

I. Protocol Synopsis

Title	<i>Natural History Study of the Development of Type 1 Diabetes</i>
Version Date	15 August 2011; Implementation Date 09 January 2012*
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	<p>Participants who are positive for at least two autoantibodies on the same Screening sample will enter Semi-annual Monitoring. Semi-Annual Monitoring will consist of an OGTT, HbA1c, and autoantibody tests. For each visit, a medical history, height, and weight will be obtained from participants. Information related to diet and activity level will be collected.</p> <p>Participants with a single autoantibody will undergo a baseline monitoring visit consisting of the same measures described in the previous paragraph. The results of these tests will determine whether they undergo Annual Monitoring or Semi-Annual Monitoring.</p> <p>Participants whose baseline monitoring tests show ≤ 1 autoantibody, normal glucose tolerance, an HbA1c $< 6.0\%$, and a DPT-1 Risk Score < 6.5 will enter Annual Monitoring. Annual Monitoring will consist of annual tests for autoantibodies and HbA1c levels. Information related to diet and activity level will be collected.</p> <p>Participants whose baseline monitoring tests show ≥ 2 positive autoantibodies, abnormal glucose tolerance (IFG, IGT, or indeterminate), an HbA1c level $\geq 6.0\%$, or a DPT-1 Risk Score ≥ 6.5 will enter the Semi-Annual Monitoring as above.</p> <p>Subsequently, participants in the Annual Monitoring Group who develop ≥ 2 positive autoantibodies, an HbA1c level $\geq 6.0\%$, or an increase in the HbA1c level $\geq 0.5\%$ compared with the previous HbA1c level will enter the Semi-annual Monitoring stage as above.</p>

*The information above reflects the revised Natural History protocol, which is scheduled to be implemented on 09 January 2012. For the existing protocol, please refer to the [TN-01 NHS Protocol Synopsis & Specimen Collection Schedule](#).

II. Study Visit Schedule Study

	Screening ⁴	Baseline Monitoring Visit ⁵	Annual Monitoring	Semi-Annual Monitoring	Annual Monitoring: Ab Neg. Controls ⁶
Clinical Studies					
Serum: Autoantibodies ¹	8.5	2.6	2.6	2.6	2.6
Plasma: Oral Glucose Tolerance Test		18	18		18
Whole Blood: HbA1c		1.2	1.2	1.2	1.2
Mechanistic Studies²					
Mechanistic Serum		5	5	5	5
Whole Blood: PBMC/Plasma ³		60	60	60	60
Whole Blood: DNA		6			
Whole Blood: RNA		6	6	6	6
Clinical Measures					
Medical history including diet and exercise information		X	X	X	X
Current medications		X	X	X	X
Height, weight		X	X	X	X
Adverse event assessment		X	X	X	X

Collection volumes are indicated for laboratory assessments as total volume of whole blood (mL) collected for adult subjects.

¹ All autoantibody assessments include GAD65, IA-2, and mIAA. At Screening, participants positive for at least one autoantibody will undergo ICA and ZnT8 testing. All Monitoring visits include ICA and ZnT8.

² Samples for mechanistic studies may be obtained in participants at any of the scheduled study visits or at interim visits. At no time will the total blood volume exceed safe limits for age and weight. For adults, blood samples will be limited to 10.5 mL/kg or 550 mL, whichever is smaller, over 8 weeks. For children, blood samples will be limited to 5 mL/kg at any single draw or 9.5 mL/kg over 8 weeks.

³ PBMC and plasma are extracted centrally by Rutgers University Cell & DNA Repository.

⁴ Participants with at least 2 positive autoantibodies at Screen will enter Semi-Annual Monitoring.

⁵ Participants with a single autoantibody at Screen will undergo a baseline monitoring visit. Participants whose baseline monitoring tests show ≤ 1 autoantibody, normal glucose tolerance, HbA1c $< 6.0\%$, and DPT-1 Risk Score < 6.5 will enter Annual Monitoring. Participants whose baseline monitoring tests show ≥ 2 positive autoantibodies, abnormal glucose tolerance, HbA1c level $\geq 6.0\%$, or DPT-1 Risk Score ≥ 6.5 will enter Semi-Annual Monitoring.

⁶ Protocol includes a cohort of autoantibody negative participants that is similar in relevant baseline characteristics to autoantibody positive participants entering the Monitoring stage.