Treatment Options for type 2 Diabetes in Adolescents and Youth

TODAY2 PHASE 1 (2011-2014)
IMMEDIATE POST-INTERVENTION PROTOCOL

Sponsored by
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George Washington University Biostatistics Center
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Table of Contents

Abbreviations Used

ADA	American Diabetes Association
AE	Adverse Event
BG	Blood Glucose
CVD	Cardiovascular Disease
DKA	Diabetic Ketoacidosis
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GI	Gastrointestinal
HbA1c	Glycated Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HOMA	Homeostasis Model Assessment
IRB	Institutional Review Board
LV	Left Ventricular
MNSI	Michigan Neuropathy Screening Instrument
MOP	Manual of Procedures
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
OGTT	Oral Glucose Tolerance Test
PCOS	Polycystic Ovarian Syndrome
PPARγ	Peroxisome Proliferator-Activated Receptor
PWV	Pulse Wave Velocity
QUICKI	Quantitative Insulin Sensitivity Check Index
SAE	Serious Adverse Event
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
TLP	TODAY Lifestyle Program
TODAY	Treatment Options for type 2 Diabetes in Adolescents and Youth
TODAY2	TODAY post-intervention long-term follow-up
TZD	Thiazolidinediones
UKPDS	United Kingdom Prospective Diabetes Study
ULN	Upper Limit of Normal

1 Introduction and Rationale

TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) was a multi-center study of the optimal approach to treatment of type 2 diabetes (T2D) in children and adolescents. Sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), TODAY began recruiting subjects in May 2002 and completed enrollment in February 2009 with a sample size of 699. The TODAY study group is composed of investigators associated with the fifteen clinical centers (Baylor College of Medicine, Case Western Reserve University, Children's Hospital Los Angeles, Children's Hospital of Philadelphia, Children's Hospital of Pittsburgh, Columbia University, Joslin Diabetes Center, Massachusetts General Hospital, Saint Louis University, State University of New York Upstate Medical University, University of Colorado Denver, University of Oklahoma Health Sciences Center, University of Texas Health Sciences Center at San Antonio, Washington University in St Louis, and Yale University), the NIDDK project office, and the coordinating center (George Washington University Biostatistics Center).

The TODAY clinical trial of experimental interventions ended in February 2011 [TODAY Study Group 2007]. It was followed by TODAY2, a longitudinal study to continue the care and observation of the TODAY cohort beyond the end of the TODAY intervention trial. TODAY2 consists of two phases.

(1) First is the immediate transition of TODAY participants to non-blinded, non-randomized standard diabetes care and management with monitoring and follow-up for up to 36 months. During this period, the findings of TODAY are analyzed and interpreted by the study group.

(2) The second phase is a protocol for long-term longitudinal follow-up of the TODAY cohort, based on findings from TODAY.

This document is the protocol for the first phase of TODAY2. The protocol was written by the TODAY Study Group, approved by an External Review Committee, and approved by the Institutional Review Boards (IRB) of each participating clinical center prior to the initiation of recruitment.

1.1 Specific Aims and Objectives

The primary objective of the first phase of TODAY2 is to continue to follow the TODAY subjects in order to begin to:

- understand the persistence of the effects of the different treatment regimens used in TODAY,
- describe the continued evolution of beta cell function, and
- describe the development of vascular complications and risk factors for complications.

1.2 Overall Design

Willing and consenting participants completing participation in TODAY continue to be followed by TODAY clinical centers for routine clinical care according to the visit schedule established for TODAY, i.e., quarterly medical visits and an annual outcome visit. All participants, regardless of their initial treatment arm in TODAY, are administered current standard of care with guidelines, recommendations, and primary medications provided by the study but with additional participant-specific treatment modalities used at the discretion of the local study clinician.

Standard practice is to treat with unblinded metformin as the only oral medication. Participants being treated with insulin at the end of TODAY continue to be treated with insulin, and participants losing metabolic control during this phase of TODAY2 are started on insulin using guidelines provided below, but with more flexibility for clinician discretion based on participant-specific circumstances. In addition, the degree of glycemic control, as reflected in routine hemoglobin A1c obtained at each visit, is reported to the clinical center and the participant. Comorbidities, such as hypertension and dyslipidemia, continue to be treated by algorithm established in TODAY.

The first phase of TODAY2 is expected to last 36 months, during which time the outcomes of TODAY are analyzed, interpreted, and used to develop a protocol for a long-term observational study of this cohort.

1.3 Background and Significance

T2D has dramatically increased throughout the world in many ethnic groups and among people with diverse social and economic backgrounds. Over the last decade, the increase in the number of children and youth with T2D has been labeled an “epidemic” [ADA 2000]. Before the 1990s, it was rare for most pediatric centers to have patients with T2D. By 1994, T2D patients represented up to 16% of new cases of diabetes in children in urban areas [Pinhas-Hamiel et al. 1996], and by 1999, depending on geographic location, the range of percent of new cases due to T2D was between 8-45% and disproportionately represented in minority populations [Dabelea et al. 1999; Rosenbloom et al. 1999]. Despite the dramatic increase in the number of cases T2D in pediatric populations, there have been no published large-scale studies investigating the pathophysiology, treatment, and complications of these disorders in children and youth.

Recent population-based data from the SEARCH study indicate that about 3,700 children and adolescents are diagnosed with type 2 diabetes annually [SEARCH 2007]. Like adults, youth with T2D have a high prevalence of comorbidities, such as hypertension, hyperlipidemia, non-alcoholic fatty liver disease, and metabolic syndrome, that are associated with increased cardiovascular morbidity and mortality. A recent review revealed that comorbidities are substantially more prevalent at diagnosis in adolescents with T2D than in those with T1D, and the progression of end-organ damage is much more rapid, including the development of micro- and macroalbuminuria and proliferative retinopathy. There have been a limited number of additional studies since the publication of that review. The long-term complications and costs associated with T2D make such studies imperative. In 2007, diabetes was estimated to cost the U.S. healthcare system approximately $174 billion annually [ADA 2008]. Much of the cost is related to the micro- and macrovascular complications of diabetes. Since long-term microvascular and cardiovascular complications relate to duration of diabetes and to control of glycemia, it could be hypothesized that the increasing number of children and youth diagnosed with T2D, if not effectively treated, could dramatically add to the economic burden of this disease over the ensuing decades. TODAY2 has identified as an important goal the study of microvascular and macrovascular complications emerging in this cohort of youth-onset T2D as they enter young adulthood.

1.3.1 The TODAY Study

Patients with T2D have dual abnormalities of insulin resistance and insulin deficiency. It is hypothesized that to achieve the level of glycemic control required to optimize long-term outcome and decrease or prevent microvascular complications, treatment regimens should theoretically be designed to improve insulin resistance and preserve residual β-cell function.

Only insulin and metformin have been approved for use in adolescents, and the other available anti-diabetic agents have not been adequately evaluated in pediatric patients. The primary hypothesis underlying the TODAY study was that aggressive treatment from the outset of diabetes would promote better glycemic control and preservation of beta cell function, compared with the traditional, step-wise approach to therapy that has been used in adults. Therefore, the TODAY Study Group designed a trial to compare standard therapy to two more aggressive approaches, one pharmacologic and one non-pharmacologic. The three treatment regimens in TODAY were: (1) metformin alone, (2) metformin plus rosiglitazone, and (3) metformin plus an intensive lifestyle intervention called the TODAY Lifestyle Program (TLP). The study recruited 699 patients, ages 10-17, who were randomized within two years of the diagnosis of T2D.

The primary objective of the TODAY trial was to compare the efficacy of the three treatment arms on time to treatment failure based on glycemic control. Treatment failure was defined in one of two ways

1. **HbA1c ≥ 8% over a 6-month period.** All regularly scheduled HbA1c values must be ≥ 8% over a 6-month period. If any one value is < 8%, after which HbA1c re-elevates to ≥ 8%, the clock restarts at the time of the re-elevation. At least two consecutive measurements must be ≥ 8% over 6 months.
2. **Inability to wean from temporary insulin therapy initiated due to metabolic decompensation.** Participants who experience metabolic decompensation requiring temporary use of insulin, who cannot safely be weaned from insulin within three months, are classified as treatment failures.

The primary outcome of treatment failure was defined in terms of HbA1c because it correlates with glycemic control and long-term diabetes outcome. Because HbA1c was the primary outcome, investigators and patients were blinded to HbA1c values.

The primary objective of the TODAY trial was to compare the efficacy of the three treatment arms on time to treatment failure based on glycemic control. The secondary aims were to:

- compare and evaluate the safety of the three treatment arms;
- compare the effects of the three treatments on the pathophysiology of T2D with regard to beta cell function and insulin resistance, body composition, nutrition, physical activity and aerobic fitness, cardiovascular risk factors, microvascular complications, quality of life, and psychological outcomes;
- evaluate the influence of individual and family behaviors on treatment response; and
- compare the relative cost effectiveness of the three treatment arms.

1.3.2 Pharmacological Treatment of Pediatric Type 2 Diabetes

Until the development of TODAY, the pharmacologic treatment of T2D in pediatric patients had not been systematically studied. Many affected youth with T2D are initially placed on monotherapy with either insulin or metformin [Jones et al. 2002; Silverstein and Rosenbloom 2000] as these agents are the only agents approved for use in children. Long-term studies indicate that adults on monotherapy do not continue to achieve glycemic targets [UKPDS 1998; Lebovitz 1999]. In addition, studies in adults suggest that although the addition of a second agent can improve glycemic control temporarily, most patients on multiple drug regimens fail to sustain long-term good glycemic control. The pharmacologic therapies for TODAY, which included using metformin alone and metformin in combination with rosiglitazone, were chosen because metformin was approved in pediatrics and because rosiglitazone would theoretically provide additional improvement in insulin sensitivity.

1.3.2.1 Metformin

Metformin improves glycemic control by improving hepatic insulin sensitivity and lowering hepatic glucose production [DeFronzo et al. 1991; Stumvoll et al. 1995; Johnson et al. 1993; Wollen and Bailey 1998; Cusi et al. 1996]. Metformin has been used in the clinical arena for more than four decades, and it has been demonstrated to be safe and effective. It is the only oral agent approved by the FDA for use in children and is considered first-line therapy by most pediatric endocrinologists [ADA 2000]. Since most patients with T2D are obese, an added benefit with metformin therapy is the lack of weight gain [Stumvoll et al. 1995; Bailey and Turner 1996; Campbell and Howlett 1995; Garber et al. 1997; Fontbonne et al. 1996]. Other established benefits include improvement in dyslipidemia, lowering of fibrinolytic abnormalities, and amelioration of PCOS [Jeppesen et al. 1994; Bailey and Turner 1996; Perriello et al. 1994].

The adverse effects of metformin include development of lactic acidosis, which is rare but potentially life-threatening [Bailey and Turner 1996; UKPDS 1998] and generally occurs in the presence of severe renal disease or cardiac failure, which are unlikely to be present in pediatric patients. More commonly, metformin may cause gastrointestinal disturbance [DeFronzo and Goodman 1995]. However, this was rarely a problem in TODAY, in which nearly 98% of participants tolerated 1000 mg of metformin twice a day, with only one episode of lactic acidosis while following 699 participants up to 6 years – and this episode was not clinically severe and was assessed by the investigator to be associated with an asthma exacerbation, not with metformin treatment.

1.3.2.2 Thiazolidinediones (TZD)

The thiazolidinediones (TZD) represent a class of oral antidiabetic agents that have been shown to improve metabolic control in adults with T2D [DeFronzo 1999]. The glucose lowering effect of this class of drugs is mediated through an improvement of insulin sensitivity [Kemnitz et al. 1994; Saltiel and Olefsky 1996; Miyazaki et al. 2001; Aronoff et al. 2000; Phillips et al. 2001]. TZDs reduce insulin resistance in adipose tissue, muscle, and liver.

TZDs are high affinity ligands of the gamma isoform of the peroxisome proliferator-activated receptor (PPARγ), a member of the nuclear receptor super family of transcription factors. PPARγ is predominantly expressed in an adipose-selective manner in both rodents and humans, although it is also expressed in other organs, including skeletal muscle and liver and pancreatic β-cells. The clinical potency of available TZDs has been shown to correlate closely with their ability to bind to the PPARγ receptor [Olefsky and Saltiel 2000].

Besides insulin-sensitizing ability, one theoretical advantage of using TZD as a therapeutic agent in T2D is the potential that these agents might preserve pancreatic insulin secretion. The mechanism by which TZDs might preserve insulin secretion is not fully understood. Hypothetically, the preservation of pancreatic function might occur through amelioration of lipotoxicity and lowering of FFA levels [Girard 2000; Greene 1999; McGarry and Dobbins 1999; Unger and Orci 2000]. Preservation of beta cell function is a key aspect of diabetes control since one of the two major pathogenic factors leading to hyperglycemia in diabetes is a reduction in insulin secretion when pancreatic beta cells can no longer compensate for insulin resistance by producing the necessary elevation of insulin levels. Accordingly, the effect of adding a TZD to metformin on beta-cell function was an important secondary outcome of TODAY. In TODAY2, we have the opportunity to evaluate the durability of this effect, if present, of initial treatment with rosiglitazone on beta-cell function after the drug is discontinued.

There were a number of known side effects of this class of drugs at the time of the design of TODAY, including fluid retention/edema, congestive heart failure, anemia, and weight gain. Edema and congestive failure usually occur with a background of cardiac or renal disease—comorbidities less likely found in pediatric patients within two years of diabetes diagnosis and not seen during TODAY. Since the design of TODAY, a number of additional studies have been completed, raising additional concerns about fluid and cardiac effects of rosiglitazone. In particular, a meta-analysis in 2007 [Nissen and Wolski 2007] raised concerns that rosiglitazone may be associated with increased risk for myocardial infarction, as well as congestive heart failure. The TODAY Steering Committee reviewed these findings and determined that the meta-analysis had a number of weaknesses. The TODAY DSMB and all 15 clinical center IRBs concurred with this conclusion and no alteration in the protocol was made. Whether rosiglitazone is associated with increase myocardial infarction remains unclear. An additional meta-analysis failed to find an association between rosiglitazone and cardiovascular death. In addition, the RECORD study, which was specifically designed to measure cardiovascular outcomes, did not find an increased risk of cardiovascular morbidity and mortality with rosiglitazone compared with metformin or sulfonylurea, although the event rate was too low to reach a conclusion about incidence of myocardial infarction. Finally, several large studies (ACCORD, ADOPT, BARI 2D, VADT) designed to examine the effects of intensive glucose control on cardiovascular outcomes did not detect increased cardiovascular events in subjects on rosiglitazone, although the studies were not designed to examine the effects of any specific medications [ACCORD Study Group 2008; Kahn et al. 2006; BARI 2D Study Group 2009; Duckworth et al. 2009]. Therefore, the true impact of TZD therapy on cardiac function remains unclear in adults and unstudied in adolescents. All participants in TODAY had an echocardiogram during the final year of that study. Continued monitoring of cardiac function is an important aim of the second phase of TODAY2.

During TODAY, there were a number of reports of decreased bone mineral density and increased fractures among adult women and men taking TZDs [Schwartz et al. 2006; Meier et al. 2008; Kahn et al. 2008]. In response to these reports, TODAY instituted monitoring of spine bone mineral density in all participants. There were no increases in fractures above expected rates for age. Bone mineral density was obtained at the end of the TODAY study and is an important aim of the second phase of TODAY2.

Finally, during TODAY, there were reports of macular edema among adults taking TZDs. In response to these reports, TODAY obtained retinopathy screening during the final year of the study. Participants with changes suggestive of macular edema were referred for further evaluation as part of TODAY. Continued monitoring of retinal changes is an important aim of the second phase of TODAY2.

No concerns have been raised by the DSMB monitoring TODAY to date.

1.3.3 Intensive Lifestyle Intervention

In the treatment of T2D in adults, it is beneficial to decrease insulin resistance by reducing body weight via a lifestyle program focused on the development of healthier dietary and physical activity habits. A number of adult studies have shown that weight loss associated with improvements in eating behavior, diet, and physical activity has resulted in significant reductions in fasting plasma glucose and insulin levels, hepatic glucose output, and peripheral insulin resistance, hypertension, and dyslipidemia [Blackburn 1995; Goldstein 1992; Wing et al. 1987; Maggio and Pi-Sunyer 1997; Henry 1986]. Three uncontrolled trials in adults with T2D treated with oral agents have shown the benefit of weight loss associated with lifestyle modification on reducing mortality [Wing et al. 1987; Lean et al. 1990; Chaturvedi and Fuller 1995]. The LookAHEAD trial is an ongoing NIH

funded multi-site controlled trial of adult patients with T2D and obesity. This trial is examining the impact of lifestyle modification (changes in eating and activity) and weight loss compared with standard care on morbidity and mortality. As the epidemic of T2D in children and youth is relatively recent, there is little controlled evidence regarding the use of lifestyle modification to improve insulin sensitivity and glycemic control, induce weight loss, or affect other outcome measures, such as dyslipidemia and hypertension, in pediatric patients with T2D. In particular, there are no studies of the long-term durability of these effects.

2 Outcomes and Objectives

2.1 Primary

The primary objective of the first phase of TODAY2 is to begin to examine the persistence of effects of the TODAY treatment assignment on long-term glycemic control following discontinuation of randomized treatment. During this period, results of TODAY were produced and used to define additional outcomes for the second phase of TODAY2.

2.2 Secondary

In the first phase of TODAY2, we continue to follow a number of secondary outcomes established for TODAY. The results of these secondary outcomes help interpret the primary effect of the TODAY treatment regimens on HbA1c. These secondary aims have been chosen because they provide insight into the mechanism by which the treatment regimens affect durable glycemic control (e.g., effects on insulin resistance, insulin sensitivity, β-cell function) or because they provide information concerning the differential risks and benefits of the three treatment arms (e.g., studies of microvascular complications and cardiovascular risk). The following sections describe the various outcome measures selected for the first phase of TODAY2.

2.2.1 Glycemic Control

Mean HbA1c levels for participants from the three original TODAY treatment arms are compared as measures of the degree and durability of glycemic control after discontinuation of initial randomized therapy. The overall target is to maintain HbA1c levels as close to the normal range as possible in order to reduce long-term diabetes complications. TODAY2 continues to use HbA1c < 6% as the target. Blood glucose testing according to standard T2D clinical management guidelines is used for monitoring and for guidance of insulin adjustment. Since HbA1c is the designated measure of glycemic control during TODAY2, home blood glucose measurements are not collected as data in TODAY2.

2.2.2 Safety

In TODAY2, subjects are treated with approved medications, i.e., metformin and/or insulin. No specific abnormalities are expected to develop in this cohort, given the well-documented safety record of these agents. However, abnormalities in laboratory tests (hemoglobin/hematocrit, liver function tests, calculated creatinine clearance), episodes of severe hypoglycemia, and incidence of side effects (e.g., gastrointestinal complaints) are tracked as outlined in detail in the section on safety and monitoring.

2.2.3 Insulin Sensitivity and Secretion

The efficacy and durability of successful treatment of T2D is determined to a great extent by the ability of a specific intervention to ameliorate insulin resistance and prolong or restore effective beta cell function. There is significant information available on the natural history of insulin resistance and secretion, and on the effect of various treatment regimens on secretion and sensitivity in adult patients with T2D. Little is currently known about these natural history and treatment issues in affected children and youth. In particular, significant questions remain about the impact of advancing pubertal status on insulin resistance and beta cell function in pediatric patients with T2D. Therefore, an important component of TODAY2 is to continue to monitor insulin sensitivity and secretion in the TODAY cohort after discontinuation of randomized therapy to determine (1) the evolution of changes in insulin secretion and sensitivity as participants emerge from puberty and enter young adulthood and (2) the effect of each of the initial therapies on the progression of changes in insulin sensitivity and secretion.

Insulin sensitivity and secretion are determined with fasting glucose, insulin, C-peptide, and proinsulin levels, OGTT-based indices, HOMA, and QUICKI measured annually.

2.2.4 Cardiovascular Risk Factors

Among children, little is known about the relationship between T2D and cardiovascular risk. Among patients with T2D in the SEARCH for Diabetes in Youth Study, 33% had total cholesterol (TC) concentration > 200 mg/dL, 24% had LDL-C concentration > 130 mg/dL, 29% had TG concentration > 150 mg/dL, and 44% had HDL-C concentration < 40 mg/dL. Most important, in this cohort, only 1% of youth were receiving pharmacologic therapy for dyslipidemia [Kershnar et al. 2006]. In another study from the same group, among youth with type 2 diabetes, 36% had elevated apoB, 36% had dense LDL, but only 23% had elevated LDL-cholesterol. Among adolescents with poorly controlled T2D, 72% had elevated apoB and 62% had dense LDL [Albers et al. 2008].

Among youth with T2D, 92% had 2 or more cardiovascular risk factors, including abnormal lipids, elevated waist circumference, and hypertension [Rodriguez et al. 2006]. Furthermore, when compared to matched control youth, those with T2D had a higher prevalence of elevated blood pressure, obesity, large waist circumference, low HDL cholesterol, high triglycerides, and high urinary albumin-to-creatinine ratio, as well as elevated inflammatory markers, such as fibrinogen, interleukin (IL)-6 and C-reactive protein, and lower adiponectin levels [West et al. 2009].

Information on overt cardiovascular complications in adolescents with T2D is limited but has included reports of increased nighttime systolic and diastolic pressure and diminished nocturnal decline in blood pressure, increased posterior and septal wall thickness, left ventricular (LV) hypertrophy, and increased aortic pulse wave velocity [Pinhas-Hamiel and Zeitler 2007]. More recent reports have confirmed and extended these findings. Girls with T2D had larger LV dimensions and LV mass along with impairment of diastolic filling and systolic longitudinal function compared to lean and overweight non-diabetic subjects. Half the group met published criteria for LVH and LV dilatation and 25% had evidence of elevated LV filling pressure in association with structural abnormalities [Whalley et al. 2009].

In addition, little is known about the non-traditional risk factors. In small series, obese children and adolescents have been found to have increased levels of fibrinogen, PAI-1, and D-dimer, as well as abnormalities in factor VIIc, von Willebrand factor, PAI-1, fibrinogen, and tissue plasminogen activator [Ferguson et al. 1998; Gallistl et al. 2000; Sudi et al. 2001]. Following weight loss interventions, decreased levels of PAI-1 and IL-6 have been

demonstrated [Estelles et al. 2001; Gallistl et al. 2001] suggesting that lifestyle interventions may be able to alter cardiovascular risk in young patients.

These studies suggest that among obese adolescent patients with T2D, there may be unfavorable patterns of both traditional and non-traditional risk factors implicated in cardiovascular morbidity and mortality. The development of cardiovascular risk is an important consideration in comparing the efficacy and long-term implications for the treatment interventions studied in TODAY. In addition, almost no longitudinal data exist regarding the evolution of CVD risk factors in youth with T2D. It has been speculated that individuals who develop T2D at an early age may develop CVD at an early age, but this has not been examined systematically. To address this, both traditional and non-traditional CVD risk factors are measured in the first phase of TODAY2 and assessed overall as well as compared across initial treatment arms. Blood pressure is measured at every visit and specimens drawn annually for repeated measurements of lipids (free fatty acids, lipoprotein subclass levels, average LDL particle density, and total apoB level), fibrinogen, c-reactive protein, plasminogen activator inhibitor-1, homocysteine (vitamin B-12 to evaluate homocysteine levels), and interleukin-6. Pulse wave velocity (PWV) is performed in the final year of TODAY2 phase 1 to measure vascular stiffness. Repeat PWV is planned for TODAY2 phase 2.

2.2.5 Microvascular Complications

Microvascular complications associated with diabetes produce significant burdens for the individual patient and are responsible for a major part of the public health care costs associated with diabetes. Microvascular complications are more common among children with T2D at the time of presentation than among those with T1D [Takahashi et al. 1990; Yokoyama et al. 2000]. There is limited evidence suggesting that progression rates of microvascular complications are also greater in youth with T2D. However, existing reports generally involve relatively few patients in a clinic setting. The TODAY cohort represents a unique population in which to study the development of microvascular complications and associated risk factors. In addition, a comparison of the effect of the treatment interventions on the prevention and slowing of rates of development of microvascular complications associated with T2D is an important secondary outcome of TODAY2 and could significantly modify the interpretation of the primary outcome results of the TODAY trial.

Quantitation of microalbuminuria is performed by obtaining spot urine measurements of microalbumin/creatinine ratio at annual visits. Abnormal values on spot urines are confirmed with two additional spot urine samples within three months; diagnosis of microalbuminuria is made as a result of two out of three positive tests. Creatinine clearance (by calculation) is determined at annual visits. Abnormal values are monitored more frequently.

The presence of peripheral neuropathy is evaluated using the Michigan Neuropathy Screening Instrument (MNSI) [Feldman et al. 1994], a simple and well-validated screening tool for detection of peripheral neuropathy in patients with T2D. MNSI screening is performed annually.

A dilated fundoscopic examination and digital fundus photos were performed at the end of TODAY and serve as a baseline for expected future monitoring of eye changes in all participants in TODAY2. These studies are repeated in the second phase of TODAY2. Patients receive retinopathy screening following ADA clinical practice guidelines, which indicate that a dilated retinal examination by an ophthalmologist or optometrist be done at diagnosis and at yearly intervals.

3 Recruitment and Enrollment

All subjects randomized into the TODAY study are eligible to participate in TODAY2. As TODAY conducted end-of-study and close-out procedures, participants were given detailed information about TODAY2, including the purpose of the study, test procedures and measurements, and risks and benefits. There are no additional inclusion or exclusions criteria for participation in TODAY2.

Informed consent and assent are obtained. The informed consent/assent process includes provision of information in verbal and written form and the opportunity for discussion and questions. The TODAY2 informed consent process (1) maximizes potential participant and family understanding of the study and (2) allows an informed decision regarding continued participation, including personal risks and benefits. This process is designed to meet the ethical obligations to the participant and improve retention by fostering a progressively increasing understanding of TODAY2 by the participant and family, as well as the development of a positive relationship with the clinic staff. It is an interactive, conversational process, with the ultimate goal of maximum understanding of TODAY2 and its impact on the family, including the responsibility of the participant to TODAY2 and the responsibility of the study investigators and staff to the participant. It is anticipated that one result of this process is maximized retention of participants in TODAY2.

Participants may consent to participate in TODAY2 in one of two ways.

1. Ongoing diabetes care and annual outcomes assessments: Participants electing this option continue to receive routine standard diabetes care, medications, supplies, and education through the TODAY2 clinical center, as well as annual outcomes assessments.
2. Annual outcomes assessments only: Participants selecting this option receive their routine diabetes care through another health care provider but agree to attend an annual outcomes assessment. These participants do not receive study-provided medications, supplies, or ongoing care, but the results of their outcomes assessments and recommendations for therapy are made available to them and their diabetes health care providers.

Participants may change between levels of participation throughout TODAY2 by changing their consent at any time.

4 Treatment Administration and Patient Management

The goal of diabetes treatment in TODAY2 is to reach and maintain an HbA1c level ≤ 6%. HbA1c is obtained at each 3-month medical visit and reported to the clinical center and the participant.

4.1 Medical Management

Other than metformin and insulin, no other oral or injected medications are currently approved for use in youth with T2D and are not provided by the study. The prescription of other medications by the treating physician is not cause for discontinuation of participation in the study. The use of other medications is tracked.

4.1.1 Metformin

All TODAY participants entering routine diabetes care as part of TODAY2 are transitioned to unblinded metformin at the dose they were receiving in TODAY. Metformin is provided by the study to all participants. To minimize variability to the extent possible in an observational study, it is the goal of TODAY2 to have participants remain on the maximum tolerated dose of metformin. Any participant not receiving 2000 mg a day of metformin is

eligible to have the dose increased as tolerated at the treating physician's discretion. The dose of metformin may be decreased at the treating physician's discretion to address occurrences of gastrointestinal complaints and other events.

4.1.2 Insulin

Insulin therapy is initiated for failure to maintain adequate glycemic control on metformin alone. This occurs in one of two circumstances:

1. *Metabolic decompensation:* Metabolic decompensation is defined as either hyperglycemia (BG > 300 mg/dL) accompanied by significant symptoms (e.g., vomiting, dehydration, lethargy) and/or moderate or large urinary ketones, or sustained hyperglycemia during home glucose monitoring (80% of BG tests are > 300 mg/dL non-fasting or > 200 mg/dL fasting for 1 week). When this occurs, the participant is evaluated clinically to determine if insulin therapy is required. All patients are educated to contact the study coordinator if they experience metabolic decompensation. This education is reinforced at study visits.

   When glycemic control is re-established following initiation of insulin for metabolic decompensation, insulin may be weaned according to the clinical center's discretion following standard of care and the individual circumstances.

2. *Failure to maintain target HbA1c:* HbA1c is measured at each medical visit every three months. In addition, the history of HbA1c prior to unblinding in TODAY is available to the clinical center staff. Based on HbA1c, insulin is initiated according to the following guidelines.
   (a) HbA1c 7.5-8.0% for six months (based only on values measured during TODAY2, i.e., not including historical values from last visits on TODAY).
   (b) HbA1c 8.0-9.0% for six months (where 6-month period includes historical values from last visits on TODAY).
   (c) HbA1c 9.0-9.5% for 3 months (where 3-month period includes historical values from last visits on TODAY).
   (d) Hemoglobin A1c > 9.5% at any time.

Other procedures relevant to add-on insulin therapy are:

- *Add-on insulin treatment regimen:* Participants who meet criteria for add-on insulin therapy continue to take metformin. Initial insulin treatment is basal insulin and the dose is increased up to 0.8 to 1.0 U/kg/day (to a maximum of 100 units), until fasting blood glucose (FBG) values between 70-150 mg/dL are achieved. Add-on basal insulin therapy is considered unsuccessful if (i) 0.8 to 1.0 U/kg/day (to a maximum of 100 units) does not bring FBG to target within 1 month or (ii) HbA1c > 8% at 3 months or (iii) HbA1c > 7% at 6 months. At that point, insulin therapy—including adding rapid, short, or intermediate acting insulin or insulin by pump therapy—may be provided at the clinician's discretion.

  Insulin dose may be decreased or discontinued at the discretion of the clinical center if HbA1c remains below 7% for 3 months and/or if there is hypoglycemia.
- *Self-monitoring of blood glucose (SMBG):* During insulin therapy, patients are asked to monitor blood glucose levels at least four times a day. Target fasting glucose and pre-meal glucose are 70-150 mg/dL and the target peak postprandial glucose is ≤ 200 mg/dL.

- *Temporary use of insulin:* Some patients may require temporary use of insulin. This may be due to (i) temporary medical conditions such as hospitalization or intercurrent illness (see section on safety) or (ii) pregnancy (see section on pregnancy). During temporary use of insulin, any type or dose of insulin can be used at the discretion of the treatment team. In such cases, an attempt is made to withdraw insulin once the acute event has resolved and metformin alone is resumed. In the case of pregnancy, participants are weaned over a 3 month period once pregnancy and lactation are complete. In the case of a temporary medical condition such as hospitalization or intercurrent illness, weaning is targeted to occur over 2 weeks if the event lasted 2 weeks or less; if the event lasted more than 2 weeks, weaning is targeted to occur over 1 month.

4.2 Ongoing Standard Diabetes Education

Standard diabetes education is provided throughout the study, as follows:

- Content is provided by the study's diabetes educator in a brief session. Content is typically provided in one-to-one sessions, but groups could be used.
- Additional 'need-to-know' information is provided to address specific educational concerns.
- Further education and/or assessment are provided for participants upon request or in the case of poor adherence or poor metabolic control.

4.3 Adjunct Care

In order to standardize treatment of comorbid conditions and to reduce the possibility of bias, algorithms are provided for treatment of dyslipidemia, hypertension, and microalbuminuria. Regular review of treatment for comorbid conditions and participant outcomes is provided by the Medical Monitoring Committee.

4.3.1 Treatment of Dyslipidemia

Target goals of therapy for dyslipidemia are LDL cholesterol < 100 mg/dL and triglycerides < 150 mg/dL. If baseline lipid levels are outside the target range in participants who are not receiving pharmacological therapy for dyslipidemia, initial therapy involves dietary counseling.

If LDL values remain over 130 mg/dL or if triglyceride levels remain over 300 mg/dL after six months of nutrition and diabetes management, pharmacological treatment is initiated and adjusted to achieve target goals according to an algorithm based on lipid levels.

Participants who are being treated with statins have dose adjusted to achieve target goals according to the algorithm based on lipid levels.

4.3.2 Treatment of Hypertension

While in the study, the target average systolic and diastolic BP is < 90^{th} percentile for age, sex, and height [NHLBI 1996], or 130 mmHg systolic and 80 mmHg diastolic.

High-normal blood pressure is defined as an average systolic or diastolic blood pressure ≥ 90^{th} percentile and < 95^{th} percentile for age, gender, and height measured at two consecutive study visits. Therapy for high-normal blood pressure includes dietary intervention consisting of elimination of added salt to cooked foods and a reduction in foods high in sodium content.

Hypertension is defined as either

(1) an average systolic or diastolic blood pressure ≥ the 95th percentile for age, gender, and height measured, or

(2) systolic blood pressure > 130 mmHg and/or diastolic blood pressure > 80 mmHg

at two consecutive study visits. Diagnostic tests include a routine urinalysis, blood urea nitrogen, and serum creatinine to screen for renal related disease. Subjects with hypertension are placed on dietary intervention consisting of elimination of added salt to cooked foods and a reduction in foods high in sodium content. In addition, initial pharmacological treatment of hypertension consists of a single ACE inhibitor with dose titrated to achieve target blood pressure. If target is not reached, additional medications may be added at the discretion of the study physician.

Participants already being treated with anti-hypertensive agents remain on such therapy, adjusted as needed to attain treatment goal.

4.3.3 Treatment of Microalbuminuria

Treatment of microalbuminuria with an ACE inhibitor is initiated at the time of diagnosis, regardless of blood pressure.

4.4 Pregnancy and Sexual Activity

Female participants of childbearing age are informed of the potential risks of hyperglycemia to a pregnancy including fetal malformations, pre-term delivery, C-section, and the potential increased risk for maternal progression of renal disease. Participants are also informed of the potential for metformin to enhance fertility. Those who consent to participate are encouraged to practice reliable birth control including systemic hormones and/or barrier methods.

In addition:

- *Safety monitoring:* Pregnancy tests are obtained from all female participants of childbearing age at each visit. Participants are asked to obtain pregnancy tests if pregnancy is suspected. The diagnosis of pregnancy can be made for study purposes by a positive urine pregnancy test in a patient who has missed one or more periods.
- *Planned pregnancy:* A patient who wishes to become pregnant is advised to come in for pre-pregnancy counseling and possible referral to a high-risk pregnancy program.
- *Unplanned pregnancy:* A patient who has become pregnant is referred to a high-risk obstetrical team with primary responsibility for the management of blood glucose levels. Data on pregnancy outcome are collected for safety evaluation.

5 Research Procedures and Approach

5.1 Data Collection

The table lists the schedule of data collection, measurements, and assessments.

Measurement/Assessment	**Follow-up Schedule** Q = quarterly A = annually
HbA1c	Q, A
Blood for storage	A
Urine for storage	A
Insulin sensitivity and secretion (a)	A
2-hour OGTT	A
Pancreatic autoimmunity	A
Serum creatinine, potassium (b)	A
Liver function tests (c)	A
Hemoglobin, hematocrit	A
Height, weight	Q, A
Blood pressure	Q A
Lipids (d)	A
Physical exam (e)	Q, A
Pregnancy and sexual activity evaluation	Q, A
Diabetes management	Q, A
Diabetes complications	Q, A
Concomitant medications	Q, A
Interim history	Q, A
Cardiovascular risk factors (f)	A
Peripheral neuropathy (MNSI)	A
Microalbuminuria	A
Standard diabetes education	Q, A
Medication dose	Q, A
Adverse events (g)	Q, A

(a) Insulin sensitivity and secretion measures include fasting glucose, insulin, C-peptide, and proinsulin. HOMA and QUICKI are computed.
(b) Serum creatinine is used to calculate creatinine clearance. We perform a test of potassium on all participants, whether on ACE-I/ARB or not; in patients who are on stable treatment with an ACE-I or ARB, annual potassium and SeCr measurements are the norm for care in adults, and this is extended to the TODAY2 sample of adolescents and young adults.
(c) If transaminases > 2.5 X ULN, safety protocol is followed.
(d) LDL, triglycerides, free fatty acids, lipoprotein subclass levels, average LDL particle density, and total apoB levels.
(e) A comprehensive physical exam including Tanner stage is performed at all annual visits. Otherwise a targeted physical exam is performed quarterly.
(f) Cardiovascular risk factors include measurement of fibrinogen, c-reactive protein, homocysteine (vitamin B-12 obtained to assess homocysteine), plasminogen activator inhibitor-1, interleukin-6. Pro-inflammatory and hemostasis markers are assayed annually.
(g) Participants are asked about adverse events (AE) at clinic visits, but AE and SAE (serious adverse events) may be reported at any time.

5.2 Participant Retention Program

Retention refers to efforts to prevent participant dropout or withdrawal from the study. It is critically important to successfully engage and retain participation over the course of the study. Challenges to retention include:

- *Burden:* Examples are the imposition caused by study procedures, frequent scheduling of procedures and study-related visits, requirements for record keeping, the necessity of frequent glucose monitoring, the interference of study activities with other things the participant would like to do.
- *Logistics:* Examples are travel required for study participation, scheduling study visits around school or work schedule, care of non-participating children while the parent is at a study visit, difficulty with dietary requirements such as limited access to fresh fruits and vegetables.
- *Environment:* Examples are lack of supportive individuals and institutions, deficits due to locale such as the lack of a grocery store or a safe place to be active.
- *Education:* Examples are low literacy, familial misinformation about diabetes, sociocultural mismatch between family and educator, language barriers.
- *Distrust:* Examples are the perception by the participant and/or family of being used as a 'guinea pig,' general suspicion of medical personnel or organizations, wariness of people of different ethnicity or race.

Specific strategies to systematically address each of these areas were developed during TODAY. Activities at both the national and local level are utilized and coordinated to maximize retention and minimize attrition. The study group maintains a database of ideas about positive approaches to participants. At the local level, study staff makes a major effort to personalize the study (mailing out personal notes, birthday cards, etc). Individual sites develop strategies to enhance retention specific to locale (i.e., different strategies may be required in Oklahoma working with rural American Indians as compared to working with urban African Americans in Philadelphia).

Attrition is monitored regularly by the Protocol Oversight and Retention Committees. An attempt is made to collect data on the reason for leaving the study in the case of a participant who withdraws. Assistance is offered to any site with a higher than average attrition rate. Sites are also encouraged to share their ideas and experiences via regular communication and conference calls for project and recruitment coordinators.

5.3 Confidentiality

The study complies with HIPAA guidelines regarding confidentiality of patient data.

Patients who participated in the TODAY study were assigned a study identification number:

- the first three digits indicate the clinical center and
- the next three digits are individually assigned to a participant by each clinical center (001-999).

In addition, each patient randomized is associated with an acrostic or 'nickname' of up to 6 alpha-numeric characters that was selected by the clinical center coordinator with input from the participant according to the following guidelines:

- neutral, i.e., not offensive, and
- unrelated to personal characteristics or identifiers, e.g., no initials or identifiable nicknames.

The purposes of the acrostic are (1) to act as a check and back-up of the study ID number in case of transcription or entry error, (2) to facilitate coordinator recall of a specific patient, and (3) to 'personalize' incentive items and other study materials provided to the participant.

All data, including forms and specimens, are labeled with the study ID, including forms and specimens. All data transferred to the coordinating center for accumulation in the central database identify the patient only with the study ID and acrostic. The coordinating center does not receive any personal identifiers.

Each clinical center maintains a file on each patient that includes personal identifiers, linking name and contact information to the study ID. These data are not entered into the study data management system or into any file intended to be sent to the coordinating center. Patient files are kept in secure locations and the clinical center is responsible for taking every other reasonable measure (those set by the state, the site, and the study) to ensure and maintain record confidentiality and patient privacy.

Training sessions cover confidentiality principles and procedures.

6 Safety and Monitoring

6.1 Data and Safety Monitoring Board (DSMB)

A Data and Safety Monitoring Board consisting of appropriately qualified independent experts is appointed to provide review of data on study progress and participant safety. The purpose of the board is to assure independent review as to whether study participants are exposed to unreasonable risk because of study participation, and to monitor study progress and integrity. Board members are chosen by NIDDK in consultation with the study investigators, and a report format and reporting frequency are developed before the start of data collection. The study chair and the coordinating center provide periodic reports on adverse events to the committee, including summary tabulations and narrative summaries on individual events. The contents of reports are determined by the DSMB.

The purpose of safety reports is to present the Data and Safety Monitoring Board with information regarding adverse events experienced by study patients as a result of undergoing the study procedures. Clinical centers report adverse events to the coordinating center in a timely fashion, including a narrative summary of the event as well as indication of the duration, perceived relationship to the study procedures, and resolution. The coordinating center summarizes and reports adverse events to the Data and Safety Monitoring Board on a semi-annual basis unless severe or unexpected adverse events occur. These are reported promptly to the DSMB.

Following each DSMB meeting, minutes are provided for the clinical centers to submit to the IRB. On an annual basis, a summary of study-wide serious adverse events is also provided.

6.2 Safety Monitoring and Risk Management

6.2.1 Laboratory Monitoring

In TODAY2, subjects undergo periodic laboratory monitoring related to known complications of obesity, diabetes, and their treatments, including annual SGPT/ALT, SGOT/AST, hemoglobin, hematocrit, serum creatinine, vitamin B12, and urine ketones if BG > 300 mg/dL at any clinic visit.

6.2.2 Potential Risks

Known adverse effects associated with metformin are primarily gastrointestinal (diarrhea, nausea, vomiting, abdominal bloating, flatulence, anorexia), hematologic (reduced vitamin B12 levels and, rarely, megaloblastic anemia), and the rare possibility of lactic acidosis. The risk of lactic acidosis associated with metformin use can be minimized by (1) monitoring liver transaminases, (2) monitoring renal function, and (3) temporary discontinuation of metformin before radiologic studies involving the injection of contrast dye, surgical procedures requiring reduced fluid intake, and serious illness that might be associated with hypoxia, dehydration, or shock.

6.2.3 Procedures to Minimize Risks

- *Anemia* may be an adverse effect of metformin. Anemia is defined as a hematocrit < 30.0%, a hemoglobin < 10 gm/dL, a decline in hematocrit by 4% between annual visits, or a decline in hemoglobin by 2 gm/dL between annual visits. If anemia is detected, a CBC with differential is obtained within one month. If anemia is confirmed, determination of a vitamin B12 level, examination of the blood smear, and other tests (as indicated) are performed at the discretion of the primary or study physician to help determine the etiology. Vitamin B12 and/or iron supplementation can be administered as clinically indicated. If anemia persists for more than six months despite appropriate therapy, consideration should be given to discontinuing or reducing the dose of metformin at the discretion of the study physician.

- *Renal insufficiency* increases the risk of lactic acidosis associated with metformin. Serum creatinine is determined annually. Using the serum creatinine, a creatinine clearance is calculated. If the calculated creatinine clearance is < 70 mL/min, metformin is discontinued for two weeks and the calculated creatinine clearance is repeated. If necessary, insulin may be temporarily used during this time. If the repeat calculated creatinine clearance is normal (≥ 70 mL/min), metformin is resumed at the previous dose. If the repeat calculated creatinine clearance is again abnormal (< 70 mL/min), or if once metformin is resumed the creatinine clearance again falls to < 70 mL/min, the treating physician should consider the risks and benefits of continuing metformin or discontinuing or reducing the dose.

- *Non-alcoholic fatty liver disease* is highly prevalent in obese adolescents with type 2 diabetes. Therefore, during this first phase of TODAY2, study participants are monitored with an SGPT/ALT and an SGOT/AST annually. If either ALT or AST level rises to > 1.5 X ULN after having been <1.5 X ULN, the treating physician should determine if an additional evaluation to exclude other cause of elevated transaminases or increased frequency of monitoring is warranted.

- Because the *risk of lactic acidosis associated with metformin may be more common in those with liver dysfunction*, metformin is discontinued when ALT or AST or both are elevated > 2.5 X ULN according to the following algorithm:
  1. Metformin is stopped immediately.
  2. ALT and AST are repeated in two weeks. If ALT or AST remain > 2.5 X ULN, the CBL performs hepatitis titers. Additional liver evaluation is done at the discretion of the clinical center based on previous history of liver disease and prior evaluation.
  3. ALT and AST are monitored at each study visit or more frequently at the discretion of the clinical center.
  4. Metformin is restarted when ALT and AST are both < 2.5 X ULN.

5. ALT and AST continue to be monitored at each study visit until stable.
This same algorithm is followed for each new episode of elevated ALT or AST > 2.5 X ULN.

Participants and their families are instructed that in the event they develop malaise, vomiting, dark urine, jaundice, or right upper quadrant abdominal discomfort, they should stop study medication and contact the study clinical center immediately. Upon notification, the center staff must obtain blood for ALT and AST as soon as possible and within one week. Based on these results, the algorithm described above is followed.

- *Gastrointestinal (GI) symptoms* are a common occurrence with metformin. These symptoms more commonly occur early in the course of treatment. Since all eligible participants have been treated with the maximal tolerated metformin dose (between 500 mg bid and 1000 mg bid) during the TODAY study, few additional gastrointestinal side effects are anticipated in these participants. If GI side effects develop and are mild, the participant is encouraged to remain on the metformin. If GI side effects are moderate or difficult to tolerate, metformin is reduced at the discretion of the clinical center. If GI symptoms resolve, metformin is re-escalated by 500 mg per day each week, at the discretion of the clinical center, until reaching the previously tolerated dose.

- *Severe hypoglycemia* is defined by the need to be treated with glucagon, the need for a third party to resolve a hypoglycemic episode, or loss of consciousness or seizure. If severe hypoglycemia occurs, medications are adjusted downward at the discretion of the clinical center. If there are no additional hypoglycemic events and if HbA1c values rise to above target (> 6%), medications may be returned to the previous dose at the discretion of the clinical center.

- *Metformin* is temporarily discontinued 24 hours before, during, and for 48 hours after any of the following events: 1) procedure involving the injection of contrast dye; 2) surgery or other procedure requiring general anesthesia; 3) any illness that could be associated with hypoxia, circulatory failure, or dehydration; 4) hospitalization. Serum creatinine should be rechecked and creatinine clearance calculated as soon as feasible (but no sooner than 48 hours after the conclusion of the event) and metformin can be restarted if the calculated creatinine clearance is $\geq$ 70 mL/min. If values remain < 70 mL/min, a creatinine clearance is repeated at the discretion of the clinical center and metformin may be restarted when the creatinine clearance is $\geq$ 70 mL/min. If creatinine clearance remains < 70 mL/min at 12 weeks, the treating physician should consider the risks and benefits of permanently discontinuing metformin or resuming it at the same or a reduced dose.

- Other indications for considering temporary or permanent discontinuation of metformin include lactic acidosis, DKA, or severe dermatological problems, such as urticaria, bullous rashes, exfoliative dermatitis, Stevens-Johnson syndrome, thought to be related to metformin.

6.3 Adverse Event and Serious Adverse Event Reporting

6.3.1 Purpose of Adverse Event Reporting

The reporting of adverse events experienced by study participants meets three important purposes:

1. We are studying children and minors who are considered a vulnerable research population.
2. We are providing medications that have side effects and safety risks.
3. We want to ensure the delivery of optimal care and management.

The timely and complete reporting of adverse events is a critical requirement in the conduct of this study.

6.3.2 Definitions of Adverse Events

- *Adverse Event (AE):* Any unfavorable and unintended change in the structure, function or chemistry of the body experienced by a study participant during the study regardless of the relationship of this change to administration of study intervention or participation in the study. Adverse events include symptoms and changes in laboratory data that are not specifically part of the primary or secondary outcomes of the study. AEs are reported only at scheduled study visits unless they meet the criteria for being serious.

- *Serious Adverse Event (SAE):* Events are divided into those that are serious (SAEs) and those that are not serious (AEs). The distinction between an SAE and an AE is a regulatory definition established by the FDA, not a clinical definition. The definition of SAE is not always related to clinical severity of the event. An AE is considered serious (SAE) when it satisfies any one of the following criteria:
  a. The event results in an inpatient hospitalization (any overnight stay associated with an admission).
  b. The event results in the prolongation of a hospital stay.
  c. The event results in permanent or severe disability.
  d. The event results in death.
  e. A pregnancy results in a congenital anomaly.
  f. The event is life-threatening.
  g. Treatment is required to prevent a serious event.
  h. The patient experiences a bout of lactic acidosis.
  i. An episode of diabetic ketoacidosis (DKA) occurs.

6.3.3 Non-serious Adverse Events

It is essential that AEs be ascertained in an unbiased manner using standard questions. Therefore, AEs are reported on a standard form that is completed by the study staff at each regular follow-up visit. AEs are ascertained by asking targeted questions relating to specific events of import in diabetic patients. AEs also include any significantly abnormal physical finding identified on examination and any significantly abnormal laboratory result obtained on the participant between visits or at the time of the visit. Questions answered YES and any new abnormal physical findings are pursued by the study staff in order to determine the seriousness of the event and the need for further evaluation, follow-up, or referral. Adverse events reported or ascertained between clinic visits are captured and reported at the time of the next scheduled visit.

Pre-existing conditions (that is, conditions present prior to randomization to TODAY) are not considered or recorded as AEs or SAEs unless the condition worsens in intensity or frequency after randomization, including during TODAY2. Likewise, continuing adverse events are not reported as AEs at subsequent visits unless they increase in severity or

frequency between the visits, they result in criteria for an SAE, and/or they resolve between visits.

6.3.4 Serious Adverse Events

Study participants are instructed to contact the clinical center with any serious adverse event meeting the above criteria. Each SAE is recorded on the study form and sent to the coordinating center as soon as possible after they occur and preferably within 24 hours of the notification of the clinic staff. This notification should occur even if data are incomplete. Additional data and follow-up information are sent subsequently as an update to the original report. The coordinating center immediately forwards SAE reports to the study group chair, the NIDDK project office, chair of the Medical Monitoring Committee, and the DSMB, which convenes expeditiously at the discretion of the chair. SAEs are also reported to the local IRB and any other institutional monitoring committee, as per local requirements.

6.3.5 Tracking of Adverse Events by the Study Group

- *Serious adverse events:* All SAEs are reported to the coordinating center within 24 hours. The coordinating center forwards all SAE reports to the chair of the Medical Monitoring Committee for consideration. The committee chair assesses each event to determine if immediate action is required by the study group in response to the event. If the chair determines that immediate action should be considered, he/she consults with other members of the committee to recommend a course of action. In addition, any SAE that results in death or permanent or severe disability and any SAE judged by the local PI as PROBABLY related to study participation are discussed by the committee as soon as feasible. Any actions recommended are communicated to the study group chair for consideration of study wide action. If the SAE is not deemed to warrant immediate study wide action, it is discussed at the next scheduled meeting of the Medical Monitoring Committee (SMC).

- *Non-serious adverse events:* Non-serious adverse events (AEs) are tabulated by the coordinating center in the same format as is done for the DSMB. Summaries of the AEs, tabulated by clinic, are provided to the Medical Monitoring Committee and reviewed on a regular basis. The committee makes recommendations for action to the study group at the next Steering Committee meeting.

- *Meetings of the Medical Monitoring Committee (MMC):* The MMC meets in person at the time of each study group meeting and by conference call at least every 2 months, or as needed to review any SAE that are designated by the clinical center as PROBABLY related to study participation. During these meetings, the committee discusses all SAEs and, when available, the summary reports of the non-serious AEs. The MMC considers whether changes in the protocol (monitoring, consent process, etc.) are indicated based on the occurrence, frequency, or severity of AEs and SAEs. The committee also evaluates whether there is any clustering of AEs by clinic. As deemed necessary, a member of the MMC communicates with the local center PI to obtain additional information about SAEs and observed local trends in non-serious AEs. The MMC reports do not refer to original TODAY treatment group. Output reported to the DSMB is by treatment group.

7 Data Processing and Management

The coordinating center develops and maintains a central database integrating all of the project data.

7.1 Data Management System

Data are entered at the clinical centers into the MIDAS web-based data entry application. The database application guides the study staff member through the data entry process. If an invalid response is entered, the computer signals and provides a message about the error and how to solve it. At any point during entry, the staff member can make an electronic note concerning a particular response. The system includes programmed skip patterns as required by the case report forms, and also includes quality control checks such as lists of valid values for multiple choice items. The system provides automated consistency checking so the study staff can resolve inconsistencies quickly without a lengthy communication with the coordinating center. The same checking is also run on the central database at the coordinating center to verify that centers are resolving consistency checks.

7.2 Quality Control

Range checks, inter-item checks, cross-table checks, and double data entry verification are used where appropriate to ensure accurate data entry. Specific quality control procedures are run to check for missing, incorrect, and questionable values immediately after they are entered. Reports with the necessary patient identifying information and the problem values are produced and sent to the clinical centers for correction. When returned, corrected values are checked again for consistency with other items. The goals are to make quality control a continuous process, to make the turnaround time between error detection and correction as short as possible, and to document any changes made to the database.

7.3 Backup, Data Security, and Confidentiality

The coordinating enter applies the Biostatistics Center's data backup and security policies to ensure the safety and confidentiality of the data. Backup procedures include: twice-weekly system backup, daily incremental backup, and off-site fire proof storage. Security procedures include: logon and link password protection, remote password logon and dial-back modems, and for internet access, separate Web servers which use SSL and encryption algorithms. Regularly updated virus scanning software is used routinely to check personal computers for computer viruses. University computing facilities provide support in the event of a disaster.

The coordinating center maintains confidentiality of patient data and emerging results per a confidentiality policy, which every staff member is required to sign annually.

7.4 Tracking Study Progress

The purpose of tracking reports is to keep the collaborative group informed of study progress, and to report special problems and resolutions. Reports are produced regularly by the coordinating center, as directed by the Steering Committee. These reports are distributed to the study group through the study website.

Tracking reports include the following types of information:

- tables describing attendance at scheduled study visits
- database inventory
- number of data edit queries generated and outstanding, by clinical center

- characteristics of the patient population, by clinical center
- progress of analysis and manuscripts

7.5 Archival and Study Close-out

At the end of the study, after all data have been received and edited, the database is archived in computer readable format, including: readme documentation files, text files of study documents (forms annotated with variable names, protocols, and manuals of procedures), data files in the form of SAS transport files and input statements, data dictionaries, and program code documenting primary derived variables.

After the results have been published, all data will be stored at the NIDDK Central Repository to be made available to other investigators.

8 Statistical Considerations

Phase 1 of TODAY2 is not driven by outcomes and hypothesis testing. Rather, it is conducted to retain the invaluable TODAY study cohort of participants under standardized 'best available' care and management and to continue to collect outcome measures while undertaking analysis and interpretation of TODAY data. The results of that analysis will guide the development of phase 2 of TODAY2.

8.1 Sample Size

TODAY enrolled 699 participants. As of April 2009 (2 months after the end of enrollment), 22 participants had officially withdrawn and about 100 had missed the last two scheduled study visits. As a clinical trial operating under intention-to-treat principles, TODAY made every effort to retain every participant at whatever level of involvement was feasible and acceptable, including periodic outreach to absent individuals.

As TODAY came to a close, participation in TODAY2 was offered to each participant. Other studies report very high rates of willingness to continue in long-term follow-up with the same study group. Therefore, a sample size in the 600s is expected. TODAY participants who initially decline to be involved in TODAY2 may later change their minds and are welcomed back.

The sample represents a subset of the TODAY study cohort. Patterns of and reasons for missing and withdrawal may be biased across TODAY treatment group, in which case the sample can no longer be considered a 'random' sample.

Power calculations will be performed for the TODAY2 phase 2 proposal, based on sample size retained and estimates of clinically significance outcome levels.

8.2 Statistical Analysis

TODAY2 phase 1 analysis is considered descriptive and exploratory, in preparation for phase 2 hypothesis testing. Statistical tests are two-sided, with the standard p-value < 0.05 indicative of statistical significance (without regard for multiple testing on the same sample) but with results interpreted in terms of clinical significance. TODAY2 phase 1 continues to collect most of the primary and secondary outcomes as in TODAY for the purpose of accumulating sequential longitudinal data on each participant to be used in TODAY2 phase 2 hypothesis testing.

Time to 'event' outcomes (e.g., loss of glycemic control, cardiovascular risk factors, microvascular outcomes) are analyzed using interval-based life-table methods. A proportional-hazards regression model is used to evaluate potential covariates that may

modify the time to event outcomes (e.g., risk population defined by race/ethnicity, age, clinical site). Longitudinal data analysis techniques are used to analyze repeated measures data (e.g., glycemia, fasting lipids, blood pressure). These include: (1) analyses of the point prevalence of a discrete characteristic (e.g., hypertension) at successive repeated visits over time [Lachin and Wei 1988]; (2) multivariate rank analyses of quantitative or ordinal measures over successive visits [Wei and Lachin 1984]; (3) parametric linear random effects model to compare participant slopes over time under linearity and normality assumptions [Laird and Ware 1982]; and (4) techniques to compare participant slopes under a generalized linear models framework [Liang and Zeger 1986].

Close attention is paid to withdrawal and missing data. Reasons are determined, if possible, and compared across TODAY treatment groups to determine bias. Detected bias may lead to approaches such as subgroup or covariate analysis.

Participants are analyzed according to their TODAY randomized treatment group assignment. Missing data are not imputed.

No interim outcome analysis is planned during TODAY2 phase 1. Output is presented to the DSMB by original TODAY randomized treatment group.

9 Study Administration

9.1 Organization

The major organizational components and their responsibilities are described:

- The *TODAY2 Steering Committee*, composed of the principal investigators of the 15 clinical centers, the coordinating center, and the NIDDK project office, is the primary decision making body for the study with overall responsibility for the design and conduct of study protocols.
- The *NIDDK project office* participates in all decision-making activities and selects and oversees the activities of the Data and Safety Monitoring Board.
- The *clinical centers* are located at Baylor College of Medicine, Case Western Reserve University, Children's Hospital of Los Angeles, Children's Hospital of Philadelphia, Children's Hospital of Pittsburgh, Columbia University College of Physicians and Surgeons, Joslin Diabetes Center, Massachusetts General Hospital, Saint Louis University, State University of New York Upstate Medical University, University of Colorado Denver, University of Oklahoma Health Sciences Center, University of Texas Health Sciences Center at San Antonio, Washington University at St Louis, and Yale University. They are responsible for recruiting patients and implementing the protocol.
- The *coordinating center* is located at the George Washington University Biostatistics Center with responsibility for coordinating all aspects of the study, including production and distribution of materials and documents, set-up and administration of the data management system, maintenance of the central database, analysis of results, and report of results in collaboration with the other investigators.
- The *Central Biospecimen Laboratory (CBL)* operates under subcontract to the coordinating center. The CBL is responsible for providing procedures for the handling, storage, and shipment of blood and urine specimens, for performing the tests and assays, for performing quality control, and for transferring results to the coordinating center.
- The *Pulse Wave Velocity Reading Center (PWVRC)* operates under subcontract to the coordinating center. The PWVRC is responsible for acquiring and shipping equipment to the clinical sites, for providing procedures and training for the collection and transfer of data, for performing quality control, and for transferring results to the coordinating center.

- The *Drug Distribution Center (DDC)* operates under subcontract to the coordinating center and is responsible for packaging and distributing study drug, providing procedures and training for ordering, handling, shipping, and storage, and working with the coordinating center to devise and implement a drug and dosage administration scheme.
- The *Data and Safety Monitoring Board (DSMB)* is composed of outside experts in the design and conduct of clinical trials, in pediatrics, and in T2D. The board is responsible for reviewing the study documents, monitoring study progress, and monitoring patient safety.
- *Working committees* include Operations, Protocol Oversight, Committee Chairs, Retention and Adherence, Medical Monitoring, Laboratory Monitoring, Publications and Presentations, Ancillary Studies.

9.2 Central Laboratories and Reading Centers

In collaboration with the coordinating center and study investigators, central laboratories and reading centers perform the following tasks:

1. Establish procedures and standards for training staff involved in the measurement, collection, preparation, handling, transfer, and all other procedures and processes.
2. Conduct training sessions and contribute training materials to the study manuals of procedures.
3. Provide or facilitate the acquisition of equipment and materials, including specifying brands, sizes, and suppliers as applicable.
4. Establish procedures for data entry and transfer of data to the coordinating center.
5. Develop procedures for the internal as well as external quality control, and provide periodic reports on the quality control surveillance.
6. Provide long-term storage of reserve specimens or materials as directed by the Steering Committee for use in ancillary or future studies.

Each director represents the laboratory or center on Steering Committee conference calls and on other conference calls where the director's participation is deemed necessary.

9.3 Training and Certification

The coordinating center arranges for study-wide, small group, site, and individual training and re-training. Study-wide training sessions are at least annual, and held in conjunction with the annual study group meeting. Investigators and outside experts may be assigned to lead sessions. The purpose of training is to assure that the study is conducted in a standardized manner across all locations (clinical centers) and time (years of follow-up). Training is based on the study manual of procedures. Throughout the study, new staff are trained by the existing clinical center study staff, which hopefully includes overlap with the previous position holder, with assistance from the coordinating center.

In order to remain certified to engage in study procedures, study staff must attend training session or make up sessions and must pass any tests or criteria established.

The clinical center must also pass certification criteria, including supplying the coordinating center with the current IRB approval letter and stamped informed consent forms.

9.4 Site Visits

The two types of site visits are (1) scheduled monitoring and (2) as needed to address specific concerns.

The coordinating center organizes site visits to audit and monitor study procedures and records, engage in local problem solving, and provided training/retraining as needed. The site visit team includes representatives from the coordinating center and, as needed, investigator(s) or coordinator(s) from other clinical centers and a representative of the NIDDK program office. Each visit follows a predetermined format and site visitors complete a checklist to record findings. The site visit team reviews study procedures and compares data collection records to listings from the central database.

Site visits conducted to address specific problems at the clinical center are attended by investigators representing study leadership, the NIDDK project office, the coordinating center, and others as needed.

9.5 Study Website

The coordinating center maintains the study website, which is a secure site requiring a user ID and password combination for access. The web server utilizes the Secure Socket Layer (SSL) protocol that encrypts all traffic to and from the server. Investigators, coordinators, consultants, and other study staff who would benefit from access to the information on the website are each given a unique user ID and password, which identifies the user to the web server and can be used to restrict access to particular web pages if desired.

The website contains study documents such as the protocol, manual of procedures, and forms, study calendar, directory, meeting and conference call information, links to other sites, tracking reports, minutes, and agendas.

9.6 Conflict of Interest Policy

The TODAY2 investigators have adopted a conflict of interest policy similar to that used by other NIDDK collaborative groups. TODAY2 collaborators are required to disclose any financial or related interest that could present an actual conflict of interest or be perceived to present a conflict of interest. Disclosure is required to protect each individual's reputation and career from potentially embarrassing or harmful allegations of inappropriate behavior, and to protect the integrity of TODAY2 study research. Forms are kept on file at the coordinating center.

The TODAY2 Operations Committee determines (1) if the disclosed interests could directly and significantly affect the performance of study responsibilities and (2) the management, reduction, or elimination of the conflict. In addition to complying with the TODAY2 conflict of interest policies, collaborators must certify that they have complied with all of their local and institutional requirements regarding conflict of interest and disclosure. This is accomplished by supplying the coordinating center with copies of the local IRB letter of approval and stamped informed consent form(s).

9.7 Publications and Presentations Policy

The TODAY2 investigators have adopted a policy similar to those used by other NIDDK collaborative groups. The policy is administered by the TODAY2 Publications and Presentations Committee with approval from the TODAY2 Steering Committee. The policy includes guidelines for authorship, submission and review of proposed publications and presentations, ownership of the data, and setting priorities for coordinating center statisticians.

9.8 Protocol Amendments

Adoption of protocol amendments requires two-thirds majority approval by voting members of the TODAY2 Steering Committee. The amended protocol is approved by the DSMB and is resubmitted to the IRB along with revised informed consent forms, if applicable.

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