5. QUALITY CONTROL AND INTERNAL MONITORING

5.1 GENERAL PRINCIPLES

Mechanisms will be instituted for continuous performance monitoring of all GoKinD units by the Executive Committee. External quality control surveillance will be instituted to assess the precision of all measurements made by the Central Biochemistry Laboratory (CBL). A quarterly report to the SHC will document the precision. Quantity and quality of DNA will be monitored. Recruitment goals will be established by the Executive Committee and a monthly report of the data generated by the call-center located at the Matthews Media Group will be created. A report tabulating the number of cases and controls entered into the study will be generated monthly. The CDC will prepare quarterly reports on the quality control of the genotype data. This report will report on any markers that are genotyped.

5.1.1 Methods in GOKIND

The measurements and methods that are conducted in GoKinD are listed in Table 5.1. An overview of the GoKinD QC monitoring is presented in Table 5.2.

5.2 PERFORMANCE MONITORING

5.2.1 Clinical Centers

Clinical Centers will be monitored for adherence to the GoKinD Protocol and Manual of Operations. The timeliness, completeness, and quality of the data forms that are sent to the COC will be monitored. Review of all performance data will be conducted with sufficient frequency to allow timely detection of deviations from expected performance.

5.2.2 Central Units

Central Biochemistry Laboratory

External quality control surveillance programs have been established to monitor the performance of the CBL. This will entail the masked submission of 10% duplicate specimens from the clinics for analysis by the laboratory. The resulting data will allow an assessment of the ongoing precision of the laboratory test results. Bench quality control assessment, though useful, is insufficient because laboratory performance alone is but one step in a chain of activities that could influence the test results. A program of external duplicate surveillance will allow assessment of the total system starting with the collection of a specimen in the clinic and ending with the entry of the data into the Coordinating Center computer. The duplicate quality control data are analyzed periodically by the Coordinating Center and presented to the SHC for review. Any deficiencies detected will be investigated and corrected.

These assessments of precision are based on a 10% sample of split duplication. They are the final step in the quality control of the CBL data that include collection in the clinics, transport of specimen to the CBL, and reporting of the results of CBL analyses to the Coordinating Center.

Two statistics will be calculated for each measurement using the split duplicates: the mean within-specimen coefficient of variation which is the average of the CVs for the n

specimen pairs and the coefficient of reliability which is an estimate of the proportion of the total variability between values that is due to differences between actual subject value and not due to measurement error.

The Centers for Disease Control and Prevention

External quality control surveillance for the handling of genetic specimens will require the massed submission of 10% (a separate 10% sample from that used for the monitoring of the biochemical measurements) duplicate genetic specimen.

The type 1 diabetes genotyping methods described in Chapter 9 have been established in the Division of Environmental Health and Laboratory Sciences. Each assay including HLA DQA1, HLA DQB1, HLA DRB1, insulin and microsatellites (AmpF/STR Green I human identification assay), will be tested routinely for reliability by employing positive and negative quality controls. The positive controls for all assays will include one or more of the following quality controls as appropriate: (1) positive control to test that reagents and instruments are functioning properly; (2) previously genotyped DNA to test for accurate genotyping; and (3) internal PCR amplification and genotyping quality controls (minimum/maximum number of amplification products per sample and minimum/maximum number of genotypes per sample). The negative control for all assays includes a PCR amplification and subsequent analysis without DNA to test for contamination. Additionally, the following quality controls will be used to test for sample mix-ups and family relationships within the trios: (1) sex confirmation; (2) microsatellite data inheritance pattern; and (3) HLA haplotype inheritance. (See Table 5.3 for an example of the quarterly quality control summary of genotypic data.)

TABLE 5.1

MEASUREMENTS AND METHODS IN GOKIND

Measurement	Method or Assay
Glycosylated Hemoglobin	High-performance ion-exchange liquid chromatography
Serum Creatinine	Automated kinetic method with Jaffe reaction
Serum Cystatin	Particle-enhanced turbidimetric (PET) assay
Urine Creatinine	Automated kinetic method with Jaffe reaction
Urine Albumin	Solid-phase fluoroimmunoassay
Serum Cholesterol	Cholesterol oxidase, spectrophotometric
Serum HDL-Cholesterol	Magnesium dextran precipitation
Blood Pressure Systolic Diastolic	Sitting, right arm reading with sphygmomanometer
Current Medication	EDIC Form 004 - Administered by Study Coordinator
DNA Extraction	Gentra's Puragene DNA extraction kit – salting out method
3 Microsatellites and sex marker	PCR co-amplification of markers followed by ABI Genescan fragment size analysis
HLA DRB1	PCR amplification followed by sequence specific oligonucleotide sequence based typing
HLA DQB1	PCR amplification followed by sequence specific oligonucleotide sequence based typing
HLA DQA1	PCR amplification followed by sequence based typing
Insulin	Allelic discrimination using fluorescent probes in a PCR based assay

TABLE 5.2

GOKIND

OVERVIEW OF QC MONITORING

PROCEDURE	MEASUREMENT	SPECIMEN REQUIREMENT	CENTRALLY ANALYZED	QUALITY	ANALYTIC PRECISION
Blood Draw	Glycosylated hemoglobin	Whole Blood	YES	NA	Split Duplicate
	Serum Creatinine	Frozen Serum	YES	NA	Split Duplicate
	Serum Cystatin	Frozen Serum	YES	NA	Split Duplicate
	Cholesterol HDL-Cholesterol	Frozen Serum	YES	NA	Split Duplicate
DNA	Genetic analysis of genes involved in type 1 diabetes susceptibility	Whole Blood	YES	YES	Split Duplicate
Renal Studies	ACR	Frozen Urine	YES	NA	Split Duplicate
Blood Pressure	Resting Systolic, Diastolic,	Sitting right arm	NO	YES	NA
Height	Height to nearest 0.1 cm[1]	1.0 cm[1]	NO	YES	NA
Weight	Weight to nearest 0.1 kg[1]	0.2 kg[1]	NO	YES	NA
Waist	Girth to nearest 0.5 cm[1]	0.5[1]	NO	YES	NA

[1]Two measurements taken and considered valid if maximum difference between them is not more than X.

TABLE 5.3

QUARTERLY QUALITY CONTROL SUMMARY OF GENOTYPIC DATA FOR THE GOKIND STUDY

Quarter:
Year:

gene/region	% positive control failures	% resolution	% negative control failures	% resolution
DRB1				
DQB1				
DQA1				
Insulin				
Microsatellites				
(THO1,TPOX,CSF1PO)				
Sex Marker				
(amelogenin)				