I. Protocol Synopsis

Title	***Natural History Study of the Development of Type 1 Diabetes***
Version Date	22 July 2009*
Conducted By	TrialNet
Study Design	Prospective cohort study
Objective	The overall objective of this study is to perform baseline and repeat assessments over time of the metabolic and immunologic status of individuals at risk for type 1 diabetes (T1D) to: (a) characterize their risk for developing T1D and identify subjects eligible for prevention trials, (b) describe the pathogenic evolution of T1D, and (c) increase the understanding of the pathogenic factors involved in the development of T1D.
Primary Outcome	The primary outcome is the development of diabetes as defined by the American Diabetes Association (ADA) based on glucose testing, or the presence of symptoms and unequivocal hyperglycemia.
Major Inclusion Criteria	(1) First degree relatives (age 1 – 45 years) of T1D probands. (2) Second and third degree relatives (age 1 – 20 years) of T1D probands: nieces, nephews, aunts, uncles, grandchildren, cousins, half-siblings.
Follow-up Schedule	The TrialNet Natural History Study is divided into three phases: Screening (Phase 1), Baseline Risk Assessment (Phase 2) and Follow-up Risk Assessments (Phase 3). Phase 1 involves overall screening and measurements of biochemical autoantibodies to determine eligibility for the Phase 2 risk assessment. The baseline risk assessment will include an OGTT, the measurement of HbA1c, testing for autoantibodies, and HLA typing (in consenting participants). Upon completion of Phase 2, participants will be classified into one of three risk categories for the occurrence of T1D within five years: < 25%, ≥25 %, and ≥ 50%. These categories are based on the OGTT results and number of confirmed positive autoantibodies. Individuals who participate in Phase 2 will also be offered the opportunity (through written consent) to enter Phase 3 for follow-up risk assessments. They will be seen at six-month intervals for the duration of the study. At each visit, procedures will include an OGTT, collection of blood for autoantibody testing and measurement of HbA1c levels.

*A revision to the Natural History Protocol is scheduled for implementation on 09 January 2012. For details regarding the revised protocol, please refer to the NHS Protocol Synopsis & Visit Schedule.

II. Specimen Collection Schedule

	Specimen Disposition[4]		Phase 1			Phase 2 Assessment	Phase 3 Assessments
	Tested	*Stored*	Initial Screening	Confirmatory Screening	Annual Rescreening		
Clinical Studies							
Serum: Autoantibodies[1]	X	X	8.5	2.6	2.6	2.6	2.6
Plasma: Oral Glucose Tolerance Test	X					18	18
Whole Blood: HbA1c	X					1.2	1.2
Mechanistic Studies[2]							
Serum: Mechanistic Serum		X				5	5
Whole Blood: PBMC/Plasma[3]		X				24	24
Whole Blood: DNA		X				6	6
Whole Blood: RNA		X				6	6

Collection volumes represent total volume of whole blood (mL) collected for adult subjects.

[1] Biochemical autoantibodies include GAD65, ICA512, and mIAA. ICA will be measured on the initial sample for those subjects who test positive for biochemical autoantibodies on the initial sample. ICA will also be measured on samples taken from subjects participating in Phase 2 and Phase 3. Residual serum ***is stored*** following autoantibody testing.

[2] Stored samples for mechanistic studies will be collected at the baseline risk assessment and at each Phase 3 visit from participants seen at Clinical Centers. For children, the total blood volume will not exceed 3mL/kg at any draw or 7 mL/kg over 6 weeks.

[3] PBMC and plasma are extracted locally by each collecting site.

[4] Specimen disposition: For samples indicated as both tested and stored, residual sample stored after testing.