tolerance.

7. Treatment assignment will be double-masked, i.e. both subjects and study personnel will be masked both to treatment assignment and treatment outcome. An unmasked Data Safety and Quality Monitoring Group (DSQ) will review emerging outcome data to protect the well-being of study participants..

6.3. Both Protocols:

1. Eligible and consenting subjects will be assigned randomly to either the intervention group or the control group.

2. An independent advisory group will review periodically the study data and be authorized to recommend to the investigators of the DPT-1 Study Group and to the NIDDK that the trial be terminated if the study objectives have been met or a safety hazard detected before the planned termination date for the study, or that the protocol be modified if a deficiency in some aspect of performance is detected.

3. The principal outcome measure of the study is the development of diabetes. To assess outcome, all subjects will have an oral glucose tolerance test (OGTT) performed every 6 months or earlier in any subject in whom symptoms of diabetes develop or elevated home blood glucose levels are found. Development of diabetes will be based on criteria modified from those established by the American Diabetes Association in 1997 (See Section 3.6).

4. All subjects will be analyzed according to their original treatment assignment, regardless of whether or not treatment is maintained.

5. All subjects will be followed for at least two years, with some subjects followed for up to eight years, unless the trial is terminated early.

7. PROCEDURES

7.1. STEP 1. SCREENING - INITIAL SCREENING FOR ISLET CELL AUTOANTIBODIES (ICA)

7.1a. Subjects:

The primary target population is individuals who are less than age 45 years and are first degree relatives (siblings, parents, children) of persons with Type 1 DM. Other relatives, (i.e. nieces, nephews, aunts, uncles, grandchildren, and cousins) up until age 20, also will be screened. Subjects will be recruited through pediatric and adult diabetes and endocrine clinics at university medical centers, and at other hospitals, clinics, health care facilities, and physician offices. Additional recruitment strategies may include activities associated with local and national American Diabetes Association (ADA) or Juvenile Diabetes Foundation (JDF) functions, local or national newspapers and magazines, and regional and national broadcasting by radio and television (broadcast and cable), including specific features and public service announcements.

7.1b. Procedure:

1. Eligibility for Screening: Relatives of person with Type 1 DM: primarily first degree relatives but other relatives less than age 20 allowed. "Type 1 DM" in proband is defined as diabetes onset prior to age 40 and received insulin therapy within one year of diagnosis. (This definition is used to limit inadvertent screening of relatives of probands with Type 2 DM, and is not intended to exclude relatives of persons who have Type 1 DM but in whom onset was after age 40. If there is ambiguity as to eligibility, such as whether a proband has Type 1 DM, this will be resolved by an Eligibility and Events Committee.)
2. Informed Consent: Informed consent (***Informed Consent Form A - ICA Screening***) for initial screening will be obtained by the time of blood sampling. The consent document will be a component of the initial data form specific to ICA screening, and must be executed by the time a blood sample is submitted for screening and on file at the ICA Core Laboratory before the sample can be analyzed. Phone numbers of DPT-1 Center personnel will be provided to address questions concerning screening consent. There will be no automatic initial screening interview, that is, there is no requirement for in-person discussion of consent in order to be screened.
3. Collection of blood sample for screening for islet cell autoantibodies: 10 ml of blood will be drawn, the serum separated and poured into screw top plastic storage vials. Refrigerated samples can be mailed within 2 days, or else frozen and shipped in batches to the ICA Core

Laboratory by overnight courier. An initial screening form must be completed and accompany the sample to ICA Core Laboratory for data entry ***(Form #DPT-001)***.

4. Initial Data Input: The ICA Core Laboratory will assign each sample a subject identification number, as provided by the Data Management Unit (DMU). Information from the initial screening form ***(Form #DPT-001)*** will be electronically transmitted to the DMU, along with ICA results, for data entry of initial demographic information and ICA results, and transmittal of results in a standard format to the relevant Center. For individuals not screened at a Center, Affiliate, or Satellite, screenee may choose a Center or a Center will be assigned by the DMU based on geographic proximity. The indicated Center will be responsible for follow-up of potential volunteers.
5. Sample Storage: Two aliquots of serum labeled with identification code, name, and sample date will be stored frozen at ICA Core Laboratory.
6. Notification of ICA Positive Results: The DMU will inform the relevant Clinical Center Trial Coordinator of positive ICA results, and will provide the Clinical Center with a copy of the initial screening form in order to facilitate contact between the Center and potential volunteers. For such ICA positive relatives, the Coordinator will contact, by telephone, the physician (if indicated on initial form) or Affiliate Coordinator or Satellite Coordinator concerning results. The relevant Clinical Center Trial Coordinator or Physician will DIRECTLY make telephone contact with both the screened individual (if adult) or guardian (if child) and the referring physician concerning results with indication as how to arrange Staging Evaluations and to provide explanation of the meaning of the test results.
7. Notification of ICA Negative Results: The DMU also will notify the relevant Clinical Center Trial Coordinator about ICA negative individuals and mail a notification letter to ICA negative persons (if adult) or guardian (if child), informing them of the results and whether they should be rescreened and, if so, when. In order to try to have results for members of the same family reported concurrently, relatives that comprise families will need to be identified as such. To facilitate concurrent reporting, when family units may not have been identified, there will be a lag added to the reporting of negative results since positive results require more time in the laboratory.
8. Rescreening: Individuals less than age 10 found to be ICA negative (initial screen < 10 JDF units) should be retested every year. ICA negative relatives between ages 10-20 years should be rescreened every 2 years, while those greater than age 20 will not be rescreened.
9. Reimbursements: Affiliates/Satellites/Centers will be reimbursed on a standardized schedule.

7.2. STEP 2. STAGING - DEFINITION of RISK CATEGORY

7.2a. Subjects:

Relatives of individuals with Type 1 DM, ages 3-45 years, who screen positive for ICA (i.e. initial screen $\geq$ 10 JDF units) at Step #1.

7.2b. Procedure:

All ICA positive individuals or their parent (if less than age 18) will be contacted by telephone by Clinical Center Trial Coordinator or Physician and referred to the most convenient Clinical Center or Affiliate Center for discussion of the study and scheduling of the next steps required for Staging of Risk of Type 1 DM. No individual should undergo staging unless they meet the eligibility criteria (Section 7.3c) that would permit their progressing to randomization and intervention. The staging informed consent (***Informed Consent Form B - Staging***) must be presented and explained in person, signed, and witnessed. Where appropriate, assent from children will be obtained (age 7-18). The informed consent explains staging and the potential for participation in one of two randomized intervention trials, and must be completed before staging evaluations may begin.

Staging should be completed expeditiously so that randomization and enrollment of eligible subjects can occur within 20 weeks from the commencement of Staging (defined as beginning as of the date of performance of the first IVGTT), and any treatment protocol begun within 24 weeks from the commencement of Staging. An extra six weeks (i.e. a total of 26 weeks for randomization and 30 weeks for treatment initiation) is permitted if a third IVGTT, ICA, or IAA is required to determine eligibility or to complete staging.

Complete staging requires that two separate intravenous glucose tolerance tests (IVGTTs) be performed at least 3 weeks apart before a volunteer can be randomized to the parenteral protocol. [The oral protocol may only necessitate one IVGTT – see below]. This necessitates two separate staging evaluations. Prior to each staging evaluation, all subjects will be prepared with adequate carbohydrate intake (minimum 150 g/day) for at least 3 days. During the first staging evaluation, in addition to an IVGTT, samples are also collected for repeat ICA, for IAA, and for DNA extraction and determination of HLA-DQA1*0102, DQB1*0602. During or after the second staging evaluation, in addition to an IVGTT and IAA, an oral glucose tolerance test (OGTT) will be performed to exclude pre-existing diabetes and to permit stratification of high risk subjects based upon glucose tolerance. The OGTT must be performed within 3 weeks prior to randomization, in order to be certain that diabetes is not present at the time of randomization.

Staging may be accomplished either as an outpatient or as an inpatient in a General Clinical Research Center (GCRC) or equivalent facility.

If the tests are done as an inpatient, the following schedule is suggested:

7.2b-1. First Staging Evaluation:

Day 1. (Evening). Admission to the GCRC.
Overnight fast (10-16 hours).

Day 2. Samples for ICA, IAA, DNA and HLA-DQA1*0102,DQB1*0602.
IVGTT.
Discharge subject.

7.2b-2. Second Staging Evaluation:

Day 1. (Evening). Admission to the GCRC.
Overnight fast (10-16 hours).

Day 2. Samples for IAA.
IVGTT.
Overnight fast (10-16 hours).

Day 3. OGTT.
Discharge subject.

7.2b-3. Intravenous Glucose Tolerance Test:

Intravenous glucose will be administered by certified personnel in a dose of 0.5 g/kg body weight (maximum dose 35 g) as a 25% glucose solution infused over a carefully defined square wave 3 min. infusion with a range of $\pm$ 15 sec. Two baseline samples will be obtained 10 and 4 minutes before glucose is administered. Samples are obtained at 1, 3, 5, 7, and 10 minutes after glucose administration is complete. A full descriptions of the procedure for the IVGTT appears in the Manual of Operations.

7.2b-4. Oral Glucose Tolerance Test:

Oral glucose will be administered in a dose of 75 grams (in adults) or 1.75 g/kg body weight to a maximum of 75 grams (in children), as a solution in flavored water, consumed within 5 min. Two baseline samples will be obtained (at -10 and 0 minutes) before glucose is consumed. Blood samples will be obtained at 30, 60, 90, and 120 minutes after glucose consumption is complete, for the determination of glucose and C-peptide levels. A complete description of procedure for OGTT appears in the Manual of Operations.

7.2b-5. Processing of blood samples:

All samples must be accompanied by specimen transmittal forms.

1. Serum sample for ICA is to be shipped to ICA Core Laboratory in New Orleans with coded ID number, name and date.
2. Serum sample for insulin autoantibodies (IAA) is to be shipped to IAA Core Laboratory in Boston with coded ID number, name and date during tolerance test.
3. A whole blood specimen for glycosylated hemoglobin (HbA1c), as well as specimens from tolerance tests (IVGTT and OGTT) for insulin, C-peptide and glucose determinations, will be shipped to Beta Cell Function Core Laboratory in Seattle with coded ID number, name, date, and time.
4. Whole blood specimens for DNA Extraction and HLA-DQA1*0102,DQB1*0602 determinations will be shipped to Class II MHC/DNA Extraction Core Laboratory in Denver with coded ID number, name and date.

7.2c. Staging of Eligibility Risk Category:

7.2c-1. Siblings/Offspring/Other Relatives:

1. **Age**

   Relatives must be $\geq$ 3 years to be eligible for Intermediate Risk protocol, and $\geq$ 4 years to be eligible for High Risk protocol.

   Siblings and offspring must be $\leq$ 45 years to be eligible for High Risk or Intermediate Risk protocols.

   Siblings and offspring > 45 years $\Rightarrow$ Not Eligible.

   Second and third degree relatives (nieces, nephews, aunts, uncles, grandchildren, cousins) must be $\leq$ 20 years to be eligible for High Risk or Intermediate Risk protocols.

   Second and third degree relatives > 20 years $\Rightarrow$ Not Eligible.

2. **ICA**.

   If initial ICA sample is negative and subject > age 20 years $\Rightarrow$ Not Eligible, and no rescreening.

   If initial ICA sample is negative and subject age 10-20 years, may repeat ICA every two years.

   If initial ICA sample is negative and subject $\leq$ age 10 years, may repeat ICA every one year.

   If initial ICA $\geq$ 10 JDF units, repeat ICA.

   If second ICA also $\geq$ 10 JDF units $\Rightarrow$ Potentially Eligible.

If second ICA sample is negative, third ICA repeated within 1 month interval.
If third ICA $\geq$ 10 JDF units $\Rightarrow$ Potentially Eligible.
If third ICA sample is negative and subject > age 20 years $\Rightarrow$ Not Eligible, and no rescreening.
If third ICA sample is negative and subject age 10-20 years, may repeat ICA every two years until age 20.
If third ICA sample is negative and subject $\leq$ age 10 years, may repeat ICA every one year.
High or Intermediate Risk criteria requires 2 of 3 ICA $\geq$ 10 JDF units. Further eligibility for High and Intermediate Risk is based on IAA and IVGTT.

3. **HLA-DQ**.
   Presence of HLA-DQA1*0102,DQB1*0602 $\Rightarrow$ Not Eligible.
4. **IVGTT**.
   Definition of risk category by IVGTT is based on first phase insulin response (FPIR), using the sum of the plasma insulin values of the 1 minute and 3 minute samples, noted as "Insulin Σ (1'+3')".
   High Risk requires IVGTT-Insulin Σ (1'+3') < 10th %ile (i.e. < 60 μU/ml if age 3-7 years, or < 100 μU/ml if age $\geq$ 8 years) on 2 separate IVGTTs.
   If 2 IVGTTs have Insulin Σ (1'+3') < 10th %ile $\Rightarrow$ High Risk.
   If initial IVGTT has Insulin Σ (1'+3') $\geq$ 10th %ile, consider IAA status.
   If 1 IVGTT has Insulin Σ (1'+3') < 10th %ile and 1 IVGTT has Insulin Σ (1'+3') $\geq$ 10th %ile, perform third IVGTT.
   If third IVGTT has Insulin Σ (1'+3') < 10th %ile $\Rightarrow$ High Risk.
   If third IVGTT has Insulin Σ (1'+3') $\geq$ 10th %ile $\Rightarrow$ Not High Risk.
   If Not High Risk, consider IAA status.
5. **IAA**.
   If IAA is $\geq$ 39 nU/ml (~3 standard deviations above mean of normal controls) on 2 separate samples:
   And Not High Risk by IVGTT $\Rightarrow$ Intermediate Risk.
   If IAA is < 39 nU/ml on 2 separate samples:
   And Not High Risk by IVGTT $\Rightarrow$ Not Eligible.
   Should repeat IVGTT every 6 months to see if has become High Risk.
   If one IAA is $\geq$ 39 nU/ml and the other IAA is < 39 nU/ml, a third IAA is performed to determine risk

6. **OGTT**.
   To be assessed by 1997 ADA Criteria (see Section 3.6.1).
   If OGTT indicates "Diabetes" ⇒ Not Eligible.
   If OGTT indicates "Impaired Glucose Tolerance" (IGT) or "Impaired Fasting Glucose" (IFG) status of glucose tolerance ⇒ High Risk (**even if not High Risk by IVGTT criteria**). (IGT and IFG individuals are eligible for High Risk intervention protocol, but are to be stratified separately from individuals with "Normal" OGTT).
   If OGTT indicates "Normal" glucose tolerance ⇒ eligible for randomization in either High Risk or Intermediate Risk intervention protocols, depending on other staging parameters.

7.2c-2. Parents:

1. **Age** - must be ≤ 45 years to be High Risk or Intermediate Risk.
   Parents > 45 years ⇒ Not Eligible.
2. **ICA**.
   If initial ICA sample is negative ⇒ Not Eligible, and no rescreening.
   If initial ICA ≥ 10 JDF units, repeat ICA.
   If second ICA also ≥ 10 JDF units ⇒ High or Intermediate Risk.
   If second ICA sample is negative, repeat third ICA within 1 month interval.
   If third ICA ≥ 10 JDF units ⇒ High or Intermediate Risk.
   If third ICA sample is negative ⇒ Not Eligible, and no rescreening.
   High or Intermediate Risk criteria requires 2 of 3 ICA ≥ 10 JDF units. Distinction between High and Intermediate Risk is based on IVGTT.
3. **HLA-DQ**.
   Presence of HLA-DQA1*0102,DQB1*0602 ⇒ Not Eligible.
4. **IVGTT**.
   Definition of risk category by IVGTT is based on first phase insulin response (FPIR), using the sum of the plasma insulin values of the 1 minute and 3 minute samples, noted as "Insulin Σ (1'+3')".
   High Risk requires IVGTT-Insulin Σ (1'+3') < 1st %ile (i.e. < 60 μU/ml) on 2 separate IVGTTs.
   If 2 IVGTTs have Insulin Σ (1'+3') < 1st %ile ⇒ High Risk.
   If initial IVGTT has Insulin Σ (1'+3') ≥ 1st %ile, consider IAA status.

If 1 IVGTT has Insulin Σ (1'+3') < 1st %ile and 1 IVGTT has Insulin Σ (1'+3') ≥ 1st %ile, perform third IVGTT.

If third IVGTT has Insulin Σ (1'+3') < 1st %ile ⇒ High Risk.

If third IVGTT has Insulin Σ (1'+3') ≥ 1st %ile ⇒ Not High Risk.

If Not High Risk, consider IAA status.

5. **IAA**.

   If IAA is ≥ 39 nU/ml (~3 standard deviations above mean of normal controls) on 2 separate samples:

   And Not High Risk by IVGTT ⇒ Intermediate Risk.

   If IAA is < 39 nU/ml on 2 separate samples:

   And Not High Risk by IVGTT ⇒ Not Eligible.

   Should repeat IVGTT every 1 year to see if has become High Risk.

   If one IAA is ≥ 39 nU/ml and the other IAA is < 39 nU/ml, a third IAA is performed to determine risk

6. **OGTT**.

   To be assessed by 1997 ADA Criteria (see Section 3.6.1).

   If OGTT indicates "Diabetes" ⇒ Not Eligible.

   If OGTT indicates "Impaired Glucose Tolerance" (IGT) or "Impaired Fasting Glucose" (IFG) status of glucose tolerance ⇒ High Risk (**even if not High Risk by IVGTT criteria**). (IGT and IFG individuals are eligible for High Risk intervention protocol, but are to be stratified separately from individuals with "Normal" OGTT).

   If OGTT indicates "Normal" glucose tolerance ⇒ eligible for randomization in either High Risk or Intermediate Risk intervention protocols, depending on other staging parameters.

7.2d. STUDY TIME LINE

The following schedule are the maximum allowable times for determining eligibility and randomizing subjects into DPT-1 protocols:

Time from initiation of Staging (first IVGTT) until randomization - maximum of 20 weeks.

Time from performance of OGTT until randomization - maximum of 3 weeks.

Time from randomization of subject until initiation of treatment (performance of intravenous insulin infusion in parenteral protocol cohort experimental treatment group, or capsules for oral protocol) - maximum of 4 weeks.

Total time from initiation of Staging (first IVGTT) until initiation of treatment (performance of intravenous insulin infusion in parenteral protocol cohort experimental treatment group, or capsules for oral protocol) - maximum of 24 weeks.

(An extra six weeks (i.e. a total of 26 weeks for randomization and 30 weeks for treatment initiation) is permitted if a third IVGTT, ICA, or IAA is required to determine eligibility or to complete staging).

All of these must be met, thus e.g. performance of OGTT with < 3 weeks left in 20 week window does not re-set the clock allowing additional days to complete Staging.

These are the maximum allowable windows - every effort should be made to complete staging, randomization, enrollment, and intravenous insulin infusion (if so randomized) as rapidly as possible.

The rationale for the above schedule change is: [a] to provide realistic times for performance of the various steps in Staging, with return of information from the Core Labs via the DMU; [b] to assure that an OGTT which verifies the subject does not have diabetes has been performed in close proximity to randomization; [c] to permit adequate time to schedule and admit randomized subjects requiring intravenous insulin infusions.

7.3. STEP 3. INTERVENTIONS

7.3a. Subjects:

Relatives of individuals with Type 1 DM; ages 4-45 years, if staged as High Risk at Step #2, or ages 3-45 years, if staged as Intermediate Risk at Step #2.

7.3b. Procedures:

If a subject meets High Risk or Intermediate Risk criteria at Step #2, the DMU coordinator will review eligibility with Center personnel. Once a patient is deemed eligible, they will be contacted by Clinical Center Trial Coordinator or Physician and an interview scheduled, at which time the trial will be described in detail and informed consent for randomization requested. The appropriate intervention informed consent (***Informed Consent Form C or D - Intervention Protocols***) will be presented and explained in person, signed, and witnessed. Where appropriate, assent from children should be obtained (age 7-18). This informed consent will explain full details of randomized intervention trial. Individuals who agree to participate will be randomized by DMU. A maximum of 4 weeks may elapse between randomization and initiation of any treatment protocol.

7.3c. Eligibility Criteria for Randomization (Generic for Both Parenteral Antigen and Oral Antigen Protocols):

A. Inclusion:

1. Willing to volunteer for randomization, give informed consent to participate in intervention protocol for which subject is eligible, and commit to adherence to treatment group assignment.
2. Age: 4-45 for parenteral antigen protocol; 3-45 for oral antigen protocol.
3. Relative of patient with Type 1 DM: primarily first degree relatives but second and third degree relatives (nieces, nephews, aunts, uncles, grandchildren, cousins) age 20 or less allowed. Definition of “Type 1 DM” in proband: proband's diabetes onset prior to age 40 and receiving insulin therapy within one year of diagnosis. (This definition is used to limit inadvertent screening of relatives of probands with Type 2 DM, and is not intended to exclude relatives of persons who have Type 1 DM but in whom onset was after age 40. If there is ambiguity as to eligibility, such as whether a proband has Type 1 DM, this will be resolved by an Eligibility and Events Committee.)
4. ICA Positive: $\geq$ 10 JDF units confirmed on two tests.

B. Exclusion:

1. History of treatment with insulin or oral hypoglycemic agent.

2. Diabetes by 1997 ADA criteria:
   - fasting plasma glucose $\geq$ 126 mg/dL, or
   - 2 hour plasma glucose $\geq$ 200 mg/dL.

   (An OGTT must be performed within 3 weeks of randomization into an intervention protocol).
3. HLA-DQA1*0102,DQB1*0602
4. Known severe active disease, e.g. chronic active hepatitis, severe cardiac, renal, hepatic, immunodeficiency and/or disease which is likely to limit life expectancy or lead to therapies such as immunosuppression during the time of the study.
5. Prior participation in trial for prevention of Type 1 DM, e.g. nicotinamide, insulin, immunosuppressive drugs. However, individuals known to be in placebo arm of a completed prior prevention trial, if meeting all other criteria, will be eligible for DPT-1 trial.
6. History of therapy with immunosuppressive drugs or glucocorticoids within past two years for a period of more than 3 months.
7. Ongoing use of medications known to influence glucose tolerance, i.e. sulfonylureas, metformin, diphenylhydantoin, thiazide or other potassium depleting diuretics, beta-adrenergic blockers, niacin. Patients on such medications should be changed to a suitable alternative and will become eligible one month after discontinuation.
8. Individuals deemed unable or unlikely to comply with protocol.
9. Pregnancy or planned pregnancy within the time frame of the study. Women of child bearing potential are not excluded from participation. Individuals will be advised not to volunteer for the study if they plan to become pregnant during the time of the study. If pregnancy occurs, protocol will be interrupted for the duration of the pregnancy. Low dose estrogen oral contraception is permitted. For the High Risk Protocol, a negative pregnancy test must be obtained in women of child bearing potential prior to each admission for periodic intravenous insulin infusion.

7.3d. Eligibility Criteria (Parenteral Antigen Protocol):

A. Inclusion:

1. Categorized as High Risk in Step #2, on basis of age, type of relative, IVGTT, IAA, and OGTT.
2. OGTT that is non-diabetic by 1997 ADA criteria.

B. Exclusion:

1. Unwilling or unable or unlikely to come for periodic intravenous infusions.
2. Unwilling or unable or unlikely to perform daily insulin injections.
3. Unwilling or unable or unlikely to comply with follow-up evaluations.

7.3e. Eligibility Criteria (Oral Antigen Protocol):

A. Inclusion:

1. Categorized as Intermediate Risk in Step 2, on basis of age, type of relative, IVGTT, IAA.
2. Normal glucose tolerance by 1997 ADA criteria:
   - fasting plasma glucose < 110 mg/dL and
   - 2 hour plasma glucose < 140 mg/dL and

B. Exclusion:

1. Unwilling or unable or unlikely to comply with follow-up evaluations.
2. OGTT that reveals Diabetes (see Generic Eligibility Criteria above), Impaired Glucose Tolerance (IGT), or Impaired Fasting Glucose (IFG) by 1997 ADA criteria.
   IGT is defined by:
   - fasting plasma glucose < 126 mg/dL, and
   - 2 hour plasma glucose 140-199 mg/dL, and

   IFG is defined by:
   - fasting plasma glucose 110-125 mg/dL AND
   - 2 hour plasma glucose < 140 mg/dL

   (Subjects with IGT or IFG are eligible for the High Risk Parenteral Trial).

7.4. COMPLETION OF ENROLLMENT IN PARENTERAL STUDY, UPDATING OF STUDY INFORMATION ON THESE SUBJECTS, & ACTIONS FOR INDIVIDUALS SUBSEQUENTLY IDENTIFIED AS "HIGH RISK"

7.4a. Completion of Enrollment:

The *High Risk Parenteral Trial* completed enrollment on October 31, 2000, with 339 subjects having been randomized.

7.4b. Updating of Study Information on Subjects in High Risk Parenteral Trial:

On the recommendation of the Data Safety and Quality Monitoring Group (DSQ), the Steering Committee initiated a "Study Update" for the High Risk Parenteral Trial on November 1, 2000. The DPT-1 Task Force on Contingency Planning earlier had developed a procedure for a detailed "Study Update", the purpose of which is to obtain complete follow-up information on all subjects randomized in either trial – in this case, the High Risk Parenteral Trial. The "Study Update" is designed to allow determination of diabetes status on all subjects, including resolution of all ambiguities, since some subjects may have had one abnormal OGTT without confirmation. It also provides a complete data set for all DPT-1 study parameters, so that it will be possible to perform data analysis to determine all outcomes, on the assumption that this "Study Update" may equate with "End of Study" data collection.

Commencing November 1, 2000, all subjects who have ever been randomized in the Parenteral Study (unless already diagnosed as having diabetes within DPT-1) will be asked to come in to complete all DPT-1 evaluations not recently performed. The Study Update period will span 5 months, through March 31, 2001. The mid-point of that period is January 15, 2001. That date will be used for data analysis and to define windows for completion of tests.

The DPT-1 evaluations need to be performed include: oral glucose tolerance (OGTT) test and HbA1c if not performed in the 3 month window prior to January 15, 2001; mixed meal tolerance test (MMTT), intravenous glucose tolerance test (IVGTT), wide range achievement test (WRAT), and islet cell auto-antibodies (ICA and insulin) if not performed in the 6 month window prior to January 15, 2001. Of the tolerance tests – each of which must be performed on a separate day – the first priority is the OGTT, next the MMTT, and last the IVGTT. Some subjects may need second or third OGTTs as well, to confirm or refute suspected but unconfirmed diabetes.

Subjects will need to be scheduled in the most convenient way possible, with the plan to complete all testing by March 31, 2001. Every effort will be made to contact every subject randomized – regardless of whether or not they have been seen recently, and whether or not they are still participating in DPT-1.

During the Study Update, all randomized subjects will continue their assigned treatment. For those in the experimental group, both subcutaneous injections and insulin infusions should continue. For those in the closely monitored group, no insulin will be taken.

7.4c. Subjects Identified as "High Risk" after Close of Enrollment in the Parenteral Trial:

Subjects who are identified as "High Risk" after the close of enrollment in the Parenteral Study, will be followed closely for the development of diabetes, as they would be if they had been randomized. It will be explained to them that enrollment has been completed, that data are being collected to determine the results of the High Risk Parenteral Trial, and that a recommendation will be made to them as soon as the information is available. They will have the opportunity to participate in the debriefing to be offered to all subjects randomized in the High Risk Parenteral Trial.

8. INTERVENTION PROTOCOL - HIGH RISK COHORT (Parenteral Antigen)

8.1. Summary:

Randomized to One of Two Treatment Arms - Experimental Group and Closely Monitored (Control) Group

The *Experimental Group* will receive:

- Continuous intravenous insulin infusions consisting of:
  - Recombinant human regular insulin
  - Every 12 months (acceptable window ± 6 weeks) for
  - 4 consecutive days duration
  - Blood glucose will be monitored q 1 h during daytime, q 2 h at night, and
  - Adjusted by algorithm
- Chronic subcutaneous insulin
  - Recombinant human long-acting ultralente insulin at an
  - Initial dose 0.25 units/kg/day
  - Dose of insulin will be divided 50% before breakfast in morning, 50% at bedtime
  - Dose altered by algorithm
  - Capillary blood glucose profile measurements every 3 months (consisting of 5 samples - before breakfast, before lunch, before supper, two hours after supper, and 3:00AM)
- Intervening outpatient visit, will occur
  - Halfway between admissions for IV infusions, i.e. every 6 months
- Oral glucose tolerance testing every 6 months

The *Closely Monitored (Control) Group* will receive:

- Outpatient visits every 6 months
- Capillary blood glucose profile measurements every 3 months (consisting of 5 samples - before breakfast, before lunch, before supper, two hours after supper, and 3:00AM)
- Oral glucose tolerance testing every 6 months

8.2. Baseline Evaluation

By baseline, all subjects will have a Mixed Meal (Boost® [previously known as Sustacal]) Tolerance Test (MMTT) for evaluation of pancreatic β-cell function by measurement of plasma C-peptide responses to this provocative mixed meal challenge. Baseline glycosylated hemoglobin ($HbA1c_)$ will be measured in the Core Laboratory. The Wide Range Achievement Test (WRAT) will be performed.

8.3. Protocol for Periodic Admissions for Intravenous Infusion:

Periodic intravenous infusions will be conducted during inpatient admissions to a General Clinical Research Center (GCRC) or equivalent facility. The target for intravenous insulin treatment is intravenous insulin, continuously, for four consecutive days, every 12 months. The definitions in regards each of these components are as follows:

- intravenous insulin - no other route of insulin administration is acceptable. (The intravenous infusion may be performed either with a bedside pump or a portable minipump).
- continuously - three interruptions in the insulin infusion up to a maximum of four hours each will be allowed
- four consecutive days - a minimum duration of two consecutive days is required to be considered as a completed infusion
- acceptable window for infusion is 12 months ± 6 weeks (the scheduling is based on the date of the original infusion, and every 12 months thereafter)

Insulin infusions not fulfilling any of the above criteria will not be considered as having been administered.

Insulin infusions that are not “acceptable” by the above protocol definition should not be routinely repeated. However, if an infusion is electively terminated prematurely for an unusual event, the subject may be rescheduled for said infusion, as convenient.

Prior to admission, subcutaneous insulin injections must be omitted for 72 hours. *In women of child bearing potential, a negative pregnancy test must be obtained prior to each admission for periodic intravenous infusion.*

The following are two sample schedules:

Schedule A (Tolerance Testing performed during admission):

Day 1. (Afternoon or Evening). Admission to the GCRC or equivalent facility.
Admission testing and physical examination.
Diet: isocaloric, served as 3 meals with no concentrated sweets, at 0800, 1200, and 1700, and consumed over a 40 minute time period. An evening snack (at 2000) containing 10% of the daily calorie allocation, will be provided to all subjects. Otherwise, only non-caloric snacks are permitted.
Overnight fast (10-16 hours).

Day 2. Determine fasting plasma glucose in local laboratory.
Glycosylated hemoglobin (HbA1c) in Core Laboratory.
OGTT.

Day 3. Determine fasting plasma glucose in local laboratory.
~0800 - Tolerance test -
Mixed Meal (Boost® [previously known as Sustacal]) Tolerance Test (MMTT) or IVGTT.
~1200 - Commence first day of intravenous infusion (following test).

Day 4. 1200 - Commence second day of intravenous infusion

Day 5. 1200 - Commence third day of intravenous infusion

Day 6. 1200 - Commence fourth day of intravenous infusion

Day 7. 1200 - Complete intravenous infusion
Take subcutaneous injection
Discharge subject.

Schedule B (OGTT performed separately):

Day 1. (Morning). Admission to the GCRC or equivalent facility, following overnight fast (10-16 hours).
Admission testing and physical examination.
Determine fasting plasma glucose in local laboratory.
Glycosylated hemoglobin (HbA1c) in Core Laboratory.
~0800 - Tolerance test -
Mixed Meal (Boost® [previously known as Sustacal]) Tolerance Test (MMTT) or IVGTT.
~1200 - Commence first day of intravenous infusion (following test).
Diet: isocaloric, served as 3 meals with no concentrated sweets, at 0800, 1200, and 1700, and consumed over a 40 minute time period. An evening snack (at

2000) containing 10% of the daily calorie allocation, will be provided to all subjects. Otherwise, only non-caloric snacks are permitted.

Day 2. 1200 - Commence second day of intravenous infusion

Day 3. 1200 - Commence third day of intravenous infusion

Day 4. 1200 - Commence fourth day of intravenous infusion

Day 5. 1200 - Complete intravenous infusion
Discharge subject.

8.4. Details of Intravenous Infusion:

The infusion will consist of Humulin®-R human regular insulin in 0.45% (half-normal) saline, administered on a schedule such as that outlined here:

Goals

- Maintain whole blood glucose 60-80 mg/dL (plasma glucose 70-92 mg/dL)
- Avoid Hypoglycemia

Infusion

- Insulin Concentration:
  - 10 units per 500 ml for subjects who weigh less than 50 kg
  - 25 units per 500 ml for subjects who weigh 50 kg or more
- Initial Basal Insulin Rate:
  - 0.015 U/kg/hr (0.15 ml/kg/hr)

Dose alterations:

- "Incremental Increase Amount": 10% of initial basal rate, calculated in ml/hr, and rounded up to nearest whole number (once established, this does not vary for any infusion period)
- "Incremental Decrease Amount": twice the "Incremental Increase Amount", calculated in ml/hr (once established, this does not vary for any infusion period)

Dose limitations:

- Maximum Infusion Rate - 0.08 U/kg/hr (rounded to nearest ml/hr)

- Minimum Infusion Rate - 0.002 U/kg/hr (rounded to nearest ml/hr) [except when interrupted for whole blood glucose < 50 mg/dL (plasma glucose < 57 mg/dL)]

Monitoring:

- Glucose values are checked every 60 minutes during the day (0800 to 2200), and every two hours from 2200 to 0800.
- With meals, additional glucose value measured 90 minutes after meal
- If change is made in infusion rate, recheck glucose level after one hour
- If hypoglycemia documented -[whole blood glucose < 60 mg/dL (plasma glucose < 70 mg/dL)] - reduce infusion rate and re-check glucose value after 10 minutes

Adjustments in Insulin Infusion Rate:

- For meals (food served at T0):
  - twice premeal basal rate (rate at T0) from T0 to T30 (0-30 minutes after start of meal)
  - three times premeal basal rate (rate at T0) from T30 to T60
  - twice premeal basal rate (rate at T0) from T60 until whole blood glucose $\leq$ 80 mg/dL (plasma glucose $\leq$ 90 mg/dL) or T180
  - then resume premeal basal rate (rate at T0)

- For bedtime snack (served at 2000 hours):
  - 2 times presnack basal rate (rate at T0) from 2000 to 2030 (0-30 minutes after start of snack)
  - then resume presnack basal rate (rate at T0)

- For whole blood glucose < 60 mg/dL (plasma glucose < 70 mg/dL) - reduce current basal rate by “incremental decrease amount”

- For whole blood glucose < 50 mg/dL (plasma glucose < 57 mg/dL) or mild symptomatic hypoglycemia - treat with 4 oz orange juice or 15 gm carbohydrate p.o. and stop (interrupt) insulin infusion. Repeat glucose measurement every 10 minutes, retreat if whole blood glucose < 50 mg/dL (plasma glucose < 57 mg/dL), and restart insulin infusion when whole blood glucose $\geq$ 60 mg/dL (plasma glucose $\geq$ 70 mg/dL) at a new basal rate reduced by

"incremental decrease amount" for each whole blood glucose < 50 mg/dL (plasma glucose < 57 mg/dL)

- For whole blood glucose > 80 mg/dL (plasma glucose > 90 mg/dL) at basal rate- "increase amount" (up to maximum dose of 0.08 U/kg/hr)

8.5. Protocol for Subcutaneous Injections:

All subjects randomized to the experimental group will administer twice daily subcutaneous injections of Humulin®-U human ultralente insulin, given every morning before breakfast and every evening at bedtime, at an initial total daily dose of 0.25 units/kg (each injection containing 0.125 units/kg), using U-100 0.3 or 0.5 cc 29 or 30 g insulin syringes.

- The dose will be adjusted at interim visits as the subject's weight changes, maintaining equal doses in each injection.
- Hypoglycemic events will be recorded. If mild hypoglycemic symptoms occur, the subjects and their families will be instructed to perform capillary blood glucose monitoring for confirmation of hypoglycemia. If the capillary sample shows a value < 50 mg/dL, the dose will be reduced by 10% (to the nearest 0.5 unit, with a minimum decrease of 0.5 unit).
- There will be no planned increases in dose except those associated with weight gain consequent to normal growth.
- During the first week after initiation of subcutaneous insulin, daily fasting glucose will be measured by home capillary blood glucose monitoring.
- At the end of the first week, and thereafter every three months, and one week following any dosage change, subjects will perform 5-point (before meals, 90-120 minutes after dinner, and 3:00AM) glucose profiles by home capillary blood glucose monitoring. If asymptomatic hypoglycemia (capillary blood glucose < 50 mg/dL) is detected on more than one sample, the dosage of each insulin injection will be reduced by 10% (to the nearest 0.5 unit, with a minimum decrease of 0.5 unit).
- Two months following any dosage reduction, 50% of the reduction will be restored (to the nearest 0.5 unit, with a minimum increase of 0.5 unit).

- During intercurrent illness, if hypoglycemia occurs, subcutaneous insulin injections may be omitted for up to 3 days. at the discretion of the Clinical Center physician.

8.6. Follow-up Evaluations:

Subjects in both arms of the study (experimental group and Closely Monitored (Control) Group) will be seen every 6 months. For subjects in the experimental group, these visits must be within 3 weeks of the time of their admission for intravenous infusion, i.e. every 12 months, and at an Intervening Outpatient Clinic Visit halfway between admissions for IV infusions, i.e. every 6 months. In both groups, on each of these occasions:

- Physical examination will be performed. Height and weight will be recorded.
- HbA1c will be determined by the Core Laboratory (as a secondary indicator both of potential diabetes if above the upper limit of normal, and as a secondary indicator of hypoglycemia if below the lower limit of normal)
- OGTT will be performed (primary study outcome). Subcutaneous injections will be omitted for 72 hours prior to OGTT. Subjects will have adequate dietary preparation (minimum 150 g carbohydrate per day) for three days prior to OGTT. OGTT will be postponed if there is intercurrent illness, but should be performed no later than 6 weeks after each 6 month anniversary date
- Blood glucose test strips will be provided to the subject.
- Islet cell autoantibodies (ICA) and insulin autoantibodies (IAA) will be determined by the appropriate Core Laboratory, as scheduled (ICA annually, IAA each 6-month visit)

In the experimental group, the following also will be done:

- Dose of subcutaneous insulin will be adjusted based on body weight
- Vials of insulin and syringes will be provided to the subjects.

In both treatment groups, every 12 months, an additional tolerance test will be performed, as follows:

- A Mixed Meal (Boost® [previously known as Sustacal]) Tolerance Test (MMTT) at the end of years 1, 3, and 5
- An IVGTT at the end of years 2, 4, and 6

In both treatment groups, every three months, subjects will perform 5-point (before meals 90-120 minutes after dinner, and 3:00AM) glucose profiles by home capillary blood glucose monitoring, with results recorded and sent to the Clinical Center Trial Coordinator. If significant

hyperglycemia (capillary blood glucose > 200 mg/dL) is detected on more than one sample, the Clinical Center Trial Coordinator will be notified, and consideration given for early performance of an OGTT.

8.7. Adverse Events Monitoring:

Adverse events will be carefully sought in all subjects. A toll-free 800 telephone line, based at the Data Management Unit (DMU), will be used by all subjects to report all adverse events. This computer based system, using simulated speech (in English or Spanish), ensures that there is uniform review of all symptoms, and allows rapid centralized tracking of all adverse events. The Clinical Center and Affiliate (if monitoring intervention) are notified immediately of any such adverse event by automated facsimile transmission.

In addition, at each visit, subjects are carefully interviewed with regards any adverse events that may have occurred.

The Wide Range Achievement Test (WRAT) will be performed at baseline, six months after enrollment, and on an annual basis thereafter in subjects ages 5-18 at time of enrollment or who attain age 5 during the study. In addition, information about accidents (including motor vehicle accidents) and school performance, will be sought.

Any Study Group member learning of the death of a subject immediately follow the "Notification of Death Procedure" (included in the Manual of Operations).

9. OUTCOME EVALUATION - HIGH RISK COHORT (Parenteral Antigen)

The principal study outcome is the development of diabetes (by criteria established by the American Diabetes Association in 1997). The Oral Glucose Tolerance Test (OGTT) is the principal study outcome test used to detect diabetes. Oral glucose is administered in a dose of 75 grams (in adults) or 1.75 g/kg body weight to a maximum of 75 grams (in children), as a solution in flavored water, consumed within 5 min. Two baseline samples will be obtained (at -10 and 0 minutes) before glucose is consumed. Blood samples will be obtained at 30, 60, 90, and 120 minutes after glucose consumption is complete, for the determination of glucose and C-peptide levels.

A Study Event (or Treatment Failure) is defined as the development of diabetes, by criteria modified from the "adult" criteria established by the American Diabetes Association in 1997. As used in DPT-1, those criteria, which must be met on two occasions (unless criteria [iv] is present) are:

[i] casual (any time of day without regard to time since last meal) plasma glucose $\geq$ 200 mg/dL, if accompanied by unequivocal symptoms (i.e. polyuria, polydipsia, polyphagia, and/or weight loss),

OR

[ii] fasting (no caloric intake for at least 8 hours) plasma glucose $\geq$ 126 mg/dL (core laboratory),

OR

[iii] 2-hour plasma glucose $\geq$ 200 mg/dL during a 75 gram oral glucose tolerance test (OGTT),

OR

[iv] unequivocal hyperglycemia with acute metabolic decompensation (e.g. ketoacidosis).

N.B. In DPT-1, unless criteria [iv] is present or the fasting glucose is $\geq$ 250 mg/dl (at the bedside or in the local laboratory on the day of testing), it is preferred that at least one of the two testing occasions involve an oral glucose tolerance test (OGTT). If the first criterion met is [iii], i.e. by the 2-hour OGTT value, the OGTT should be repeated within 60 days. It is essential that every effort be made to obtain the necessary tests to establish the diagnosis of diabetes.

For fasting hyperglycemia, a tentative diagnosis may be made, based on measurements made in a local laboratory if FPG $\geq$ 160 mg/dL on two separate days within one week, with confirmation by FPG $\geq$ 126 mg/dL on two separate days within one week, as performed in the Core Laboratory. OGTTs will be scheduled every 6 months. If a single OGTT meets the criteria for diabetes, a repeat OGTT will be scheduled within 2 months. There will be strict attention to detail in the performance of OGTTs. Subcutaneous injections will be omitted for 72 hours prior to OGTT.

Subjects will have adequate dietary preparation (minimum 150 g carbohydrate per day) for three days prior to OGTT. OGTT will be postponed if there is intercurrent illness, but must be performed no later than 6 weeks after each 6 month anniversary date.

If a diagnosis of diabetes is made outside of the study, the Eligibility and Events Committee will review the criteria for establishing the diagnosis. The subject will be asked to complete all measures that are scheduled for collection at the time of a Study Event or Study End.

As a subsidiary outcome, pancreatic β-cell function will be assessed by measuring C-peptide response during each OGTT.

Subjects will have a Mixed Meal (Boost® [previously known as Sustacal]) Tolerance Test (MMTT) at the end of year 1, year 3, year 5, and at the time of their completion of intervention (either if there is a Study Event, i.e. Treatment Failure, or at Study End). For those subjects who develop diabetes, the MMTT at Study End will be performed 8-16 weeks after the diagnosis has been made, having withheld long acting insulin the night before and all insulin the morning of the MMTT. If fasting blood sugar is greater than 250 mg/dl, the MMTT will not be performed, and then only a fasting C-peptide will be measured.

Subjects will have an IVGTT at the end of year 2, year 4, year 6, and at Study End, unless the subject has developed diabetes, in which case the IVGTT will not be performed.

During any MMTT or IVGTT, pancreatic β-cell function will be assessed by measuring C-peptide responses during these provocative challenges.

The sequence for performing tests when more than one are due in any one evaluation period is: OGTT (glucose primary end point) > MMTT (C-peptide secondary end point) > IVGTT. Tests must be performed in the fasting state on separate days.

HbA1c and ICA and IAA will be determined as well. The WRAT should be administered.

10. INTERVENTION PROTOCOL - INTERMEDIATE RISK COHORT (Oral Antigen)

10.1 Summary:

Randomized to One of Two Treatment Arms - Experimental Group and Control Group

The *Experimental Group* will receive:

- Oral insulin
  - Recombinant human insulin crystals
  - Dose: 7.5 mg/day as single daily dose one-half hour before breakfast
  - Taken as capsule (or, if the subject cannot swallow capsules, dissolved in juice or sprinkled on food)
- Outpatient visits every 6 months
- Oral glucose tolerance testing every 6 months
- Intravenous glucose tolerance testing every 12 months
- Mixed meal tolerance testing every 36 months

The *Control Group* will receive:

- Oral placebo
  - Placebo crystals similar in appearance and taste to oral insulin crystals
  - Dose: volume equivalent to oral insulin (7.5 mg/day) as single daily dose one-half hour before breakfast
  - Taken as capsule (or, if the subject cannot swallow capsules, dissolved in juice or sprinkled on food)
- Outpatient visits every 6 months
- Oral glucose tolerance testing every 6 months
- Intravenous glucose tolerance testing every 12 months
- Mixed meal tolerance testing every 36 months

10.2. Baseline Evaluation

By baseline, all subjects will have had a Complete Intravenous Glucose Tolerance Test (IVGTT) with evaluation of pancreatic β-cell function by measurement of plasma insulin response to this challenge, and an Oral Glucose Tolerance Test (OGTT) with evaluation of pancreatic β-cell function by measurement of plasma C-peptide responses to this challenge. In addition, at baseline, all subjects will have a Mixed Meal (Boost® [previously known as Sustacal]) Tolerance Test (MMTT) with evaluation of pancreatic β-cell function by measurement of plasma C-peptide

responses to this provocative mixed meal challenge. Baseline glycosylated hemoglobin (HbA1c) will be measured in the Core Laboratory.

10.3. Protocol for Oral Medication:

All subjects enrolled in the intervention protocol will be randomized to take oral medication (oral insulin or oral placebo, provided in identically appearing capsules) on a daily basis one-half hour before breakfast, taken either as a capsule or, if the subject cannot swallow capsules, the contents thereof dissolved in juice or sprinkled on an appropriate food (e.g. apple sauce).
Adverse events and hypoglycemic symptoms will be systematically recorded.

10.4. Follow-up Evaluations:

Subjects in both arms of the study (Experimental and Control) will be seen every 6 months. On each of these occasions:

- Physical examination will be performed. Height (stadiometer), weight, and recumbent blood pressure will be recorded.
- HbA1c will be determined by the Core Laboratory
- Islet cell autoantibodies (ICA) and insulin autoantibodies (IAA) will be determined by the appropriate Core Laboratory
- OGTT will be performed (primary study outcome), with measurement of glucose and C-peptide. Subjects will have adequate dietary preparation (minimum 150 g carbohydrate per day) for three days prior to OGTT. OGTT will be postponed if there is intercurrent illness, but should be performed no later than 6 weeks after each 6 month anniversary date.
- Labeled bottles of capsules (oral insulin or placebo) will be provided to the subject.

In all subjects, every 12 months, an additional tolerance test will be performed:

- A “Complete” IVGTT for measurement of glucose and plasma insulin

In all subjects, every 36 months, and at Study End, an additional tolerance test will be performed:

- A MMTT for measurement of glucose and C-peptide

In both treatment groups, every three months, subjects will perform 5-point (before meals 90-120 minutes after dinner, and 3:00AM) glucose profiles by home capillary blood glucose monitoring, with results recorded and sent to the Clinical Center Trial Coordinator.
If symptoms of diabetes develop and/or significant hyperglycemia (capillary blood glucose > 200 mg/dL) is detected on more than one occasion, the Clinical Center Trial Coordinator will be notified, and consideration given for early performance of an OGTT.

10.5. Adverse Events Monitoring:

Adverse events will be carefully sought in all subjects. A toll-free 800 telephone line, based at the Data Management Unit (DMU), will be used by all subjects to report all adverse events. This computer based system, using simulated speech (in English or Spanish), ensures that there is uniform review of all symptoms, and allows rapid centralized tracking of all adverse events. The Clinical Center and Affiliate (if monitoring intervention) are notified immediately of any such adverse event by automated facsimile transmission.

In addition, at each visit, subjects are carefully interviewed with regards any adverse events that may have occurred.

Any Study Group member learning of the death of a subject immediately follow the "Notification of Death Procedure" (included in the Manual of Operations).

11. OUTCOME EVALUATION - INTERMEDIATE RISK COHORT (Oral Antigen)

The principal study outcome is the development of diabetes (by criteria established by the American Diabetes Association in 1997). The Oral Glucose Tolerance Test (OGTT) is the principal study outcome test used to detect diabetes. Oral glucose is administered in a dose of 75 grams (in adults) or 1.75 g/kg body weight to a maximum of 75 grams (in children), as a solution in flavored water, consumed within 5 min. Two baseline samples will be obtained (at -10 and 0 minutes) before glucose is consumed. Blood samples will be obtained at 30, 60, 90, and 120 minutes after glucose consumption is complete, for the determination of glucose and C-peptide levels.

A Study Event (or Treatment Failure) is defined as the development of diabetes, by criteria established by the American Diabetes Association in 1997. As used in DPT-1, those criteria, which must be met on two occasions (unless criteria [iv] is present) are:

[i] casual (any time of day without regard to time since last meal) plasma glucose $\geq$ 200 mg/dL, if accompanied by unequivocal symptoms (i.e. polyuria, polydipsia, polyphagia, and/or weight loss),

OR

[ii] fasting (no caloric intake for at least 8 hours) plasma glucose $\geq$ 126 mg/dL (core laboratory),

OR

[iii] 2-hour plasma glucose $\geq$ 200 mg/dL during a 75 gram oral glucose tolerance test (OGTT),

OR

[iv] unequivocal hyperglycemia with acute metabolic decompensation (e.g. ketoacidosis).

N.B. In DPT-1, unless criteria [iv] is present or the fasting glucose is $\geq$ 250 mg/dl (at the bedside or in the local laboratory on the day of testing), it is preferred that at least one of the two testing occasions involve an oral glucose tolerance test (OGTT). If the first criterion met is [iii], i.e. by the 2-hour OGTT value, the OGTT should be repeated within 60 days. It is essential that every effort be made to obtain the necessary tests to establish the diagnosis of diabetes.

For fasting hyperglycemia, a tentative diagnosis may be made, based on measurements made in a local laboratory if FPG $\geq$ 160 mg/dL on two separate days within one week, with confirmation by FPG $\geq$ 126 mg/dL on two separate days within one week, as performed in the Core Laboratory. OGTTs will be scheduled every 6 months. If a single OGTT meets the criteria for diabetes, a repeat OGTT will be scheduled within 2 months. There will be strict attention to detail in the performance of OGTTs. Subjects will have adequate dietary preparation (minimum 150 g carbohydrate per day) for three days prior to OGTT. OGTT will be postponed if there is intercurrent illness, but must be performed no later than 6 weeks after each 6 month anniversary date.

If a diagnosis of diabetes is made outside of the study, the Eligibility and Events Committee will review the criteria for establishing the diagnosis. The subject will be asked to complete all measures that are scheduled for collection at the time of a Study Event or Study End.

As a subsidiary outcome, pancreatic β-cell function will be assessed by measuring C-peptide response during each OGTT.

Subjects will have a Complete IVGTT (with evaluation of pancreatic β-cell function by measurement of plasma insulin responses to this challenge) every 12 months, and at Study End, unless the subject has developed diabetes, in which case the IVGTT will not be performed.

Subjects will have a Mixed Meal (Boost® [previously known as Sustacal]) Tolerance Test (MMTT) with evaluation of pancreatic β-cell function by measurement of plasma C-peptide responses to this provocative mixed meal challenge every 36 months, and at the time of their completion of intervention (either if there is a Study Event, i.e. Treatment Failure, or at Study End). For those subjects who develop diabetes, the MMTT at Study End will be performed 8-16 weeks after the diagnosis has been made, having withheld long acting insulin the night before and all insulin the morning of the MMTT. If fasting blood sugar is greater than 250 mg/dl, the MMTT will not be performed, and then only a fasting C-peptide will be measured.
The sequence for performing tests when more than one are due in any one evaluation period is: OGTT (glucose primary end point) > MMTT (C-peptide secondary end point) > IVGTT. Tests must be performed in the fasting state on separate days.

HbA1c and ICA and IAA will be determined at each 6 month visit.

12. OTHER ASSESSMENTS

12.1 Additional Assessments

In addition to the primary and secondary outcomes noted for both Intervention Protocols, samples will be collected and stored for possible future analysis of the following:

- HLA Class II Analysis
- Beta Cell Function/Insulin Sensitivity Testing
- Immunological Mechanisms
  - T-Cell Function Testing
  - Autoantibody Markers for Biochemically Defined Islet Cell Antigens

12.2 Long Term Follow-Up of Subjects Developing Diabetes – Implementation

Subjects developing diabetes will be asked to participate in yearly follow-up evaluations to include:

- Interval history form noting height, weight, blood pressure, insulin regimen and doses, other medications (besides insulin) used, number of episodes of severe hypoglycemia, number of episodes of hypoglycemic with loss of consciousness and/or seizures.
- Mixed Meal Tolerance Test (MMTT) with evaluation of pancreatic β-cell function by measurement of plasma C-peptide responses to this provocative mixed meal challenge. Performance of the MMTT shall be after an overnight fast $\geq$ 8 hours. Subjects will take their usual insulin the evening before the MMTT, but omit insulin the morning of the MMTT (except those treated with insulin pumps could continue their basal infusion). All subjects will attempt to have a fasting glucose value of 100-250 mg/dl the morning of the test. If outside this range or if a subject has symptomatic hypoglycemia during the night before, the test will be rescheduled.
- HbA1c
- Autoantibody Markers for Biochemically Defined Islet Cell Antigens
- Blood sample collected and stored for possible future analysis (similar to Section 12.1)

(For subjects who had diabetes diagnosed prior to the implementation of this provision in Fall 2000, subjects will be recalled for this evaluation as soon as possible and yearly thereafter).

12.3 – Contact of Subjects Not Being Followed

12.3.a – Determination of Diabetes in Subjects Not Being Followed

Subjects Screened, Staged, or Randomized may be contacted periodically for follow-up information by the DMU or a DPT-1 investigator. This contact will be by letter, by phone, and/or in person by the DMU or by a DPT-1 investigator.

Sample follow-up information to be requested:

- Do you have diabetes?
- What was your date of diagnosis?
- What symptoms did you have?
- What was your initial treatment?
- What is your current treatment?
- May we send you a request to release medical information about your diabetes?

12.3.b – Participation in Ancillary Studies by Subjects Not Being Followed

Subjects eligible for approved ancillary studies may be contacted by the DMU or a DPT-1 investigator. All ancillary studies must have approval of the IRB at the institution that the study is to be carried out.

Sample follow-up information to be requested for subjects eligible for ancillary studies:

"You are eligible to participate in a study related to DPT-1. This is an approved ancillary study to the DPT-1. Please contact XXX for further information" and/or "May XXX contact you to discuss the study?"

13 . STATISTICAL ANALYSES

Policies with regard to interim analyses are implemented by the DMU. In general, accrual, eligibility, and evaluability are to be monitored and reported. Efficacy results are masked, as appropriate, in interim reports.

Subject accrual is monitored through ongoing comparisons with the planned study accrual and actual study accrual in terms of the projected study duration. Tables which reflect these data are produced quarterly for review by the Planning Committee and used to assess whether accrual has exceeded targeted levels or is substantially less than projected accrual, so that corrective action can be taken.

Monitoring studies for treatment arm differences is built into protocol design, and carried out in cooperation with the external Data Safety and Quality (DSQ) Monitoring Group. Two procedures are used. One is an optimal two-stage procedure in which the arms are compared after about 40% of planned accrual. If the arms fail to differ by more than a previously specified amount, then there is a high level of assurance that continued accrual as planned will not result in a statistically significant difference. This form of stochastic curtailment is utilized for protocols in which it is possible to evaluate the relevant outcome measure in a rapid fashion relative to accrual to permit such a determination to be made. A second form of monitoring occurs when treatment differences are of such magnitude to suggest that it would be unethical to continue the trial beyond that point. An appropriate p-value is determined recognizing the consequence of multiple comparisons.

Testing for differences in proportions will be based upon exact methods unless frequencies are sufficient to allow the Chi-square statistic. The method of Kaplan-Meier is used to construct survival curves and the logrank statistic to compare them. Multivariate analyses will be based on applications of the Cox proportional hazards general linear model.

Additional criteria for monitoring and analyses will be developed and reviewed periodically by the DSQ. This group, appointed by the NIDDK, is responsible for sequential monitoring of the accrued study data, particularly as it relates to identification of hazards to study volunteers and recommendations for early stopping of the trial.

14 . RANDOMIZATION PROCEDURES

The Data Management Unit (DMU) is responsible for central registration and random assignment to study arms of all subjects enrolled in intervention protocols. Criteria for registration are contingent on individual protocols, as defined. All data are to be reported to the DMU. When a subject meets criteria for High or Intermediate Risk status, the Clinical Center will be notified as to potential for enrollment in the relevant protocol, or need for further testing, as appropriate. On the basis of confirmed High or Intermediate Risk status, individuals will be invited into the appropriate intervention trial if they meet the entry criteria for that trial. For those that do not, follow up will be conducted at the intervals defined in the protocol, with possible entry into a trial at a later date.

14 .1. Automated Registration Procedures:

The registration process for both components of the study will be initiated via telephone call to the DMU's automated subject registration system. This microcomputer-based system will be available at all times for subject registration. Each center is assigned a unique identification code to enter the system. An interactive set of data requests is followed to complete a registration. The system uses touch-tone telephone keyboard input and communicates with the caller using synthetic speech. At each step, the system requires confirmation via telephone keyboard input to ensure that the data, such as subject identification number or treatment assignment number, are properly understood.

The automated system maintains marginal totals for center and stratum balancing. A block design is used to randomize and maintain balancing within predefined limits. A hard copy log of each registration attempt (successful or unsuccessful) is maintained in the DMU and will be reviewed daily by the DMU Manager who confers with individual investigators to resolve problems that may arise. The modularity of the system is designed to easily accommodate new centers and/or studies. In addition, the system can readily accommodate studies requiring callbacks for randomization and the accession of laboratory results supplied independently (but via telephone) which are then used for stratum assignment and randomization. The system also has the capability to provide messages as reminders for specific data submission requirements.

At the completion of each day's registrations, the data will be transferred electronically to the DMU's central computer for processing. Within 24 hours a computer generated letter is mailed to the caller confirming the telephone transaction and providing additional detail regarding data submission requirements. The system also produces letters to each reference laboratory to alert them of a registration and to advise them to anticipate receipt of sera. The

notification letters also serve as a vehicle by which the laboratory results may be communicated to the Clinical Center and to the DMU. A telephone call to the automated registration system will establish eligibility for entry into the intervention trial so that the clinical center can place a second call to the system and, if the eligibility criteria are met, the system will perform the randomization and treatment assignment. A new confirmation letter will be generated at that time to confirm the information provided by telephone. The subject will be assigned a medication code number and this number will be also be communicated to the Central Pharmacy (CP), which will then label the appropriate medication and ship to the Clinical Center.

For the High Risk Protocol, participants will be stratified for randomization into two strata based on the OGTT:

- normal OGTT by 1997 ADA criteria

  versus

- impaired glucose tolerance (IGT) or impaired fasting glucose (IFG).

Subjects will also be stratified by Center.

If two or more members of the same family are eligible for an intervention protocol, they will be randomized individually and separately.

In cases where there are questions regarding eligibility, the DMU will attempt to resolve the problem by consultation with the Clinical Center. If resolution is not possible, the matter will be referred to an Eligibility and Events Committee for a decision. The Eligibility and Events Committee will include at least the Director of the DMU, 2 Clinical Center Principal Investigators, and at least one Trial Coordinator. This committee will discuss cases by conference call with one individual of group (rotating) responsible for final recommendation.

15 . POLICY AND STRUCTURE

15 .1. Philosophy

The Diabetes Prevention Trial - Type 1 Diabetes (DPT-1) has been organized on the premise that significant advances can be made by a cooperative approach to the design and conduct of human clinical intervention trials both to prevent or delay the development of Type 1 DM and to preserve β-cell function in recent onset Type 1 DM. The goal is to create a dynamic and flexible environment where investigators can work together to develop and implement research protocols.

The philosophy underlying development of the DPT-1 is that through the establishment of this network, multiple trials can be conducted, in a serial fashion, or in different disease stages. Although the initial plan calls for specific trials for prevention of Type 1 DM, it is anticipated that the DPT-1 network will facilitate other trials as well. For example, the DPT-1 may seek separate funding to conduct a trial in new onset Type 1 DM to test the suitability of some new therapeutic agent which might result in stabilization of β-cell function.

15 .2. General Responsibilities of all members of the DPT-1:

Each member of the DPT-1 supports the concept of inter-institutional studies by pooling clinical case material and laboratory resources with other collaborating members, and of participating in study committees for the purpose of developing new ideas and analyzing or evaluating the results of studies related to the prevention and/or stabilization of human Type 1 DM. All members of the DPT-1 agree that all eligible subjects will be offered entry into the studies developed by the DPT-1. Eligible subjects who refuse to enter studies developed by the DPT-1 may be followed by the members of the DPT-1 but may not be treated or entered into any other treatment studies. Subjects accepted into studies of the DPT-1 (including screening, staging, and intervention studies) may not be involved in any other studies except as explicitly authorized by the Ancillary Studies Working Committee. All members of the DPT-1 agree that they will not simultaneously engage in other studies evaluating the efficacy of agents for prevention or delay of Type 1 DM in relatives eligible for screening in DPT-1.

All samples and data from subjects accepted into DPT-1 studies are the property of the DPT-1 Study Group and may not be used or presented without the explicit permission of the DPT-1 Study Group. The Ancillary Studies Committee will review and approve use of all samples. The Publications Committee will review and approve all presentations and

publications. Policies regarding authorship will be developed and implemented by the Publications Committee.

All members of the DPT-1 agree that there will be no measurements of outcome measures outside of the Core Laboratories.

15 .2a. Policies

15 -2a-1. Ancillary Studies

Ancillary studies will be evaluated with careful consideration of their potential impact on the objectives and performance of the DPT-1. Ancillary studies which complement the objectives and thereby enhance the value of the DPT-1 are to be encouraged. Such studies should augment and protect the continued interest of both subjects and investigators. To protect the integrity of the major study, a proposal to conduct an ancillary study must be reviewed and approved by the Ancillary Studies Committee before its initiation. In some cases, ancillary studies must also be approved by the Steering Committee. All approved ancillary studies will be reviewed yearly by the Ancillary Studies Committee for progress and impact on the DPT-1 as a whole.

Definition Of An Ancillary Study: An ancillary study is defined as research or data collection involving DPT-1 subjects using any technique, medication, procedure, questionnaire or observation other than those set forth in the DPT-1 Protocol.

The investigator or co-investigator responsible for the conduct of an ancillary study must be a member of the DPT-1 Study Group.

Reason for Requirement of Approval: Investigators and subjects are entitled to prior assurance that all ancillary studies are of high scientific merit and that no ancillary study will:

- Cause a deviation from the Protocol;
- Complicate interpretation of the study results;
- Potentially adversely affect subject cooperation;
- Jeopardize the public image of the study;
- Create a significant diversion of the study resources locally or at the Data Management Unit, a Core Laboratory or any other DPT unit;
- In any way negatively influence the cooperative spirit of the collaborating investigators;
- Otherwise compromise the scientific integrity of the study.

Levels Of Approval Required For Ancillary Studies: There are two levels of approval for ancillary studies:

Level I: Approval by the Ancillary Studies Committee.

Level II: Further approval by the Steering Committee.

In general , Level I approval will suffice if the ancillary study involves analyzing available data from the DPT-1 for questions not addressed in the major study, and no additional tests or observations will be made on the subjects. Other types of ancillary research will customarily require both Level I and Level II approval. The decision regarding the necessary level of approval will be made on a case by case basis by the Chairman of the Ancillary Studies Committee in consultation with the Operations and/or Steering Committees.

After approval by the Ancillary Studies Committee and the Steering Committee, final approval is contingent upon the Ancillary Studies Committee receiving a letter signed by the principal and all collaborating investigators in which they agree to abide by the policies for ancillary studies herein described including that regarding publication pr presentation of results.

Funding Of Ancillary Studies: The DPT-1 will not provide funds for ancillary studies. In particular, no funds are provided for Coordinating Center, Data Management Unit, or Core Laboratory activities or services in support of ancillary studies. If funds are needed, the investigator must explore other avenues such as: (1) submission of a research grant application; or (2) use of other source of funds (i.e., a foundation, drug company, etc.). The anticipated source of funds must always be identified.

Publication Of Ancillary Study Results: All manuscripts, abstracts or presentations for scientific meetings based on ancillary study data must be reviewed and approved by the DPT-1 Publications/Presentations Committee before publication or presentation.

15 -2a-2. Publications

During the planning or conduct of the DPT-1, there will be no effort to publicize study plans or results which have not been reviewed and approved by the participants. Together with the Operations Coordinating Center, the Publications and Presentations Committee will coordinate, monitor, review and assume responsibility for arranging the preparation of all press releases, interviews, presentations and publications relating to the DPT-1. Recommendations will be presented to the Operations or Steering Committee of the DPT-1 for approval. Copies of approved material will be provided promptly to NIDDK.

The Publications Committee shall:

- Recommend policy and procedures for review and approval of all communications regarding the DPT-1 to outside groups.

- Identify publications to be written during the course of the study, with target dates for each.
- Propose policy guidelines for authorship of DPT-1 publications, and/or recommend to the Steering Committee senior authors and co-authors for each paper.
- Monitor the writing of each paper to ensure publication in a timely fashion.
- Establish standards of excellence for DPT-1 publications.
- Review, edit, and approve all DPT-1 publications and presentations prior to submission, enlisting the special assistance of the DPT-1 committees whenever appropriate. The review will be conducted pursuant to the following editorial policy:
    a) To ensure that all publications preserve the scientific integrity of the DPT-1.
    b) To correct factual and conceptual inaccuracies if necessary.
    c) To safeguard the rights of volunteer participants.
    d) To prepare comments to assist collaborating scientists in publishing papers of the highest quality and clarity.
    e) To inform the Steering Committee, NIDDK, and advisory groups of all public dissemination of DPT-1 information.
    f) To avoid conflict with and/or duplication of other DPT-1 publications.
- Review, suggest necessary revisions, and approve any publications arising from approved ancillary studies prior to their submission for publication. In addition to the issues cited in the editorial policy above, proposed publications of ancillary studies will be scrutinized to ensure that their presentation will not threaten the viability of the DPT-1, if still ongoing.
- Suggest appropriate journals for DPT-1 publications and monitor the process of publication.
- Perform other writing, reviewing, or editing tasks assigned by the Steering Committee or Operations Committee.

15 -3. Structure Of The DPT-1

15 .3a. Committees

15 -3a-1. Steering Committee

Function of the Steering Committee: The Steering Committee has overall responsibility for the design, planning, execution, and publication of the research performed by the DPT-1 Study Group. The Steering Committee will approve all protocols, changes to protocols, and manuals of operations. The Steering Committee, together with NIDDK, is responsible for the addition or the deletion of Clinical Centers.

Examples of Steering Committee functions include (but are not limited to):

- Selection of a Study Chair
- Responsibility for approval and final development of Study Protocols
- Defining the structure of and making appointments to the various committees
- Responsibility for implementation of studies at the various Clinical Centers
- Maintenance of surveillance of the DPT-1 performance
- Development of the Policies of the DPT-1 itself, and formulation and development of policies for the various committees, centers, and reference laboratories
- Receiving and acting upon reports and recommendations of various committees
- Reviewing matters relevant to the administrative, financial, medical, legal, and ethical considerations, or functions of the DPT-1

Membership of the Steering Committee:

Voting members:

Director of the Operations Coordinating Center (1)
Director of the Data Management Unit (1)
Chair of the Planning Committee (1)
Directors of each of the Clinical Centers (9)
Directors of each of the Core Laboratories (4)
Representatives of the funding institutes of NIH (3)
The Chair may be selected from any of the voting members except the NIH.

Non-voting members:

Representative from the American Diabetes Association (1)
Representative from the Juvenile Diabetes Foundation (1)
Directors of each of the Affiliate Centers

Rules of the Steering Committee:

- The Steering Committee meets in person at least annually.
- Additional meetings of the Steering Committee may be called by the Chair of the Steering Committee or by a majority of the members of the Steering Committee.
- These additional Steering Committee meetings may be in person or by other means.
- Notice of all Steering Committee meetings must be given at least two weeks in advance of such meetings. Such notice must specifically reference the adoption of any DPT-1 Protocol or changes to an approved DPT-1 Protocol, if such are to be on the agenda. Adoption of any DPT-1 Protocol and changes to any approved DPT-1 Protocol may not arise from the floor.

- Fifty percent (50%) of the voting membership of the Steering Committee constitutes a quorum. Seventy-five percent (75%) of the voting membership of the Steering Committee constitutes a quorum for consideration of adoption of a DPT-1 Protocol or for changes to an approved DPT-1 Protocol.
- Any action items may be approved by majority vote of the Steering Committee. A supermajority of 67% is required for adoption of a DPT-1 Protocol or for changes to an approved DPT-1 Protocol.
- Adoption of any DPT-1 Protocol or changes to an approved DPT-1 Protocol must be reviewed by the Data Safety and Quality Monitoring Group (DSQ) and by NIH.
- The Steering Committee selects its Chair by majority vote.
- All votes regarding personnel will be by secret ballot.
- Each one person on the Steering Committee has one vote even though that person may have more than one of the positions listed above.
- The Chair votes only to break a tie.

The Chair of Steering Committee:

- The Chair serves at the pleasure of the Steering Committee for an undesignated term.
- It is the intent of the Steering Committee that the Chair of the Steering Committee have substantial authority to act for the Steering Committee to further the goals of the DPT-1.
- The Chair may create Working Committees as needed, and shall appoint the members and the chair of these Working Committees.
- The Chair appoints committee chairpersons and may rotate these positions annually. All committee chairs serve for undesignated terms.

15 .3a-2. Planning Committee:

Function of the Planning Committee: The Planning Committee coordinates operation of the Working Committees and integrates the Working Committees' input into the Steering Committee agenda.

Membership of the Planning Committee:

Chair
Chairs of each Working Committee
Chair of Steering Committee
Operations Committee Members

Rules for the Planning Committee: The Planning Committee meets as needed either in person or by other means.

15 .3a-3. Working Committees:

Working Committees each have specifically designated functions.

Current committees include:

- Eligibility and Events Committee
- Treatment Committee
- Ancillary Studies Committee
- Publications and Presentations Committee
- Communications and Public Relations Committee
- Clinical Center Directors Committee

15 .3a-4. Executive Committee:

Function of the Executive Committee: The Executive Committee coordinates the fiscal aspects of the three U01 grants funding the DPT-1 and advises the Steering Committee of its actions.

Membership of the Executive Committee:

The PIs of each the 3 U01 grants (3)

Director of the Data Management Unit (1)

Representative of NIDDK (1)

Rules of the Executive Committee: The Executive Committee meets as needed either in person or by other means.

15 .3a-5. Operations Committee:

Functions of the Operations Committee: The Operations Committee is responsible for implementing the decisions of the Steering and Planning Committees and manages the day to day operations of the studies created by the DPT-1.

For protection of subjects, the Operations Committee may suspend enrollment in any DPT-1 protocol, with the concurrence of the Chair of the Data Safety and Quality Monitoring Group (DSQ). The Director of the Data Management Unit has the authority to suspend any DPT-1 protocol on an emergency basis for up to 48 hours, while seeking concurrence of the

Operations Committee and of the Chair of the DSQ. Such actions will then be brought to the DSQ and/or to the Steering Committee (as appropriate) at the earliest opportunity.

Membership of the Operations Committee:

Chair of Steering Committee

Representative of the Operations Coordinating Center

Representative of the Data Management Unit

Representative of the NIDDK

Rules for the Operations Committee: The Operations Committee meets as needed either in person or by other means.

15 .3b. Study Units

15 .3b-1. Clinical Coordinating Centers:

Together, the two Clinical Coordinating Centers oversee the activities of the Clinical Centers. The intent of the DPT-1 is that these two Coordinating Centers have identical policies and procedures. The two Clinical Coordinating Centers are integrated via the Executive Committee.

15 .3b-2. Operations Coordinating Center (OCC):

The Operations Coordinating Center has both Scientific and Administrative functions. Scientific functions include providing overall leadership to the DPT-1; protocol and manual preparation and development; manuscript coordination, tracking, submission; developing meeting agendas; and overseeing the performance of quality control audits. Administrative functions include coordinating interactions among the Clinical Centers, and between the Data Management Unit, Core Laboratories, and NIDDK; financial management; interactions with sponsoring agencies; communication with DPT-1 membership, including circulation of DPT-1 information, newsletters, operations manuals, protocols, manuscripts; maintenance of membership rosters and committee lists.

15 .3b-3. Data Management Unit (DMU):

The Data Management Unit is responsible for all data management and statistical considerations for the DPT-1. The DMU has both administrative and scientific functions. The administrative functions include providing for central registration and random assignment of all subjects enrolled in trials; preparation of data management aids; maintaining subject and protocol

files; providing statistical reports on progress of trials at all meetings; and serving on all DPT-1 administrative committees. Scientific functions include review of all proposed protocols and development of statistical design for each study; analysis of study results; review of all manuscripts for statistical considerations; development and testing of predictive models for disease progression; and conduct of statistical research concerning intervention trials in Type 1 DM.

15 .3b-4. Central Pharmacy:

The Central Pharmacy is responsible for dispensing all therapeutic agents and placebos used in DPT-1 studies. The Central Pharmacy shall distribute these agents to Clinical Centers in a masked manner as directed by the DMU.

15 .3b-5. Core Laboratories:

The OCC is responsible for the coordination of the Core Laboratories used in the DPT-1. There will be four Core Laboratories. These are responsible for measurement of the critical variables in the study protocols. The core laboratories include:

15 .3b-5.1. ICA Laboratory: The Immunology Core Laboratory will serve as the central laboratory for measurement of various autoantibodies to islet cell markers, and for measurement of anti-islet cellular immunity. It may also conduct a standardization and proficiency program to assist other investigators wishing to perform ICA analysis; and may develop and standardize improved methodology for assessment of anti-β cell immunity during multicenter intervention trials.

15 .3b-5.2. IAA Laboratory: The Insulin Autoantibody Core Laboratory will serve as the central laboratory for measurement of insulin autoantibodies.

15 .3b-5.3. Class II MHC and DNA Extraction Laboratory: This laboratory will extract and preserve DNA from all subjects staged for eligibility for enrollment in intervention protocols, and determine the presence of HLA-DQA1*0102,DQB1*0602. The Class II MHC and DNA Extraction Typing Core Laboratory may provide more complete class II HLA typing (e.g. DQα, DQβ, DRβ) of all individuals entered into trials. It may also explore other genetic markers that influence susceptibility or progression of Type 1 DM.

15 .3b-5.4. β-Cell Laboratory: The Beta Cell Function Core Laboratory will serve as the central laboratory for assessment of beta cell function by measurements of immunoreactive insulin and C-peptide, plasma glucose, and glycosylated hemoglobin HbA1c. It may also

develop and standardize improved methodology for assessment of β-cell function during multicenter intervention trials for prevention of Type 1 DM.

15 .3b-6. Clinical Centers:

Each designated site with responsibility for interfacing trial conduct with the OCC, the DMU, the core laboratories, and Affiliates and Satellites and for screening of potential subjects, enrollment of subjects, and conduct of the protocols of the DPT-1 will be known as a Clinical Center and will receive support from the Cooperative Agreements funded by the NIH. Each Clinical Center will have access to an NIH supported General Clinical Research Center (GCRC) or equivalent facility (similar to a GCRC) so that inpatient costs on such equivalent facility do not require support by the DPT-1 Cooperative Agreements. Clinical Centers will assume primary responsibility for coordinating screening with their Affiliates and Satellites and perform in-patient intravenous insulin infusions as part of the Parental Antigen Protocol.

The Clinical Centers are responsible for implementation of the protocols of the DPT-1, including screening of potential subjects, staging of subjects, enrollment of subjects, and conduct of the Protocols. Each Clinical Center will have a Principal Investigator, a full time Trial Coordinator, other investigators, and ancillary personnel as needed. The Principal Investigator will work with the Operations Coordinating Center, Chair of the Steering Committee, and NIH Staff assigned to this project to conduct the study in accordance with the Protocol and Manual of Operations. The Clinical Centers are expected to meet the patient recruitment goals as specified by the OCC and will work with the OCC, DMU, and all Core Laboratories to reach study goals and maintain quality of the data. In addition, each Clinical Center may have Affiliates (other academic centers suitable for screening and staging of subjects, and conduct of intervention protocols) and/or Satellites (various medical settings suitable for screening subjects) interdigitating with it and responsible to it. Clinical Centers are responsible for supervision, training, and completion of certification requirements of their Affiliates and Satellites. Clinical Centers are responsible for the regional screening of potential subjects and therapy for those subjects selected for intervention trials.

15 .3b-7. Affiliated Centers

Medical Centers with the capability to screen patients, perform tolerance tests (intravenous glucose, oral glucose and mixed meal) and conduct various aspects of the Treatment

Protocols may participate in the DPT-1 through affiliation with a designated Clinical Center and will be known as Affiliated Centers. These Affiliates must sign a Letter of Agreement outlining the details of their participation in the study. Affiliates will be paired with a Clinical Center. This matching may be based on satisfaction with prior relationship (e.g. screening program already active) or on geographic or other considerations. An Affiliated Center will be responsible to the parent Clinical Center and its activities intertwined with those of the Clinical Center. An Affiliated Center will not receive core funding but will be reimbursed in a task and patient specific manner at standardized rates set by the Steering Committee. An Affiliated Center will be directed by a Principal Investigator who is a physician.

Affiliated Centers involved in Staging shall have the capability to perform intravenous and oral glucose tolerance tests and aid in the outpatient follow-up of trial participants. Personnel performing IVGTTs must be certified.

Affiliated Centers wishing to perform intravenous insulin infusions must have available a GCRC or equivalent facility, and must obtain certification to perform intravenous insulin infusions. An "equivalent facility" is defined as dedicated inpatient beds staffed by personnel experienced in the conduct of research protocols and in performance of intravenous insulin infusions, with institutional commitment to provide such beds at no extra expense to the DPT-1.

An Affiliated Center may apply to be converted to a Clinical Center based on its ability to screen and enroll substantial numbers of subjects, access to a General Clinical Research Center (or equivalent facility) and other criteria. If a conversion application is approved by the Steering Committee, conversion will be implemented as funds permit.

15 .3b-8. Satellite Sites

Medical settings suitable only for the screening of subjects may participate in the DPT-1 by affiliating with a designated Clinical Center (matching of Satellite and Center influenced by prior relationship, potential geographic considerations, etc.), and will be known as Satellite Sites. Satellite Sites will be responsible to a parent Clinical Center. Satellite Sites will be reimbursed for screening on a per subject basis at rates set by the Steering Committee.

Satellites generally will not perform Staging or Intervention. This will be accomplished at the geographically most convenient Affiliate/Center or at the Center primarily relating to the Satellite Site, based on convenience of the subject.

15 .3c. Monitoring Groups

15 .3c-1. Clinic Monitoring Group

The Clinic Monitoring Group (CMG) is appointed by the Steering Committee Chair to provide internal monitoring of all aspects of the performance of the Clinical Centers. The CMG is comprised of three physician investigators, one of whom is appointed as Chair, and one Trial Coordinator, who serve for an undesignated term. The Operations Committee serve as ex-officio members. The OCC and DMU provide the CMG with the operational study data (as opposed to outcome study data) that will enable them to monitor clinic performance in meeting screening and enrollment goals and adherence to the protocol. The CMG will establish criteria and procedures for internal clinic monitoring. Major deficiencies in performance by a clinic that cannot be otherwise resolved will be reported to the Steering Committee for resolution. The CMG will also review proposals by Affiliated Centers to convert to Clinical Centers. An evaluation and recommendation will be prepared and forwarded to the Steering Committee for action.

15 .3c-2. Laboratory Monitoring Group

The Laboratory Monitoring Group (LMG) is appointed by the Steering Committee Chair to provide internal monitoring of all aspects of the performance of the Core Laboratories. The LMG is comprised of three physician investigators, one of whom is appointed as Chair, and one scientist external to the trial, who serve for an undesignated term. The Operations Committee serve as ex-officio members. The LMG will establish criteria and procedures for monitoring of laboratory performance. Serious deficiencies in performance by a laboratory that cannot be otherwise resolved will be reported to the Steering Committee for resolution.

15 .3c-3. Safety Monitoring Group

The Safety Monitoring Group (SMG) is appointed by the Steering Committee Chair to provide internal monitoring of safety aspects of DPT-1. It reviews potential safety issues identified by the investigators, suggests definitions for Safety Alerts that might cause review of various aspects of the protocols, and assures that various aspects of the protocol are designed and conducted in such a way as to assure the safety of research volunteers. The SMG is comprised of at least four physician investigators, one of whom is appointed as Chair, who serve for an undesignated term. The Operations Committee serve as ex-officio members. The SMG will establish criteria and procedures for internal monitoring of study safety. Recommendations will be made to the Steering Committee for action.

15 .3c-4. Data Safety and Quality Monitoring Group

An external oversight committee, the Data Safety and Quality (DSQ) Monitoring Group is appointed by NIDDK and is composed of members not directly involved in the study. The DSQ will review the conduct and results of the study for safety and efficacy with authority to recommend protocol or procedural changes or early termination of the study. The DSQ is advisory both to NIDDK and to the DPT-1 Study Group.

Functions of the DSQ: Subjects and study personnel will be masked to accumulating outcome data. Therefore, an independent external advisory group will review periodically the aggregate study data and be authorized to recommend to NIDDK that the trial be terminated or the protocol modified if predefined study objectives have been met or a safety issue identified. Because the members of this committee must be unmasked to all data, they, therefore, may not be involved in the conduct of the DPT-1 or the clinical care of any subjects involved in DPT-1 studies.

Specific study problems may be referred to this committee by the Chair of the Steering Committee and the Group may offer advice to the study group related to any aspect of performance of the study.

Membership of the DSQ:

Voting Members and Chair

Selected by NIDDK

Non-voting Members

Chair of the Steering Committee

Director of the Operations Coordinating Center

Director of the Data Management Unit

Representative of the funding institutes of NIH

Rules for the DSQ: This committee meets at least yearly and at such other times as needed either in person or by other means.

The DSQ will be administered through NIDDK.

16 . HUMAN SUBJECTS

16 .1. Subject Population:

Screening will be conducted over four years; some 15,000 non-diabetic relatives of persons with Type 1 DM will be screened each year (60,000 individuals overall). From these, approximately 340 subjects, age 4-45, are expected to be enrolled in the parenteral antigen protocol, and approximately 490 subjects, age 3-45, are expected to be enrolled in the oral antigen protocol. Overall, based on 4 year accrual and 6 year total study, the sample size for the parenteral antigen protocol is designed with a power of 80% to detect a 35% difference in the annual hazard rate for the onset of Type 1 DM, expected to be 21% per year in the control group, assuming $\alpha = 0.05$ (two tail test), and allowing for a 10% drop-out rate. Similarly, based on 4 year accrual and 6 year total study, the sample size for the oral antigen protocol is designed with a power of 80% to detect a 50% difference in the annual hazard rate for the onset of Type 1 DM, expected to be 6% per year in the control group, assuming $\alpha = 0.05$ (two tail test), 4 year accrual, 6 year total study, and allowing for a 10% drop-out rate.

16 .1a. Gender and Ethnic Diversity

Both men and women, and members of all racial and ethnic populations will be screened and (if they meet the appropriate criteria) offered enrollment in the intervention studies. Enrollment is expected to reflect the known differences in frequency of Type 1 DM amongst different racial and ethnic groups. In the United States, non-Hispanic whites comprise the majority of cases of Type 1 DM, accounting for 86% of all cases, with blacks (9%) and Hispanics (5%) comprising most of the remainder (21-22). The disease is exceedingly rare in Asians (0.25%) and American Indians (0.048%). The low frequency of Type 1 DM in Asians is also noted when comparing disease frequency in different countries (21). It has been shown that the differences in disease frequency are, in large part, accounted for by differences in frequency of the HLA Class II genes that confer both risk of Type 1 DM and protection from Type 1 DM (23). Amongst the different ethnic groups, in the context of susceptible HLA genes, the pathogenesis of Type 1 DM appears to be the same. Moreover, there are no data to suggest that the interventions to be used in the DPT-1 protocols will have different effects based on gender, race, or ethnicity. Therefore, we will vigorously recruit minority subjects, but will not alter the sample size to provide sufficient power to separately analyze different ethnic groups. We will track outcome by ethnicity, in the event that unexpected trends emerge that may be related to ethnicity.

Prior screening studies of relatives of Type 1 DM probands have revealed an equal distribution of males and females. Therefore, it is anticipated that approximately half of the DPT-1 study population will be males and approximately half will be females.

Special efforts will be made to recruit amongst minority groups in order to attain enrollment proportional to the frequency of the disease in the population of the United States. Such special efforts to enhance minority recruitment for screening will include: dissemination of information about the study through such organizations as the National Medical Association, the Committee on Diversity of the American Diabetes Association, the InterAmerican College of Physicians and Surgeons, and the National Association of Latin American Health Professionals; preparation of Spanish language recruitment and information materials; public service announcements, and public affairs and features presentations in publications, television, radio and other media directed at minority audiences; and involvement of community and religious organizations, and minority community leaders.

The distribution of subjects screened, staged, enrolled, and retained on protocol, by gender and by race and ethnic group, will be monitored by the Clinic Monitoring Group through the DMU and reported annually to the Steering Committee. If the study population does not reflect the recruitment targets, corrective action will be taken. Should this occur, attempts will be expended to determine why particular groups are underrepresented, and strategies devised to overcome obstacles. Such efforts might include attempts to secure funds to provide for reimbursement of costs incurred by potential minority volunteers for subject participation, e.g. costs for travel, lost wages, etc.

16 .1b. Protection of Human Subjects

Screening will be conducted amongst non-diabetic relatives of persons with Type 1 DM. This will involve taking of a blood sample. Subjects who screen positive, will be invited to consent to undergo eligibility risk staging, which involves further blood sampling for metabolic, genetic, and immunological testing. Data will be maintained and analyzed at the DMU. Subjects qualifying for enrollment in one of the intervention protocols will be invited to consent to be randomized and enrolled. This will involve further monitoring and testing at regular intervals for the duration of the study, and may involve administration of one of the experimental interventions. At each step, subjects (or their guardians) will be invited to provide written informed consent after the protocol has been fully explained to them. Participation is completely voluntary and subjects may withdraw from the research studies at any time. The protocol and

consent forms will be approved by Institutional Review Boards (IRBs) at each of the participating Centers or Affiliates.

A careful system has been developed for monitoring of potential adverse events. This includes use of a toll-free 800 telephone line, based at the Data Management Unit (DMU), which will be used by all subjects to report all adverse events. This computer based system, using simulated speech (in English or Spanish), ensures that there is uniform review of all symptoms, and allows rapid centralized tracking of all adverse events. The Clinical Center and Affiliate (if monitoring intervention) are notified immediately of any such adverse event by automated facsimile transmission. In addition, at each visit, subjects are carefully interviewed with regards any adverse events that may have occurred. For subjects in the parenteral protocol, achievement will be evaluated by use of the Wide Range Achievement Test (WRAT). In addition, in the parenteral protocol, information about accidents (including motor vehicle accidents) and school performance, will be sought.

Confidentiality of records of all subjects will be maintained. Subjects will not be identified by name in published reports or presentations of any kind without their express written consent.

16 .1c. Risks and Benefits

The identification of individuals with increased risk of Type 1 DM potentially could have psychological sequelae. It has been shown that identification of positive ICA may result in anxiety in some individuals, but that this dissipates over time (24). All subjects identified as having increased risk of Type 1 DM will be counseled by study personnel, who will provide information on the interpretation of data and its potential impact on the subject. Although the study does not directly provide formal psychological counseling, appropriate referral sources will be identified for those rare subjects who need further assistance in this sphere.

The risks of blood sampling by venipuncture and of catheter insertion for sampling and infusions include: commonly the occurrence of discomfort and/or bruise at the site of puncture; occasionally, fainting; and less commonly, infection, or the formation of a small blood clot or swelling of the vein and surrounding tissue, or bleeding at the needle puncture site.

Subjects in the experimental group of the parenteral insulin protocol will be administered insulin by infusion and will take subcutaneous insulin injections. Whenever insulin is given there is the possibility of hypoglycemia. Such can be readily treated by consuming sugar. Subjects will be asked to periodically obtain blood glucose profiles to verify that subtle hypoglycemia has not ensued.

No specific benefit can be promised subjects who participate in this study. However, since subjects are at high risk of developing diabetes, the close observation and frequent testing for diabetes - in both treatment groups - may permit earlier detection of Type 1 DM than would otherwise be the case. It is thought that early detection of Type 1 DM and initiation of appropriate treatment may decrease risk of both the immediate and long term consequences of diabetes.

These aspects of the study are fully explained to subjects during the eligibility staging.

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18. PROTOCOL HISTORY

PROTOCOL APPROVED IN PRINCIPLE BY STEERING COMMITTEE - 1/12/94
PROTOCOL UPDATED BY OPERATIONS COORDINATING CENTER - 1/28/94
PROTOCOL FURTHER UPDATED - 4/94 (As Outlined Below)

CHANGES INCLUDED IN 4/94 UPDATE OF DPT-1 PROTOCOL

In addition to typographical and grammatical corrections, and changes made to ensure consistency throughout the protocol, the following sections have been updated in the 4/94 printing of the protocol:

Sections 4, 5, 7 - Clarifies that "Second and Third Degree" or "Other" relatives refers to nieces, nephews, aunts, uncles, cousins, grandchildren - up to 20 years of age

Section 7.2d. Study Time Line - Approved by Steering Committee, 4/7/94

Section 8. Intervention Protocol (High Risk Cohort) - Includes language identifying the two treatment groups as *Experimental Group* and *Standard Group.*

Section 14.2a-1. Ancillary Studies Policies - Adapted from DCCT, as approved by Steering Committee 1/12/94

Section 14.2a-2. Publications Policies - Adapted from DCCT, as approved by Steering Committee 1/12/94

Section 14.3b-7. Affiliated Centers - Includes clarification of definition of "or equivalent facility", from Bulletin #7, 3/31/94

Appendix 1. DPT-1 Organizational Charts - Has been included. Other appendices renumbered.

PROTOCOL FURTHER UPDATED AND APPROVED BY STEERING COMMITTEE - 12/6/94 (As Outlined Below)

CHANGES INCLUDED IN 12/94 UPDATE OF DPT-1 PROTOCOL

Section 3.6.1. Oral Glucose Tolerance Test Criteria - moved from other sections.

Sections 4, 7.1b., 7.3b. Explains that ambiguities in determination of Type 1 DM in proband will be resolved by an Eligibility and Events Committee.

Sections 8.1, 8.5, 8.6. Capillary blood glucose profile measurements to be performed every 3 months rather than every 2 months, and 3:00AM sample included.

Section 8.4. Intravenous Insulin Infusion - Fluid and Volume for Dilution, Initial Dose and Adjustment Schedule for Insulin Infusion Modified.
Secttion 8.7. Adverse Events Monitoring - New Section Adopted.
Sections 10, 11. Intermediate Risk Cohort (Oral Antigen) Intervention Protocol and Outcome Evaluations - New Sections Adopted.
Section 12. Old Section 10 Renumbered.
Sections 13-18. Old Sections 12-17 Renumbered.
Section 17. References Updated.

PROTOCOL FURTHER UPDATED AND APPROVED BY STEERING COMMITTEE - 2/96 and 5/96, AND UPDATED BY OPERATIONS COORDINATING CENTER - 5/96

CHANGES INCLUDED IN 5/96 UPDATE OF DPT-1 PROTOCOL
Sections 1, 3, 8. Includes language identifying the control group in the Parenteral Protocol as *"Closely Monitored (Control) Group"* instead of *"Standard Group"*.
Section 1. Deletes projection of starting time of Oral Protocol.
Sections 3.6, 6.3, 9, 11. Clarifies Principal Study Outcome Criteria (Modified from Adult 1979 NDDG Criteria).
Section 4 - Masking. More completely defines masked data and specifies which local measurements are permitted. Notes split duplicate samples to be collected for quality control.
Sections 5, 7.2c-1.4. Clarifies overlap of 8 year olds (4-7 and 8-45 rather than 4-8 and 8-45).
Sections 6.1, 8.1, 8.5, 8.6. Clarifies timing of morning ultralente insulin simply as "before breakfast".
Sections 6.2, 10.1, 10.3. Permits oral capsules to be dissolved in juice if subject cannot swallow capsules.
Section 7.1b.9. No longer specifies in Protocol a minimum number of samples for reimbursement.
Sections 7.2b-4; 9, 11. Deletes maximum concentration for oral glucose solution.
Section 7.2d. Adapts Time Line also for Oral Protocol.
Section 8.3. Clarifies criteria for "acceptable" insulin infusion, and repeating same.
Sections 8.3, 8.6, 9. Clarifies that 72 hours (rather than 3 days) is duration of omission of subcutaneous insulin.
Section 8.5. Changes 55 mg/dL to 50 mg/dL as threshold for insulin dose changes.

Section 8.6. Clarifies test timing; deletes capillary collection tubes.
Section 8.7. Clarifies timing of administration of WRAT.
Sections 8.7 and 10.5. References "Notification of Death" Procedure.
Section 9. Notes WRAT to be administered at Study End.
Sections 9, 11. Defines sequence of tolerance tests. Modifies name of "Eligibility and Events Committee."
Section 10.4. Adds subject performance of blood glucose profiles every three months. Deletes routine blood counts and chemistries.
Section 15.3a-3. Updates current working committees,
Sections 15.3c-3, 15.3c-4. Adds Safety Monitoring Group and renumbers subsequent paragraph.

PROTOCOL FURTHER UPDATED AND APPROVED BY STEERING COMMITTEE - 1/97 and 6/97, AND UPDATED BY OPERATIONS COORDINATING CENTER - 8/97

CHANGES INCLUDED IN 8/97 UPDATE OF DPT-1 PROTOCOL

To conform with the 1997 Expert Committee Report of the American Diabetes Association, throughout the protocol changes have been designating the disease as "Type 1 Diabetes Mellitus" (abbreviated Type 1 DM) rather than "Insulin Dependent Diabetes Mellitus" (abbreviated IDDM), and revising the criteria for diabetes. The changed criteria slightly alters both the eligibility criteria and the outcome criteria. This impacts on the following sections:
Sections 3.6, 3.6.1, 6.3, 7.2c-1.6, 7.2c-2.6, 7.3c.B.2, 7.3e, 9, 11, 14.1.
Sections 5, 7.2c-1.5, 7.2c-2.5. Amends the definition of "positive" cutoff for IAA be changed from the "mean + 5 SD" (80 nU/ml) to the "mean + 3 SD" (39 nU/ml).
Sections 7.2b, 7.2d. Amends the Study Time Line to allow an extra 6 weeks for staging if a third ICA or IAA is required, in addition to allowing for such if a third IVGTT is required.
Section 7.2b-5. Notes that the ICA Lab has moved to New Orleans.
Section 8.3, 8.4. Amends the Insulin Infusion Protocol to include a bedtime snack for all subjects, regardless of age.
Section 8.5. Bullets added to make easier reading.
Sections 8.6, 9, 10.4, 11. Amends the time window for OGTT to within 6 weeks of each 6-month visit, rather than within 4 weeks.

Sections 9, 11. Amends time frame for repeat OGTT to "within 2 months." Amends time frame for MMTT after diagnosis of diabetes to "8-16 weeks after diagnosis made." Deletes End of Study IVGTT in subjects developing diabetes.
Some minor typographical and grammatical changes are made as well.

CHANGES INCLUDED IN 5/99 UPDATE OF DPT-1 PROTOCOL

Section 2. Brief paragraph added about theoretical possibility of increased risk.
Section 7.2. References to "Abbreviated" IVGTT omitted. Noted that only one IVGTT may be required for Oral Protocol. IVGTT criteria corrected.
Sections 9 & 11. Need for separate days and fasting state noted for tolerance tests.
Outline of Schedule for Oral Protocol corrected to include Form PQ.

PROTOCOL FURTHER UPDATED AND APPROVED BY STEERING COMMITTEE - 6/00

CHANGES INCLUDED IN 8/00 UPDATE OF DPT-1 PROTOCOL

At the Steering Committee meetings in January 2000 and June 2000, upon the recommendation of the Treatment and Planning Committees, it was decided that yearly evaluations of DPT-1 subjects should continue after the diagnosis of diabetes. This has led to the following changes:
New Section 2.1 – Long Term Follow-Up of Subjects Developing Diabetes – Rationale
New Section 12.2 – Long Term Follow-Up of Subjects Developing Diabetes – Implemenation
Section 3.1 – Alteration of Objective 4 to include follow-up beyond diagnosis. Addition of Objective 5 related to natural history of Type 1 diabetes disease process.

At the Steering Committee meetings in June 2000, plans were approved to permit contact of subjects not being followed, both to determine presence of diabetes and/or to seek participation in approved ancillary studies. This has led to the following changes:
New Section 12.3 – Contact of Subjects Not Being Followed
New Section 12.3.a – Determination of Diabetes in Subjects Not Being Followed
New Section 12.3.b - Participation in Ancillary Studies by Subjects Not Being Followed

In addition, the following protocol changes have been made:
Sections 6.1, 6.2 – Amends projected total number of subjects screened.
Section 6.3 – Amends projected follow-up time on protocol.

PROTOCOL FURTHER UPDATED AND APPROVED BY STEERING COMMITTEE - 10/00

CHANGES INCLUDED IN 10/00 UPDATE OF DPT-1 PROTOCOL

At a special Steering Committee meetings in October 2000, plans were approved to complete enrollment in the High Risk Parenteral Trial on October 31, 2000. Plans were also approved to initiate a potential end-of-study "Study Update" to be conducted between November 1, 2000 and March 31, 2001. Finally, a recommendation was made concerning subjects subsequently identified as "High Risk". This has led to the following changes:
New Section 7.4 – Completion of Enrollment in Parenteral Study, Updating of Study Information on These Subjects, & Actions for Individuals Subsequently Identified As "High Risk"
New Section 7.4.a – Completion of Enrollment
New Section 7.4.b – Updating of Study Information on Subjects in High Risk Parenteral Trial
New Section 7.4.c – Subjects Identified as "High Risk" after Close of Enrollment in the Parenteral Trial
In addition, the new name of Sustacal, "Boost" has been inserted throughout.