

**The VA Diabetes Trial
Follow-up Study
(VADT-FS)
CSP #465-F**
VA Diabetes Trial Follow-up Study (VADT-FS)

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Version 4.1

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Approval Confirmation

This document has been reviewed for study content and found acceptable for distribution. Any questions or comments pertaining to this document should be addressed to: Tamara Paine, the Study Project Manager, at tamara.paine@va.gov, 708-202-5785 for attention.

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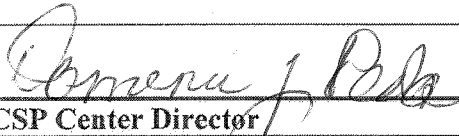
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This document has been summarized for my review by the CSPCC study team. I am aware it is being distributed at this time. I require a brief review of the following sections of the document by the person(s) indicated below before distribution:

 CSP Center Director	7 Aug 2017 Date signed
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Distributed on _____ by Tamara Paine via email.

CSP 465-F Protocol 4.0	Changes to CSP 465-F Protocol 4.0 – 4.1	
	From 4.0	To 4.1
Cover page	Version 4.0 November 26, 2013	Version 4.1 July 6, 2017
Page 34		<p><i>Added Early Analysis</i></p> <p>The major protocol amendment for the VADT-F was that a mid-point analysis would be conducted and reported, which was made and published as planned. We now plan for an early analysis to take place shortly before data is fully completed with adjudicated outcomes and locked. There is to prepare to submit an important presentation in time to take place at the American Diabetes Association (ADA) 2018 which is planned to be made in conjunction with publication of the corresponding manuscript. Below we provide the full justification for this analysis.</p> <p>A major concern about an early analysis of clinical trials is that it can potentially bias investigators involved in the study protocol and thus integrity of reported data. However, this concern does not apply to this proposed early VADT-F analysis. As active intervention ceased 10 years ago at the conclusion of the VADT, and there are no longer research personnel that have clinical contact with the study subjects, there is no way for investigators to influence patient care or outcomes. The outcomes are being collected through database search and surveys. In addition, the investigators will be still blinded to the individual treatment level data, which will become available for analyses before the final presentation. Thus, the potential for bias is not a threat to the VADT-F.</p> <p>On the other hand, there will be substantial benefit to the diabetes community as we present in a timely manner this important study about whether or not there is a delayed effect of the intensive treatment, and all presentations and papers will use fully completed and locked data. We therefore believe that the benefits of an early analysis provide substantial benefit to the diabetes community and do so at essentially no risk to the integrity of the VADT-F</p>

VA Diabetes Trial Follow-up Study (VADT-FS)

CSP #465-F

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The VA Diabetes Trial Follow-up Study (VADT-FS)

PREFACE

CSP #465, “Glycemic Control and Complications in Diabetes Mellitus Type 2,” was a randomized unblinded clinical trial comparing tight glycemic control to standard glycemic control and was conducted at 20 VA medical centers. One thousand seven hundred and ninety one patients were randomized over the 2 ½ year accrual periods and then followed for an additional 5 years. Follow-up averaged between 5 and 7 years depending upon when the patient was enrolled in the study. Patients were seen on average every three months in the VA Outpatient Clinics. Hypertension and hyperlipidemia were aggressively treated in patients in both treatment arms. Education regarding diet, exercise, smoking cessation and management of hyper and hypo-glycemic reactions was also provided. Data were collected throughout the study on the patients’ physical status, adverse and serious adverse events, concomitant medications, and study end points including mortality. The study was conducted under an FDA IND and consisted of broad use of all anti-diabetic treatments commercially available between 2000 and 2008 including oral medications and insulin. Study required medications and all study clinic visits were provided free of the usual VA co-pay. Active clinical follow-up of the sample ended on May 31, 2008. With the end of the clinical trial the patients were transitioned back to usual patient care services.

It is important to clarify that with the completion of the active clinical trial and transitioning of patients to this observational trial, all responsibility for the care, treatment and oversight of the study patients became the responsibility of the patients’ Primary Care Physician. The VA Diabetes Trial Follow-up Study (VADT-FS) is not collecting adverse or serious adverse events, is not required to file FDA reports or actively treat or have any “hands-on” care responsibility for the study participants.

The ongoing VADT-FS consists of centralized computer database searches and annual survey questionnaires related to quality of life and self-reported events pertinent to the CSP #465 study.

The VADT-FS is very limited in scope compared to the clinical trial and is restricted to the activities stipulated in the proposal contained on the following pages.

VADT Follow-up Study (VADT-FS)

Abstract:

Diabetes affects nearly 1 in 10 Americans over the age of 45 and is associated with a doubling of mortality compared to age-adjusted controls, with about 75% of these deaths being due to cardiovascular (macrovascular) disease. With the high life-time risk of hyperglycemia-related diabetic retinopathy, nephropathy and neuropathy (the so called “microvascular” complications of diabetes), there is a consensus that striving for tight glycemic control should be a high priority for individuals with early onset diabetes (i.e., onset before age 40 with a life expectancy of more than 20 years). However, there is considerable controversy over the importance of routine tight glycemic control in those with later onset disease, since these patients have a relatively low life-time risk of major microvascular complications but a very high risk of cardiovascular events and mortality. Certainly, glycemic control, as measured by A1c, has been associated with an increased risk in macrovascular complications in many observational studies, however evidence from randomized controlled trials on the effectiveness of intensive glycemic control in reducing macrovascular complications in those with type 2 diabetes is lacking. Therefore, for the majority of people with diabetes in the US (over age 50 without known microvascular complications), it remains controversial as to how much effort, cost, patient burden and exposure to unknown long-term complications of newer medications is justifiable in the pursuit of tight glycemic control.

Therefore, in 1999 the Veterans Administration Diabetes Trial (VADT) was funded, a randomized controlled trial designed to answer the question, “Does intensive glycemic management using the most effective hypoglycemic medications available result in decreased cardiovascular morbidity and mortality.” The VADT was highly successful in recruiting and retaining study subjects and in implementing its study protocol. In particular, the VADT maintained a median A1c in the intensive therapy arm that has averaged 1.6 points lower than that in the conventional treatment group. The clinical trial ended in May 2008. The main results of the VADT were presented at the American Diabetes Association Annual Scientific Meeting in June 2008 and published in the New England Journal of Medicine in January 2009. During the main trial, intensification of glycemic control did not reduce cardiovascular events implemented in people with excellent non-glycemic risk factor control. However, there is reason to believe that many of the macrovascular and microvascular complications potentially prevented by the 5-8 years of good glycemic control achieved in the VADT will occur years after completion of the VADT experimental protocol. This could result in the initial results of the VADT providing an incomplete picture of the true overall benefits of intensive glycemic control. In particular, the results of the United Kingdom Prospective Diabetes Study (UKPDS) follow-up and EDIC study (the follow-up of the DCCT study population) make a compelling argument for continued follow-up of the VADT study population, in that they suggest that cumulative years of tight glycemic control may have a multiplicative effect on later CV risk (like compound interest). If this is true, then long-term follow-up would likely be necessary in order to fully appreciate the importance of intensive glycemic treatment. Therefore, the VADT study group proposed a longitudinal observational follow-up study of the VADT with the following objective: 1) to determine the long term effects of intensive glycemic control in type 2 diabetes on major cardiovascular complications (primary outcome), and 2) to determine the long term effects of intensive glycemic control in type 2 diabetes on five secondary outcomes: a) cardiovascular mortality, b) major microvascular complications, c) health-related quality of life, d) total mortality, and e) major microvascular or

macrovascular (*end-stage renal disease, amputation for either ischemic or non-ischemic gangrene, CV-related death, or nonfatal MI, stroke, or new CHF*). This began in mid-2008 with funding through 2012. In December 2011, additional funding through 2018 was requested and was received.

Background and Significance

Diabetes is a highly prevalent disease that has a profound impact on premature disability and mortality in the Western world (Camacho, 2000; CDC, 2005; Haffner, 1998; Ryerson, 2003). Diabetes affects nearly 1 in 10 Americans over the age of 45, is associated with a doubling of mortality compared to age-adjusted controls, and accounts for roughly 15% of all health care expenditures in the US (Druss, 2002; Hogan, 2003; Ryerson, 2003). Of the over 5 million veterans served by VHA, almost 20% have diabetes (VA Achievements in Diabetes Care, VA Fact Sheet, February 2006; Miller, 2004). In FY1998, the total cost of VA inpatient and outpatient use by veterans with diabetes was over \$1.6 billion and VA patients with diabetes received 30% of all VA pharmacy prescriptions, accounting for approximately 28% of all pharmacy dollars expended, in FY2000 (Kupersmith, 2007; Miller, 2004; Maciejewski, 2004; Weinstein, 2004). The prevalence of diabetes (both diagnosed and undiagnosed cases) has also reportedly increased by 4- to 8-fold over the past 25 years, and the current epidemic of obesity guarantees that this trend will continue (Honeycutt, 2003). Better understanding how to optimize care of diabetes is therefore one of the most important medical and public health priorities of today.

Whether tight glycemic control reduces major cardiovascular complications is a critically important unanswered clinical question. There is a clear consensus that if tight glycemic control is shown to reduce major cardiovascular complications over a 15-year period, then health systems and clinicians should prioritize achieving tight glycemic control in almost all patients with diabetes since 75% of people with diabetes die from cardiovascular disease (Vijan, 1997; Honeycutt, 2003; Engelgau, 2004). Microvascular complications of diabetes (nephropathy, retinopathy, and neuropathy), which are already known to be reduced by improved glycemic control, can be devastating as well, and there is strong evidence in type 1 diabetes and new onset type 2 diabetes that intensive glycemic control reduces microvascular complications and may reduce long-term CV events. However, it has, as outlined in detail below, become quite clear that these results may not apply to today's typical type 2 diabetes patient, who is often older and has multiple comorbidities. In particular, recent results from large randomized studies (including the Veterans Affairs Diabetes Trial, VADT) in more advanced type 2 diabetes patients indicate that modest microvascular benefit and no overall CV benefit results from improved glycemic control during the 3.5-5 year time frame of the studies. Therefore, the critical question of whether tight glycemic control ($HbA1c < 7.0$) reduces *clinically relevant* microvascular disease and CV events in patients receiving current day standard excellent blood pressure and lipid management is only partially answered; and thus remains one of the most important clinical and public health questions of today.

What is clear from several early studies of glycemic control is that some of the most interesting and important benefits resulting from improved glucose lowering on both macrovascular and, to a lesser extent, on microvascular outcomes have come long after the initial period of glycemic intervention, at a time when there was no longer any difference in glycemic separation between study groups. This concept of vascular metabolic memory or the "legacy effect" is of critical importance in light of less impressive results in the shorter-term that were recently reported in The Action to Control

Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) and the VADT. Unfortunately, the important long-term findings from The Diabetes Control and Complications Trial (DCCT) and The United Kingdom Prospective Diabetes Trial (UKPDS) became apparent after the design and initiation of each of the more recent randomized trials - which were only 3.5-5.5 years in length. Fortunately, plans for a longer and relatively inexpensive observational follow-up of the VADT were put in place and preliminary data from the first phase of this study demonstrate the feasibility of obtaining 15 year follow-up data and adequate statistical power to detect a clinical meaningful reduction in major cardiovascular complications. Continued follow-up of this VADT cohort is crucial since this would provide the only data regarding the long-term effect of a glycemic intervention which was aggressive yet relatively safe (as the ACCORD study increased mortality) and undertaken in people with advanced type 2 diabetes with a heavy cardiovascular burden.

Cardiovascular Outcomes

What have we learned from controlled clinical trials?

Most, but not all, observational studies have demonstrated that glycemic control is associated with reduced risk of both microvascular and CV complications (Selvin, 2004; Stratton, 2000; Adler, 1999; Haffner, 1998; Kirkman, 2006; Meigs, 1997; Reaven, 2005). As summarized below, evidence from randomized controlled trials on whether tight glycemic control results in a reduction of CV complications in those with diabetes is mixed at best.

The Diabetes Control and Complications Trial (DCCT)

In this landmark trial of young people (age 13-39 years old at entry) with type 1 diabetes, good glycemic control led to impressive microvascular benefit with reduced albuminuria, retinopathy progression and neuropathy (DCCT, 1993). Although there was a trend towards improved CV outcomes, the number of events was small and there was no significant CV benefit during the course of the trial.

The United Kingdom Prospective Diabetes Trial (UKPDS)

The UKPDS, conducted in newly diagnosed type 2 diabetes with an average age 53, found a small but not statistically significant decrease in cardiovascular outcomes over a 9-10 year period in the overall treated vs. control group. However, a smaller subset of more overweight subjects treated with metformin did demonstrate a significant reduction in CV events (UKPDS, 1998a, UKPDS, 1998b).

The Veterans Affairs Diabetes Trial (VADT), Action to Control Cardiovascular Risk in Diabetes (ACCORD), and Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE)

Similar to the UKPDS, more recent trials in type 2 diabetes have also found no clear CV benefit over a 4-6 year time period. The VADT, ACCORD, and ADVANCE studies examined type 2 diabetes populations who were in general receiving excellent management of other CV risk factors. Achieved glycemic control was also substantially better in the intensive groups of each of these studies than in the UKPDS, although only the VADT achieved superior glycemic separation between standard and intensive groups. While the UKPDS involved individuals with newly diagnosed diabetes, VADT patients

had an average duration of diabetes of 11.5 years at entry; ACCORD, 10 years; and ADVANCE, 8 years. All participants had either prevalent CV or substantial CV risk at entry. The VADT (median follow-up 5.6 years), ACCORD (median follow-up 3.4 years), and ADVANCE (median follow-up 5 years) showed no cardiovascular benefit of more intensive glycemic control (Duckworth, 2009; ACCORD Study Group, 2008; ADVANCE Collaborative Group, 2008). In fact, the glycemic arm of ACCORD was stopped 18 months early because the intensive glycemic control arm, which achieved an A1c of 6.4%, was associated with a 22% increase in all cause mortality and a 35% increase in cardiovascular mortality (ACCORD Study Group, 2008). Publication of these 3 landmark studies so close in time also stimulated several meta-analyses of these and other major trials of glycemic control. Overall, the meta-analyses found modest benefits of glycemic control on myocardial infarction, but not on stroke, cardiovascular mortality, or all-cause mortality (Turnbull, 2009; Ray, 2009; Montori, 2009). A fourth recently published meta-analysis reached essentially the same conclusion (Boussageon, 2011). Probably because of the increased mortality risk of very aggressive control seen in ACCORD, one of the meta-analyses concluded that "...the possibility of harm with more-intensive glycaemic treatment cannot be ruled out." (Turnbull, 2009). Therefore, the risk/benefit ratio of intensive glycemic control in people with type 2 diabetes of longer duration and with greater prevalence of CV disease over the typical 3-5 year study time frame is far from clear.

What have we learned from post-trial observation of patients who had been in controlled clinical trials?

Despite these largely negative results during the interventional phase of the trials, long term observational follow-up studies have provided a substantially different, and more complex understanding of improved glycemic control and CV complications, at least in type 1 and earlier stages of type 2 diabetes.

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC)

The DCCT/EDIC study was an observational follow-up study of the DCCT, in which type 1 diabetes participants continued to be carefully monitored for diabetes complications after completion of the active intervention trial phase was completed. During this follow-up phase, A1c levels in both treatment groups approached each other and were not significantly different throughout the follow-up period. Thus, the extended follow-up was largely monitoring development of complications resulting from the prior reductions in glycemia. The main long-term study results were published when mean total follow-up (including the active trial phase) was ~17 years, and showed that the intensive glycemic group had a 42% reduction in CV events (Nathan, 2005). It is important to note that no statistically significant CV benefit was seen during the 6.5 years of the active DCCT. If there had not been a long term post-trial observational period, the conclusion would have been that good glycemic control had no CV benefit. In fact, this was not the case, but instead, emergence of benefit was delayed. This long-term benefit due to previous intensive glycemic therapy is often referred to as "metabolic memory".

The United Kingdom Prospective Diabetes Trial (UKPDS)

As in the follow-up of type 1 diabetes patients, data from a 10 year observational follow-up of the type 2 diabetes UKPDS cohort also revealed delayed benefits of improved glycemic control (Holman, 2008). These benefits, as in the DCCT/EDIC occurred despite relatively similar A1c levels in both groups following completion of the active trial phase.

During the interventional part of the trial, the benefits of glycemic control were most evident for microvascular endpoints. However, during the 10 year observational follow-up, other consequences of good glycemic control emerged, including reduced incidence of diabetes-related death, myocardial infarction and death from any cause. Importantly, reductions in hard outcomes required time to become apparent. The myocardial infarction and mortality benefits did not appear until about the 6th and 9th year of post-trial follow-up, respectively. These important findings suggested that the phenomenon of "metabolic memory" is seen in type 2 as well as in type 1 diabetes. Moreover, as was true for the DCCT/EDIC, if there had not been a long term post-trial observational period in the UKPDS, the conclusion would have been that good glycemic control had no clear CV benefit. In fact, this was not the case since there was a substantial benefit, but again, its emergence was delayed.

Why is long term observational follow-up of the VADT cohort crucial?

The lessons of the DCCT/EDIC and the UKPDS follow-up studies are that some of the most important findings come long after the initial intervention. The important CV benefits of glycemic control in type 1 diabetes in DCCT/EDIC were seen after about 17 years of follow-up (including 12 years after the end of the intervention trial). The important CV benefits of glycemic control in type 2 diabetes in the UKPDS Follow-up were seen after about 20 years of follow-up (including 10 years after the end of intervention). Observational periods need to be long, or incomplete, indeed erroneous, conclusions can be reached. The practical implications are enormous. The major killer of people with type 2 diabetes is CV disease. Intensive glycemic control is expensive, increases risk for hypoglycemia and requires substantially more effort on the part of the patient and the physician than non-glycemic pharmacologic prevention/treatment of CV disease. Therefore, extended follow-up of the VADT cohort is crucial since it will answer whether or not the very large human and financial investment in attaining meticulous glycemic control to an A1c < 7% actually reduces vascular outcomes over the long-term in patients with advanced type 2 diabetes and excellent non-glycemic risk factor control. By the end of the current funding of the VADT follow-up study in mid 2012, there will be only 4 years of follow-up. The experience of DCCT/EDIC and UKPDS Follow-up Studies has shown this is not long enough. Indeed, because of inherent delay in data capture in several national databases, our 4 year follow-up actually represents far less observation time for several major endpoints. For example, recent mortality data have an ~ 1.5 year delay before they can be accessed in the National Death Index database. Therefore, we will have only approximately 2.5 years post-trial follow-up on this important endpoint if the VADT-FS is not extended, not nearly enough to ascertain a complete and accurate picture of glycemic intervention.

The VADT Follow-up Study will provide unique information, complementary to other studies.

It is essential to note that an extended follow-up of the VADT cohort is not redundant with other studies. Indeed, it will be complementary. The DCCT/EDIC studied young participants with type 1 diabetes with few comorbidities not older type 2 diabetes patients. There are also many differences between the UKPDS and the VADT. First, the UKPDS was conducted in newly diagnosed type 2 individuals with little CV disease; while the

VADT enrolled people with diabetes diagnosed on average 11.5 years previously and with prevalent CV disease or substantial CV risk factors. Second, the A1c separation between intensive and control groups (1.5%) was nearly twice as large in the VADT compared to the UKPDS (0.9%) on average. Moreover, the glycemic separation in the VADT was achieved within 6 months and maintained for the duration of the study. In the UKPDS, A1c levels in the “intensive” treatment arm rose steadily throughout the study and had reached an A1c of about 8-8.2 % by the time the study concluded. Third, in contrast to UKPDS, both treatment groups in VADT maintained mean LDL cholesterol, triglycerides, and blood pressure levels below the target levels of the American Diabetes Association. The UKPDS patients had less than optimal lipid control (LDL-C about 127 mg %) and, arguably, less than optimal systolic blood pressure (~ 137 mmHg) (Holman, 2008). This will allow the VADT Follow-up to answer a question which the UKPDS could not answer, namely whether or not, over a prolonged post-trial observation period intensive glycemic control produces benefits beyond that achieved by optimal treatment of other CV risk factors (Duckworth, 2006; Duckworth, 2009; Meyers, 2006; Riche, 2007). Fourth, the UKPDS was predominantly a study of monotherapy, without the use of modern glycemic treatment regimens, such as combination therapy with glitazones. The ACCORD study group is also conducting a follow-up study, but this does not render the VADT-FS unnecessary. Indeed, the results from these two follow-up studies will undoubtedly be complementary and provide a more complete understanding of the long-term effects of improved glycemic control. Although study participants were relatively similar in age, duration of diabetes and CV risk, there were substantial differences in study design and conduct. Within the VADT, A1c separation was greater than in ACCORD (1.5% difference versus 1.1%) and occurred over different A1c ranges. In ACCORD, the standard group achieved a median A1c of 7.5%; the intensive group, 6.4%. In the VADT, the standard group achieved a median A1c of 8.4%; the intensive, 6.9%. The VADT trial was longer (5.6 years) than the glycemic arm of ACCORD (3.4 years). While there was excellent and essentially identical non-glycemic risk factor management in VADT, the ACCORD study, by design, was a multifaceted trial which also compared blood pressure target levels and lipid control strategies. Finally, while the long term data from ACCORD will be extremely interesting and important, it is unlikely that the ACCORD protocol will ever be recommended for use in practice given its significant 22% increase in all-cause mortality found in short-term follow-up. Thus, the VADT Follow-up Study is the only study in progress that can provide critical information on long-term CV effects (or lack of them) of an aggressive, but reasonably safe, glycemic intervention in those with advanced diabetes.

Microvascular Outcomes

Although the primary outcome assessed in this application has been, and will continue to be, a composite of cardiovascular outcomes, a secondary outcome includes microvascular disease, so it is appropriate to consider that as well.

What have we learned from controlled clinical trials?

Follow-up of the VADT cohort will also permit assessment of long term impact on glycemic control on microvascular endpoints, for which there is limited randomized controlled trial data. Diabetes is the leading cause of irreversible blindness, renal failure and amputation in adults in the US, and each of these microvascular complications are strongly associated with poor glycemic control (CDC, 2005). Randomized controlled

trials in both type 1 and type 2 diabetes have produced grade A evidence that improved glycemic control reduces onset of early microvascular findings (such as new retinopathy and proteinuria) and progression from early to moderate disease (e.g., progression from background retinopathy to requiring retinal photocoagulation [laser therapy]) (DCCT Research Group, 1993; UKPDS Study Group, 1998a; Duckworth, 2009; ACCORD Eye Study Group, 2010). This is supported by findings from most, but not all, older, smaller trials from Norway, Denmark, Sweden, Japan, the Kroc Foundation and by the VA Cooperative Study in Diabetes Mellitus (VACSDM), the feasibility trial for the VADT (Kroc Collaborative Study Group, 1984; Dahl-Jorgensen, 1988; Feldt-Rasmussen, 1991; Reichard, 1993; Shichiri, 2000; Levin, 2000; Beulens, 2009). Although the UKPDS found a statistically significant reduction in the need for retinal photocoagulation, no randomized clinical trial has reported any improvement in patient function (such as vision, pain or health-related quality of life), end-stage events (such as end-stage renal disease or amputations) or diabetes-related mortality over 8 months to 10 years (Kroc Collaborative Study Group, 1984; Dahl-Jorgensen, 1988; Feldt-Rasmussen, 1991; Reichard, 1993; DCCT Research Group, 1993; UKPDS Study Group, 1998a; Shichiri, 2000; Levin, 2000; Duckworth, 2009; ACCORD Eye Study Group, 2010). Demonstrating improvements in these clinically relevant outcomes however is the most important measure of the value of improved glucose control. However, progression of microvascular complications to clinical endpoints is slow and as with CV disease, long-term follow-up is essential to firmly establishing a causal link. Unfortunately, as noted above, the VADT, ACCORD and ADVANCE study durations were only 3.5 to 5.6 years, much shorter than needed to observe differences in transition to end-stage complications.

What have we learned from post-trial observation of patients who had been in controlled clinical trials?

The extraordinary importance of long term follow-up to determine benefits of glucose lowering on microvascular complications is well illustrated by the DCCT/EDIC study. While there was an effect of blood glucose improvement on a surrogate renal outcome (proteinuria) in DCCT, there was no demonstrable benefit on a hard outcome like glomerular filtration. However, the DCCT/EDIC did demonstrate that those individuals who had had good control during the DCCT had kidney protection at 17 years of follow-up, a dozen years after the interventional trial ended, evidenced by fewer patients with creatinine > 2 mg/dl (Nathan, 2005). It is also important to note that no hard renal endpoint benefit was noted in an earlier EDIC/DCCT publication, with a four year post-trial observation period, so it takes substantial time for this to emerge (DCCT/EDIC Research Group, 2000).

To our knowledge, there is very little other clinical trial data on long term impact of glycemic control on hard microvascular endpoints. The UKPDS reported a sustained benefit on a composite microvascular endpoint, but this was solely due to a reduction in retinal photocoagulation (Holman, 2008). Although this outcome may establish the physiological effects of glycemic control, retinal photocoagulation is a low-risk outpatient procedure and most patients who undergo appropriately timed photocoagulation do not have diabetes-related short-term visual impairment. Furthermore, retinal photocoagulation was not a pre-specified outcome in the original UKPDS protocol. Finally, the VADT had much better blood pressure control than the UKPDS. Since improved blood pressure

control substantially reduces renal and retinal diabetes complications, the impact of intensive glycemic control on even the intermediate outcome of photocoagulation may now be substantially less, especially in older patients like those in the VADT. In contrast, it could be greater since a greater proportion of VADT patients began the study with early diabetic retinopathy.

This suggestion of delayed hard endpoint microvascular benefit in DCCT/EDIC and the lack of other clear clinical trial hard endpoint data in those with type 2 diabetes will make the VADT Follow-up even more valuable.

Objectives

CSP #465-F is an observational follow-up study of the surviving VADT cohort (the VADT-FS), which has two major objectives:

1. To determine the long term effects of intensive glycemic control in type 2 diabetes on major cardiovascular complications (primary outcome), and
2. To determine the long term effects of intensive glycemic control in type 2 diabetes on five secondary outcomes: a) cardiovascular mortality, b) major microvascular complications, c) health-related quality of life, d) total mortality, and e) major microvascular or macrovascular (*end-stage renal disease, amputation for either ischemic or non-ischemic gangrene, CV-related death, or nonfatal MI, stroke, or new CHF*).

Research Design and Methods:

Study Subjects.

VADT Recruitment & Baseline Information: To be eligible for the VADT, subjects had to be over 40 years old, have type 2 diabetes and be non-responsive ($A1c > 7.5\%$) to a maximum daily dose of one or more oral agents or on insulin. Any of the following conditions resulted in exclusion of the patient from enrollment in the VADT:

- angina pectoris, Canadian Class I-II
- congestive heart failure, Class III-IV
- stroke, incapacitating or in last 6 months
- AMI or invasive cardiovascular procedure within the past six months,
- ongoing diabetic gangrene,
- BMI > 40,
- hemoglobinopathy that interferes with A1c monitoring,
- serum creatinine > 1.6 mg/dL,
- fasting C-peptide < 0.21 pmol/ml,
- ALT > 3 times normal or serum bilirubin > 1.9 mg/dL,
- malignancy or noncardiac life-threatening diseases making life expectancy < 5 years,
- autonomic neuropathy,
- symptomatic pancreatic insufficiency (endocrine or exocrine),

- recurrent seizures within the past year,
- hypopituitarism,
- pregnancy, lactation, or planning a pregnancy,
- active psychosis or substance abuse,
- lack of access to a person who can assist or be called in an emergency,
- underlying conditions that in the site PI's judgment may prevent adherence to protocol,
- current participation in another clinical trial.

Almost 18,000 patients were pre-screened using medical record review and those who appeared potentially eligible after pre-screening were contacted for detailed screening. 1,791 subjects were enrolled into the VADT over a 30-month period. The most common reasons for exclusion were A1c < 7.5% (34%), not on insulin or a maximum dose of an oral agent (16%), unwilling to participate (12%), renal insufficiency (8%), PI did not approve patient (5%, with the most common reasons given being patient lives too far away, has multiple comorbid conditions, or has history of frequent no-shows), and BMI > 40 (5%). The baseline characteristics of the 1,792 subjects enrolled are shown below in Table 1.

VADT-FS Main Cohort

In brief, subjects have been recruited to receive periodic surveys and to have VA EMR data collected centrally, as well as allow reviewing their non-VA hospital records. Consented subjects are very similar to surviving VADT not-consented subjects on a host of baseline attributes, demonstrating the sample is highly representative.

VADT-FS Mortality Analysis Cohort

In addition to the VADT-FS Main Cohort, the Ann Arbor Center has received IRB approval to conduct long-term mortality analyses on all original VADT subjects except for the 152 subjects who withdrew consent during the VADT (N=1639, 91.5% follow-up). The VA Ann Arbor IRB granted a "HIPAA waiver" in July 2011 that permits determination of cause of death using National Death Index data using a special analytic protocol that protects patient anonymity. Investigators at the Ann Arbor VA HSR&D are very experienced in conducting such analyses. Per IRB protocol, these analyses will be conducted in a fully blinded fashion (ie, the data manager accessing the follow-up mortality information will merge this information to the VADT unique ID, but will not have access to the VADT dataset itself, and the investigators and data analyst will not have access to subject's true identity or treatment arm. Below, we refer to this cohort as the "VADT-FS Mortality Analysis Cohort" to distinguish it from the Main Cohort. VA Ann Arbor HSR&D will send the data to Hines CSPCC in a secure way following VA regulations for the interim and final analyses.

Table 1. Baseline characteristics of VADT enrollees (N =1,791)

Age (yrs)	60.5 ± 8.7
Duration of diabetes (yrs)	11.5 ± 7.5
Men	1,736 (96.9%)
Race/Ethnicity	
Non- Hispanic White	1,112 (62.1%)
Non- Hispanic Black	299 (16.7%)
Hispanic	291 (16.2%)
Other	90 (5.0%)
Currently employed	735 (41%)
College graduate	367 (20%)
Previous macrovascular event	724 (40.4%)
Current cigarette smoker	257 (14%)
Hypertension	1293 (72%)
Diabetic neuropathy	761 (43%)
BMI (kg/m ²)	31 ± 4
A1c(%)	9.4 ± 1.4%
Systolic BP (mmHg)	132 ± 17
Diastolic BP (mmHg)	76 ± 10
Total cholesterol (mg/dL)	183 ± 47
LDL cholesterol (mg/dL)	108 ± 32
HDL cholesterol (mg/dL)	36 ± 10
Triglycerides (mg/dL)	212 ± 275

The intervention and control subjects were similar in major demographic characteristics, baseline metabolic control and in key CV risk factors, suggesting that randomization was successfully achieved.

VADT Protocol and Subject Follow-up:

Detailed information on the VADT protocol can be found in the main manuscript published in January, 2009, in the New England Journal of Medicine (Abraria et al., 2009), however, here we include some background and key aspects relevant to the VADT-FS. The VADT was designed to do the best job possible of isolating the effects of hyperglycemia in patients with type 2 diabetes. In order for the study to address different levels of glycemic control, and minimize potential medication specific effects, the protocol strove for both treatment groups to receive near-equal distribution of therapeutic classes (insulin segretagogues and sensitizers, exogenous insulin) with ultimately, the main difference between treatments arms expected to be related to the dose of insulin. In addition, the VADT protocol tried to achieve optimal management of all other CV risk factors in both intervention and control patients to answer the question, “What is the incremental benefit of intensive glycemic control once blood pressure, lipids and other CV treatments are optimized.

The success of the VADT protocol in achieving the above goals has been impressive and is a tribute to the hard work and dedication of the VADT site investigators, and especially, the nurse coordinators. The VADT achieved and has maintained substantial A1c separation since year 1 1/2 of the trial (averaging a 1.5 point A1c median separation, with the A1c being 6.9 in the intensive arm and 8.4% in the standard treatment arm.

The goal of complete matching of the standard and intensive arm subjects with respect to the number of hypoglycemic medications has not been completely achieved. However, the two groups are much more similar in this regard than might be expected given the large A1c separation. In year 5 of follow-up, the average number of glycemic medications was 2.6 in the standard treatment arm and 3.4 in the intensive treatment arm. Most of this difference is due to a higher use in the intensive arm of glimepiride (Amaryl) (45% vs. 58%), rosiglitazone (Avandia)(54% vs. 66%), and precose (Acarbose)(2% vs. 15%). In year five of the study, 75% of standard therapy patients were on insulin compared to 88% of the intensive therapy patients (Duckworth et al., 2009).

Treatment of CV risk factors in the VADT has been superb in both treatment arms as per protocol. For example, in year 5 of follow-up, 95% of patients were on aspirin or some other anti-platelet/anti-coagulant, 84% were on a statin, and the mean blood pressure was 126/70mmHg. Each of the above have been achieved almost identically in the standard and intensive therapy arms. With regard to lipid levels, in year five the VADT study population had a mean LDL cholesterol of 84mg/dL \pm 29 and a median of 77mg/dL, with almost 80% of the study population having levels < 100mg/dL. Intolerance of statin therapy was the main reason for not achieving an LDL < 100mg/dL(Duckworth et al., 2009).

VADT-FS Recruitment

All active VADT study subjects will be approached for participation in the VADT-FS. To maximize retention it was imperative that consent for VADT-FS be initiated prior to May 2008, when the study protocol ended, subject contacts with the nurse coordinators ended and patients returned to routine primary care. Therefore, we planned to initiate the IRB approval process in Fall 2007 in anticipation of beginning the consent process in Spring 2008. We planned to utilize the then current site coordinators to inform subjects of the purpose, procedures and requirements of the VADT-FS, and obtain informed consent. Some of the study sites were unable to complete recruitment by the conclusion of the main study protocol and their funding for the nurse coordinator have stopped. Due to little local study activity and/or regulatory issues at the local sites, five of the twenty sites were prematurely closed. For similar reasons, other sites are considering closing in the future. A sixth site was suspended (due to issues having nothing to do with the VADT or the VADT-FS). In order to prevent losing the consented patients at these sites and for the smooth continuation of the currently consented patients, several strategies were planned and have been undertaken. These are under the direction of the follow-up study's new Co-Chairmen at the Hines and Phoenix VAMCs and the two national coordinating centers, Ann Arbor VA HSR&D (AA HSR&D) Center of Excellence and The Hines VA Cooperative Studies Program Coordinating Center (Hines CSPCC) as follows.

Currently, there are three groups of patients. Group #1 consists of those VADT patients who consented to participate in VADT-FS but who are at sites where the VADT-FS has been closed. Group #2 consists of those VADT patients who consented to participate in VADT-FS and who are at sites where the VADT-FS is still open. Group #3 consists of individuals who were in VADT, but never consented to the VADT-FS. The requested process for each group would be different.

Group #1

For this first group, those VADT patients who consented to participate in VADT-FS but who are at sites where the VADT-FS has been closed, the VADT-FS consent form is no longer active. We plan to take either of two approaches. In one approach, we plan to contact these individuals regarding their local site study closure. We will invite them to continue participation, and have the informed consent process handled centrally by the national study staff (who will be located at Hines); Hines would also become the sole IRB for the VADT-FS.

The process would be as follows:

1. National study staff at Hines will obtain participant contact information from the Ann Arbor HSR&D and the Hines CSPCC.
2. National study staff will mail a cover letter addressing local site closure and the informed consent forms (including HIPAA) to all patients at closed sites whose initial consent forms are no longer valid. The cover letter would explain that the study was closed at their hospital, but that oversight would be transferred to Hines, and inviting them to continue participation. The complete consent form would have this change (i.e, transfer of oversight to Hines IRB) highlighted.
3. Seven to fourteen days after the mailing, the National study staff will attempt to contact the individual by phone to see if he or she has any questions about the

study or forms.

4. After approximately two weeks, those who have not yet responded will undergo a repeat mailing and follow-up phone contact by the National study staff.
5. Those who do not respond after two rounds of contact will be considered passive refusals for re-entry into the study.

A second approach would be to work with formerly local PIs at closed sites to re-open those sites and consent patients locally. Those patients would then be transferred to the supervision of the Hines IRB, as described under Group #2, below.

Group #2

For this second group, those VADT patients who consented to participate in VADT-FS and who are at sites where the VADT-FS is still open, we plan to transfer oversight to the Hines IRB which would become the sole IRB for the VADT-FS.

The process would be as follows:

1. National study staff at Hines will obtain contact information from the Ann Arbor HSR&D and the Hines CSPCC.
2. National staff will mail an explanatory and “opt-out” letter to all VADT-FS participants at open sites. The letter would explain that the study was continuing unchanged except that oversight would be transferred to Hines. It would give them an opportunity to opt-out of further participation, should they choose not to be “transferred”.
3. If the subjects do not respond two weeks after the initial mailing, they will be mailed the letters again.
4. After the second mailing and no response in two weeks, the subjects are considered enrolled under the oversight of the Hines IRB since they have had the opportunity to opt out and did not do so.
5. Then local sites can be closed out with instructions from the Project Manager.

Group #3

For this third group, those VADT patients who had never previously consented to participate in VADT-FS and who are at sites where the VADT-FS is still open, we plan to recruit potential participants in a non-targeted fashion and subsequently transfer oversight to the Hines IRB (as with group #2) which would again become the sole IRB for these VADT-FS participants.

1. Local staff would use non-targeted recruitment approaches similar to a newspaper or flyer advertisement that are consistent with Hines IRB policy. These flyers, ads or information sheets would include contact information for the VADT-FS study.
2. Once consented, these subjects would fall into Group #2 category and would be handled in a similar fashion as that group.

The local site investigators, their ACOS for R & D, and the Chairperson of the local IRB

will be informed of all these processes, and may contact the National Co-Chair's Office with questions.

Therefore, in the consent process we ask permission for conducting an annual survey and allowing the research team to follow their future health care and outcomes using a variety of data sources, including inspection of their VA and non-VA medical records, data from the Centers for Medicare and Medicaid Services (CMS), and VA and US death records (see Data Collection section below). We inform them that they will receive a small payment of a \$10 gift card for completion of the questionnaire and that the questionnaire has been pilot tested to make sure that it usually takes no longer than 30 minutes to complete. Subjects are also informed that they can choose to complete the questionnaire by phone if they prefer. Each subject is asked to assign a surrogate authorized to report vital status or health events (and provide a release of information) if the study subject is unable to do so. Of course, subjects are also informed that participation in the VADT-FS is completely voluntary and that they can revoke their consent at any point in the future.

We cannot be certain what will happen to the risk factor management of the VADT cohort once they return to routine VA primary care. If the previous experience of the DCCT-EDIC (Nathan, 2005) and the UKPDS Cohort hold true, then eventually both arms may converge toward a median A1c of about 7.8 – 8.0%. We suspect that the two study arms will have excellent and similar CV risk factor management during the observational follow-up period. Blood pressure and LDL levels are currently comparable in the two study arms, and based upon current VA-wide levels, we expect that blood pressure and LDL will remain generally well controlled during follow-up, at least compared to national averages. (Kerr, 2004; Asch, 2004; Kupersmith, 2007; Saydah, 2004)

VADT-FS Retention and Completion of Follow-Up

Consented VADT-FS study subjects will be followed until the end of the study unless they withdraw their consent. The VADT-FS will also utilize several techniques to maximize a high level of study subject retention. For example, subjects who do not respond to the 3 mailed survey contacts will be contacted by phone and if that is not successful we will then try to contact their designated surrogate. If a subject does not complete the survey in a given year, the following year we will once again attempt to contact them as outlined above, unless they have withdrawn their consent. In addition to obtaining contact information on the study subject and their surrogate at the time of recruitment, we will obtain contact information for someone not living with the study subject who the study subject feels is likely to know how to contact the study subject over the next 10 years.

Data Collection Sources:

In order to ensure the integrity of the data a new unique ID number has been assigned to all patients involved in the VADT-FS. The unique ID consists of a five-digit number randomly assigned and has no reference to the original study ID or study site. The Hines CSPCC retains the cross-link between the Long Term Follow-up ID and the CSP #465 Study ID.

a) *Self Report*. All consenting subjects have been given a toll free number and a return prepaid envelope to use to notify the Clinical Data Collection Center in Ann Arbor when any of the following occurs: 1. self-reported health status, 2. occurrence of study end-points (see below), and 3. outpatient visits, hospitalizations and procedures, including whether this care was provided inside or outside of VHA (names of hospitals and permission for medical record release will be obtained if non-VA inpatient care or procedures were received in the prior year in those not Medicare eligible (age <65). The initial mailed survey instrument is accompanied by a \$10 gift card, and we will follow the modified-Dillman protocol thereafter (Dillman, 2007). A thank-you/reminder letter will be sent within 2 weeks of the first mailing. This letter will serve to thank those who have responded and encourage non-responders to submit their survey questionnaires. Individuals still not responding within 2 weeks of the post-card mailing date will be sent a second survey packet. One month following the 2nd mailing, a final mailing packet will be sent to those individuals who have not responded to the earlier mailings. Address information will be updated continuously during the trial; the main source of new address information will be the U.S. post-office. The addresses will be stored and updated by Hines CSPCC or Ann Arbor HSR&D via an electronic database behind the VA firewall (SharePoint). Access to this database will be limited to study personnel at each site that have a need to know. At 3 months we will attempt to contact subjects by phone, and if after intermittent attempts over 4 weeks do not succeed in reaching the subject, they will be considered a non-responder for that contact period.

Updates

The survey response rate was 83.6% in 2009, 81.2% in 2010, and 82.7 in 2011. Other than informing the Ann Arbor site about events that require adjudication, VADT-FS investigators are blinded to survey results. However, preliminary survey results and other endpoint data are periodically compiled by the Hines statisticians and presented to the DMC.

Assessment of VA electronic medical information systems files. We expect most VADT-FS patients will continue to get the majority of their care within VHA. In addition to VA's current central inpatient, outpatient, pharmacy and lab data repositories, newer data sources such as the Corporate Data Warehouse and National Diabetes Cube are expected to serve as a source for other important clinical information such as blood pressure.

We have obtained signed informed consent from most of the study subjects for access to their EMR during the informed consent process. We will continue to attempt to consent those who, for whatever reason, did not consent in the first place, we may have to re-consent those at sites where the VADT-FS has closed unless the site can be re-opened (see above). The Data Coordinating Center at Hines will be in charge of accessing information from the VA's central data repositories every 6 months (such as the Medical SAS datasets at Austin, which contain inpatient and outpatient data, and the DSS lab and pharmacy National Data Extracts). The Data Collection Center in Ann Arbor will be in charge of obtaining medical record information on selected patients with potential primary endpoints for adjudication by the Endpoint Committee. Both Hines and Ann Arbor have extensive experience with these respective activities in their past work, and have approved procedures for high-level data security. The VA diabetes registry and VA-CDC TRIAD study (which were collected and administered by the proposed Clinical Data Collection Center in Ann Arbor) revealed a

substantial portion of VA patients get their eye care, emergency care (such as heart attacks and strokes) and some elective procedures outside of VHA, requiring us to not rely solely on VA information systems, which is why we plan to collect information on non-VA events and obtain non-VA medical records for those reporting hospitalization and possible non-fatal primary endpoints for those patients younger than 65 (CMS data will be used for those > 65).

Updates

Our survey results have found that 92% of VADT-FS patients report getting the majority of their care within VHA and out-of-VA use has been much less than anticipated, thereby allowing excellent capture of patient information from central VA sources. Previous estimates were based on results found in the typical veteran utilizing the VA, whereas, the VADT appears to have recruited a sample with less dual-use. In the first 3 years of the VADT-FS, of the 54 self-reported new study end-points requiring adjudication (MI, stroke, CHF or amputation by patient survey) only 15 have required obtaining outside hospital records for adjudication. As outlined in the original protocol above, obtaining outside records is still required for those under age 65 reporting an MI or stroke patients at non-VA facilities and for those reporting amputations at outside facilities regardless of age, and we have had 100% success rate in obtaining non-VA records to date.

The Ann Arbor Center has IRB and VA CO permission to access the electronic medical record of VADT subjects at all study sites, so transfer of VA records to the Ann Arbor is unnecessary. This has greatly improved the efficiency and completeness of records available for review and adjudication. Although the process of obtaining records from non-VA facilities is very time consuming, the number of records that we need to obtain has been less than anticipated. In the first 2 years of the VADT-FS only 15 of the 130 (11.5%) self-reported new study end-points (MI, stroke, CHF or amputation by patient survey) have required obtaining outside hospital records. This and utilizing remote electronic access to VA EMR records has allowed for some reductions in the budget, particularly important in a time of increasing budget constraints.

c) Medicare data: Most subjects upon VADT completion were eligible for Medicare. By agreement between the VA and CMS, data on use of Medicare resources for medical services and records are available through the VIREC located at the Hines VA. VADT-FS investigators at the Clinical Data Collection Coordinating Center in Ann Arbor have previously worked with this database, which provides fairly comprehensive information on inpatient and outpatient utilization, diagnoses, procedures and outcomes for those veterans 65 years or older. Approval to access this information is included in the informed consent process. There was one caveat however – there was currently a hold on release of CMS information to VA investigators, due to a recent highly publicized data breach. It was a temporary situation, and that permission to access these data will be granted as it has been in our past studies. However, if access to CMS data on the subset of patients age 65 or older is not possible in the future, we would return to Cooperative Studies to expand our budget to allow seeking outside records for all non-fatal possible primary endpoints reported occurring at non-VA facilities.

Update

Medicare data for VA patients was not available during the first 2.5 years of the

VADT-FS, but it is now available. The Ann Arbor Center recently obtained IRB permission to obtain these data. Ann Arbor investigators are in the process of obtaining the data for the VADT-FS subjects aged 65 or older dating back to the start of the original VADT. From this point forward, the Medicare data for subjects will be updated as soon as it becomes available and will be combined with the VADT-FS data, along with information from the VA SAS Medical Datasets, maintained by the Austin Information and Technology Center. Past research has demonstrated that the combined Medicare/VA dataset is very accurate for major outcomes (Petersen 1999; Kiyota 2004), and we will use these data to identify subjects inside and outside of VA who have heart attacks, strokes, amputations, CHF admissions and dialysis based on diagnosis (ICD-9 codes) and procedure codes (CPT codes). 70.1% of VADT-FS subjects will be aged 65 or older at the beginning of this renewal, June 2012.

d) Mortality records. Mortality data will be obtained from the VA Vital Status files, which combine death dates from all sources currently available to VA researchers, including the Medical SAS Inpatient Datasets, the Veterans Benefits Administration's (VBA) Beneficiary Identification and Resource Locator System (BIRLS), the Medicare Vital Status file, National Death Index (NDI) and the Social Security Administration (SSA) death file. Since the Vital Status file contains Medicare data, as noted above, it is now currently available for research purposes. However, if the Vital Status file is not available in a timely fashion we will obtain mortality information from other accessible VA data sources including BIRLS, the Medical SAS Inpatient Datasets and the SSA death file. BIRLS, which is a primary data source for death information, contains approximately 10.7 million records and has an estimated 94.5% to 96.5% sensitivity (Fisher, 1995). A review of major US mortality databases found that the BIRLS-Death File had a high accuracy rate (Dominitz, 2001) and compares favorably with other national mortality databases. For classification of cause of death, hospital records and NDI will be obtained from individual hospitals and adjudicated by the Endpoint Committee (since cardiovascular death is a primary study end-point).

Update

In addition to Medicare data (see above), we are now obtaining data on fatal cardiovascular events from the NDI, which is maintained by the National Center for Health Statistics of the Centers for Disease Control and Prevention. The Serious Mental Illness Treatment Resource and Evaluation Center (SMITREC), a unit housed within Ann Arbor's COE HSR&D, maintains NDI data on all VHA users nationwide. The Ann Arbor Coordinating Center has an existing agreement with SMITREC to acquire the NDI information for our sample without charge. At present, SMITREC has NDI data available up until December 2008 and we expect to obtain 2009 data soon. There is an 18-24 month delay in obtaining NDI data, but this will still allow us to have at least 13 years of follow-up of disease-specific mortality by the end of the VADT-FS. If obtaining NDI data from SMITREC becomes problematic in the future, the Ann Arbor site will obtain these data directly from the NDI or from the VA appointed NDI data steward.

The lag for the VA Vital Status files is only about 6-12 months so this file will allow us to have 1 year additional follow-up for total mortality than we will have

for disease-specific mortality. Therefore total mortality will be obtained from the VA Vital Status files, which combine death dates from all sources currently available to VA researchers, including the Medical SAS Inpatient Datasets, the Veterans Benefits Administration's (VBA) Beneficiary Identification and Resource Locator System (BIRLS), the Medicare Vital Status file, and the Social Security Administration (SSA) death file. A review of major US mortality databases found that these sources are quite accurate for mortality (Dominitz, 2001).

Measuring Endpoints:

The following endpoints will always be adjudicated: 1) non-fatal cardiac-related admissions to non-VA hospitals in those which hospital discharge data are not available (those <65 years old who report such events on the survey), and 2) all amputations (to determine if the amputation was ischemic [a primary endpoint], non-ischemic gangrene [a secondary endpoint] or traumatic [neither a primary nor secondary endpoint]). Death and hospital discharge records will be relied upon for other endpoints at VA facilities (using central VA data) and CMS data will be used to capture events at non-VA facilities for over 65. Past experience has shown that discharge diagnosis for MI and stroke are highly accurate that the patient has truly had these events, and therefore such designations are generally relied upon in observational studies. This of course is not done in experimental studies in which investigators in the field may bias endpoint determination, a concern that does not exist in this observational follow-up study with central data collection.

When endpoint assessment and adjudication is needed, this will be conducted by the Endpoints Committee using an approach almost identical to the process used in the VADT study protocol. (Goldman, 2006) The Endpoints Committee will be comprised of a four person team to include two cardiologists, a neurologist, and a vascular surgeon, each of whom will be masked to subject's previous treatment assignment in VADT. There will be no changes from the VADT protocol in the *process* for adjudicating primary endpoints, but some "softer" endpoints will be dropped from the primary composite outcome (see below). As per the current end-point evaluation process, all reported hospitalizations, deaths or new symptoms or diagnoses that are even remotely suggestive of a primary endpoint, will have summary clinical information prepared for review by the Endpoint Committee. These clinical summaries of potential study endpoints will be prepared by the staff at the Ann Arbor Clinical Data Collection Site, under the direction of Rod Hayward, MD and Sarah Krein, PhD, RN. All Ann Arbor personnel and the Endpoints Committee will be blinded as to the subjects' previous randomized treatment status. Data sources for identification of potential end-points can be detected by patient self-report, by VA or CMS electronic information system data, or through death indices. The clinical summary information will be reviewed by the Endpoints Committee, who can render a decision or request additional information.

Endpoints that will be collected include:

(1)*Mortality*: categorized as, a) deaths secondary to cardiovascular disease including sudden death not otherwise explained, b) deaths secondary to neoplasm, c) deaths secondary to other causes, d) undetermined.

(2)*Major cardiac events*: categorized as, a) acute myocardial infarction resulting in hospitalization, b) stroke, c) new onset congestive heart failure, d) other.

(3) *Other cardiac event*: categorized as, a) cardiac surgery, b) cardiac angioplasty, c) other.

(4) *Peripheral vascular disease*: categorized as, a) surgical amputation for ischemic diabetic gangrene, b) arteriovascular events requiring bypass or angioplasty.

(5) *Renal Insufficiency*: categorized as, a) estimated GFR* 16 to 30 w/o dialysis (stage 4 chronic kidney disease), b) End-stage renal disease (ESRD) defined as GFR<15, dialysis or kidney transplantation.

(6) *Severe Visual Impairment*: defined as poor or worse visual function on the general visual function question on the National Eye Institute Visual Function Questionnaire.(Mangione, 2001; Naeim, 2006; Raphael, 2006)

(7) *Other major procedures/diagnoses*: categorized as, a) photocoagulation or vitrectomy, b) amputation.

(8) *Self-reported health status*: diabetes-related quality of life, using an instrument adapted for type 2 DM patients from the DCCT (Duckworth, 1998; Saudek 1996). This survey tool has been used since the inception of the VADT and will be continued in the annual survey.

* $GFR (mL/min/1.73 m^2) = 175 \times (Cr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$

As mentioned previously, the composite endpoint of the VADT-FS is somewhat more restrictive than that for the VADT. However, the protocol for determining all components of the VADT-FS's composite endpoint will be identical to that used during the VADT (outlined in Appendix B), with two exceptions. Due to the absence of routine study examinations in the VADT-FS, we do not have standard collection of periodic electrocardiograms, visual acuity, or retinal examinations after May 2008, the end of the VADT. By VADT protocol, new ECG findings consistent with a myocardial infarction (such as new q-waves) could have resulted in a determination of the subject reaching the AMI endpoint even in the absence of symptoms, hospitalization or a clinical diagnosis. However, in the absence of standard collection of ECG's from study subjects, we feel that to use ECG's ordered for clinical indications as part of the primary composite endpoint could introduce substantial ascertainment bias (only those having ECG's ordered by their providers can meet the primary endpoint through this criterion). In addition, although this endpoint has been shown to be diagnostically valid (high specificity for the subject having truly had a sub-clinical AMI), the clinical implications of these subclinical events are less clear. For example, the economic costs and patient morbidity are minimal to none in the short-term and the long-term morbidity and mortality risk implications of these subclinical infarctions have not been well studied. Therefore, since the VADT-FS proposes dropping "softer" endpoints from the primary composite outcome (see below), dropping subclinical heart attacks could be justified on those grounds alone. For the above reasons, only acute myocardial infarctions that result in hospitalizations will be considered as part of the primary composite endpoint for the VADT-FS.

Although eye disease is not a component of the VADT-FS's primary outcome, it is a very important component of a secondary outcome (major microvascular events). As above, the discontinuation of standard routine physical examinations makes continuation of visual acuity and retinopathy stage determinations problematic. Fortunately, there is now available a patient self-report visual function tool that has been developed with NIH support.(Mangione, 2001; Naeim, 2006; Raphael, 2006) This National Eye Institute Visual Function Questionnaire includes a validated single question for general visual function, and those reporting poor or worse function on this item have been validated to have substantial functional impairment impacting their quality of life (Mangione, 2001 and personal communication with Dr. Carol Mangione in January 2007). Although caution is always advised when including a new measure during the course of a longitudinal study, we feel that the adoption of this validated item measuring marked visual impairment is preferable to dropping measures of visual function altogether. Patients with reported visual problems will be informed that they can complete their surveys either using the assistance of their designated surrogate or by telephone, whichever they prefer.

Primary study end-point:

Major CV events (non-fatal MI resulting in hospitalization, non-fatal stroke, new CHF, amputation for ischemic diabetic gangrene, or CV-related death).

The proposed primary end-point of the VADT-FS is slightly more restrictive than the primary end-point of the VADT [excluding some CV procedures and subclinical AMI's based upon ECG changes alone] because the increased statistical power of the VADT-FS will allow greater focus on major clinical outcomes and avoid outcomes that are more difficult to discern (e.g., worsening of symptoms) or are more discretionary (e.g., cardiac

procedures).

Major secondary end-points:

1. CV mortality
2. Major microvascular complications (end-stage renal disease, or amputation for non-traumatic, non-ischemic diabetic gangrene).
3. Health-related quality of life (as measured by the modified DCCT tool on a 0-100 point scale)
4. Total mortality

Update

We have revised the composition of our adjudication team, which now includes 2 hospitalist physicians and a cardiologist. This change was made because fewer neurological and cardiac outcomes are being adjudicated in the VADT-F than in the original VADT, making hospitalists an excellent choice for the adjudication committee.

We propose adding a fifth secondary end-point: Major microvascular or macrovascular complication (*end-stage renal disease, amputation for either ischemic or non-ischemic gangrene, CV-related death, or nonfatal MI, stroke, or new CHF*).” *This secondary endpoint was added for two reasons. First, this is a composite of all major micro- and macro-vascular endpoints and therefore has better statistical power and great clinical importance. Second, this also helps when making direct comparisons with other trials.* The addition of this outcome was recommended by the Executive Committee, who is blinded to all outcome data in the VADT-FS and therefore this recommendation was made without any knowledge of results to date. (Note: New CHF will be determined by a subject having either: 1. A hospital stay with a primary discharge diagnosis of CHF, or 2. chart review finding an ejection fraction on echocardiogram estimated as being below 40%.)

Healthcare Utilization & Cost Data

Initial collection of recent data on healthcare utilization and costs incurs a fairly modest cost, but such data collection can be much more expensive when done retrospectively. Therefore, we will obtain permission to collect this data, but no initial funds are being requested for data cleaning and analysis. (Barnett, 2003; Wagner, 2003; Phibbs, 2003) Funds for analysis of data on total direct healthcare costs will be requested in a separate proposal, and funds for formal cost-effectiveness analysis will only be requested if the intervention is eventually shown to produce statistically significant benefit. This is similar to incurring the small costs of storing extra sera to be analyzed as indicated. We estimate that the cost to obtain and store this data at the same time that we obtain information on potential outcomes to be < \$10,000 a year.

Update

We propose stopping the collection of full cost data, in part to trim the budget during a time of increased budgetary constraints, but also because we feel that we now have adequate data for cost accounting. If future cost analyses are needed, the costs associated with study events to date (i.e. amputations, renal failure, visual

impairment, MI, etc) can be used to estimate the costs of subsequent events. However, in addition to the major complications and procedures listed above in the Endpoints Section, we will also continue to collect information on the number of outpatient visits, hospital and ICU days, and total pharmacy costs, since these are easily collected centrally and account for the majority of medical care costs associated with diabetes care and complications.

Study Organization and Administration:

Study Co-Chairs

Central Office had approved a change in co-Chairmanship from Drs. Abaira and Duckworth who will continue to serve as the co-Chairs Emeritus of the study to Drs. Reaven and Emanuele. The co-Chairs will have primary responsibility for oversight of the study, in close collaboration with the Executive Committee, the Cooperative Studies Program Coordinating Center at Hines and the Clinical Data Collection Center in Ann Arbor. They will also serve as the Co-Chairs of the Executive Committee.

The Cooperative Studies Program Coordinating Center

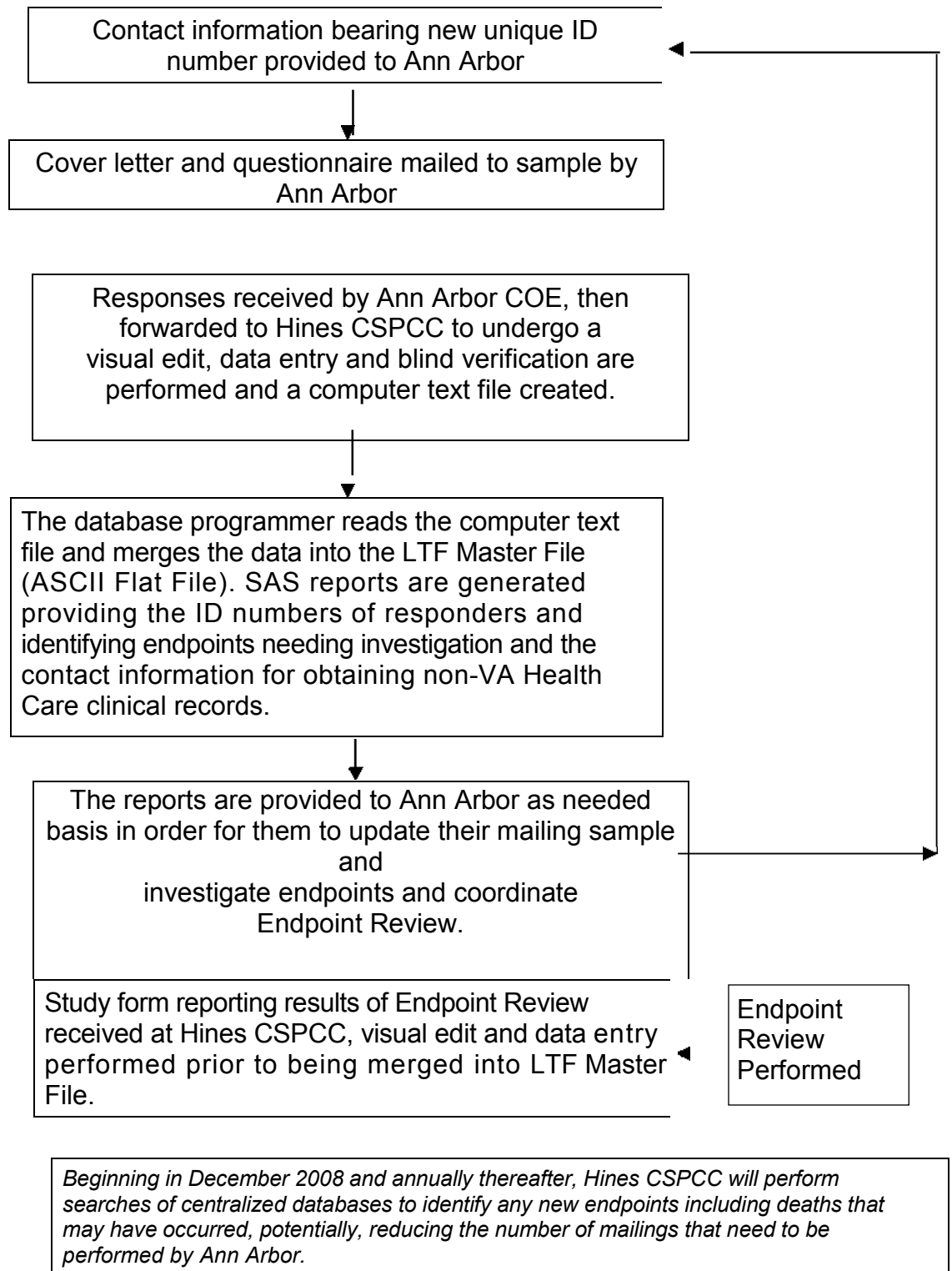
The Hines Cooperative Studies Program Coordinating Center (CSPCC) will continue to serve as the Data Coordinating Center for the study. The Hines CSPCC will coordinate all administrative activities for the study. The Hines CSPCC will have principal responsibility for all analyses. They will also prepare the endpoint analyses needed for interim reports and will be responsible for archiving and documentation of all study data at completion of the study.

The study subjects will be contacted annually, with the initial contact scheduled that began in June 2009 so as to establish a baseline for the quality of life data. Responders data will be received by the Ann Arbor who will send the data to Hines CSPCC, at the Ann Arbor the surveys will undergo an initial visual edit and then forwarded for data entry and verification before being added to the Master Study Data Base. Response information will be provided to the Ann Arbor VAMC to allow for repeat mailings and reminders to be sent to non-responders. The anticipated data flow is presented in Figure 1.

Although all data will eventually reside at the Hines CSPCC, personnel at the Ann Arbor VAMC will be responsible for updating the patient's contact information so as to facilitate the annual survey mailings. The Hines CSPCC will forward any updates in contact information that they receive to Ann Arbor for incorporation in the Contact Data Base. Ann Arbor VAMC will periodically (at least annually) provide the Hines CSPCC with a copy of the most recent Contact Data Base. At Hines CSPCC the Contact Data Base will be stored in a computer directory separate from the study data, the file will be encrypted and password protected.

Computer programs developed by the Ann Arbor will evaluate the health survey responses received to determine if a new end point has been reported or is suspected. Ann Arbor VAMC will be provided information on any endpoints that need further investigation, i.e. collection of non-VA medical record information and adjudication, blinded to the treatment.

Figure 1. **Data Flow**



The adjudication form for each event investigated will be forwarded to the Hines CSPCC for data entry and inclusion in the Study Master File.

The Clinical Data Collection Center

The Ann Arbor HSR&D Center of Excellence (COE) will have principal responsibility for centralized data collection of medical record information necessary for adjudicating endpoints (data not readily available from national data sources) and providing this data to the Data Coordinating Center at Hines for integration with the comprehensive study database. The Clinical Data Collection Center will also have principal responsibility for informing the Hines CSPCC of updated contact information on study subjects and answering patient questions related to the study. Further, this site will continue to collect resource utilization and cost information, as it has since the beginning of the VADT. Finally, they will be in charge of obtaining and preparing clinical summaries for endpoint adjudication by the Endpoint Committee, completing the final adjudication form and forwarding it to Hines CSPCC for inclusion in the Master File.

Update

Ann Arbor Coordinating Center: During the course of data collection for the VADT-FS thus far, it has become clear that there are clear advantages to having the VA Ann Arbor HSR&D Center of Excellence take over all central data collection activities. The Ann Arbor Center was in charge of many of these activities from the outset of the VADT-FS, so this is just a consolidation of data collection activities. The Ann Arbor Center has extensive experience and ongoing studies that utilize all of the datasets being used for central data collection in the VADT-FS. In addition to improved economies of scale, consolidating all these activities at the Ann Arbor Center will decrease the chances of confusion or miscommunication that can occur when responsibilities are divided across Centers. The Ann Arbor HSR&D Center will access the information from VA's central data repositories every 6 months (such as the Medical SAS datasets at Austin, which contain inpatient and outpatient data, the DSS lab, the Pharmacy Benefits National Data Extracts, and Medicare files) and review medical record information on selected patients with potential primary endpoints for adjudication by the Endpoint Committee (see below). They will also continue to conduct the patient survey. The Ann Arbor Center will then deliver these data to the Hines Cooperative Studies Center for data analysis, along with full documentation of data collection details. Dr. Hayward will lead this effort and be directly responsible for oversight and coordination of these data collection activities. All investigators and staff in Ann Arbor are working with fully blinded data except for the data manager, who needs access to unique patient identifiers to allow her to obtain new follow-up data from central databases. Jennifer Davis is an experienced and expert data manager, but she has no access to other VADT or VADT-FS data, and has no other role in the VADT-FS other than the initial data pull and is blinded to treatment arm.

Hines VA Coordinating Center: The Hines Cooperative Studies Center will continue to be in charge of all statistical analyses, including verification that all primary analyses conducted are fully prespecified. All analyses must be initially approved by the Hines statistician and final analyses and output verified by Hines

statistician(s).

Executive Committee

The Executive Committee will be the major decision-making body with primary responsibility for study management. The committee will direct operational aspects of the study, decide on all proposed changes in the protocol, and decide on all uses of study data. In the latter role, the committee will make all decisions regarding publication policies and will review all manuscripts and abstracts from the study and approve these for submission. Initially, the Executive Committee will have monthly conference calls, with the frequency of ongoing conference calls to be decided by the Executive Committee members.

Data Monitoring Committee:

Since the VADT-FS is an observational study and includes no research related clinical interventions, the main task of the Data Monitoring Committee will be to assure data quality, ongoing blinding of the study results, adherence to the pre-specified analysis plan, overall study progress and whether assumptions regarding statistical power are met. In addition to overseeing the integrity of scientific quality of data, this committee will examine unblinded analyses of primary and secondary endpoints every year. Since the intervention will no longer be in effect there will be no interim monitoring rule. The study biostatistician will present the Committee with interim reports and unblinded outcome data annually. The study Chairs and other Executive Committee members will not be privy to these interim reports. The previous CSP #465 Data Monitoring Committee was asked to participate and continues to serve as the DMC for the follow-up study.

Endpoint Evaluation Committee

The composition and procedures of this Committee were outlined above under *Measuring Endpoints*.

Analysis Plan.

Statistical power

We considered a 20% reduction in primary events to be a reasonable goal of intensive glycemic control over the anticipated 15-year study time period. This effect size was chosen by taking into consideration both the probability of observing an effect of that size given the level of achieved A1c separation, and the perceived value to the patient of this level of benefit relative to the risk and burden of intensive glycemic control. In addition, a 20% reduction is consistent with the lower limits of the 95% confidence intervals of the level of association between A1c and cardiovascular events reported in observational analyses (Nathan, 2005; Selvin, 2004).

Given the current rate of overall events observed in the VADT, Table 2. below shows the expected statistical power that the VADT-FS will have for its primary and secondary outcome measures. As a continuous measure, statistical power for health related quality of life will be even better.

Table 2. Power Calculations for VADT-FS*

	Overall Study Event Rate	At 6 year Follow-up (end of VADT)	At 10 year Follow-up†	At 15 year Follow-up†
	(events per 1000 person-years)	Statistical Power to detect a Hazards Ratio of 0.8*		
CV events (Primary Outcome)‡	51.9	0.93	0.98	0.99
CV Mortality	5.5	0.00	0.08	0.31
Micro-vascular events§	31.4	0.00	0.35	0.71
Total Mortality	13.7	0.00	0.14	0.43

* All power calculations are for 2-tailed testing and assume $\alpha=0.05$.

† Estimates assume 85% retention of study subjects from the VADT and attrition due to mortality.

‡ Major CV events include: non-fatal heart attack, non-fatal stroke, new CHF, amputation for ischemic diabetic gangrene, or CV death).

§ Microvascular events include: end-stage renal disease, irreversible severe visual impairment [i.e., excludes visual acuity problems correctable by cataract surgery], or amputation for ischemic diabetic gangrene).

Update

Given the achieved sample size of the VADT-FS Main Cohort (N= 1031 as of July 31, 2011), the updated power at 15-year follow-up is now 86.3%, which is still excellent. Based on additional information, the power for detecting effects for CV and total mortality are better than what we previously thought but are still under 30%. Although power for mortality is still poor, these results will be useful for inclusion in future meta-analyses.

Objective #1: To determine the long term effects of intensive glycemic control in type 2 diabetes on major cardiovascular complications (primary outcome).

The primary outcome measure is the time to the first of any of the following events: nonfatal heart attack, nonfatal stroke, new congestive heart failure, amputation for ischemic gangrene, or cardiovascular death. The assessment of endpoints comparing the

original study glycemic treatment arms will be analyzed as per original intent-to treat using methods identical to the current VADT study. Life table methods and the log-rank test will be used to compare complication-free survival between the two treatment groups. (Halpern, 1987) Preliminary analyses suggest that the treatment groups were quite similar on important factors at baseline, so we do not anticipate needing to use Cox proportional hazards regression to control for baseline confounding. (Halpern, 1987) However, Cox proportional hazards regression methods will be used to perform a time-dependent covariate survival analysis of the primary outcome. This analysis will adjust for risk factors post intervention such as A1 c, weight, BMI, SPB, DBP, cholesterol, HDL, LDL, use as time dependent covariates. The progress report will include these post-intervention risk factors summarized over time as available through database search.

Objective #2. To determine the long term effects of intensive glycemic control in type 2 diabetes on four secondary outcomes: a) cardiovascular mortality, b) major microvascular complications, c) health-related quality of life, d) total mortality, and e) major microvascular or macrovascular (end-stage renal disease, amputation for either ischemic or non-ischemic gangrene, CV-related death, or nonfatal MI, stroke, or new CHF). Statistical analyses for secondary outcomes will be identical to those used for the primary outcome, with the exception of microvascular complications and health related quality of life. Since one of the microvascular complications, severe visual impairment, is from the annual survey, survival analysis is not appropriate for the inaccuracy of the time of the record but logistic regression analysis. Since health related quality of life is a continuous measure, survival analysis will not be appropriate for this secondary outcome. The Student t-test will be used to evaluate for differences in mean quality-of-life scores in the two treatment arms, with use of robust methods if there is evidence that variance estimates vary between the two groups. It is well known that if there is a substantial difference in survival between intervention groups, health related quality of life results can be misleading unless the survival differences are accounted for. Therefore, if there are substantial differences in survival between treatment groups, an alternative analysis accounting for missing data due to mortality is a Bayesian imputation approach. (Revicki, 2001) Again, since substantive differences in baseline attributes did not occur, we do not feel that controlling for potential confounders using ordinary least squares regression is necessary.

Update

We have added a composite measure “Major Microvascular & Macrovascular Events, which is simply an aggregate of the primary outcome with the secondary outcome for microvascular outcomes. Statistical analyses for secondary outcomes will be identical to those used for the primary outcome, with the exception of health related quality of life. Since health related quality of life is a continuous measure, survival analysis will not be appropriate for this secondary outcome. The Student t-test will be used to evaluate for differences in mean quality-of-life scores in the two treatment arms, with use of robust methods if there is evidence that variance estimates vary between the two groups. It is well known that if there is a substantial difference in survival between intervention groups, health related

quality of life results can be misleading unless the survival differences are accounted for. Therefore, if there are substantial differences in survival between treatment groups, an alternative analysis accounting for missing data due to mortality using a Bayesian imputation approach (Revicki, 2001), which will be done by Ann Arbor according to their IRB permission on mortality data collection on all VADT population except the terminated. Again, since substantive differences in baseline attributes did not occur, we do not feel that controlling for potential confounders using ordinary least squares regression is necessary. For the quality of measure, we will deal with confounding due to systematic mortality differentials between treatment arms by using selection models, as recommended in *Assessing Quality of Life in Clinical Trials: Methods and Practice* (eds. Fayer P, Hays R, April 2005.)

Update: (Early Analysis)

The major protocol amendment for the VADT-F was that a mid-point analysis would be conducted and reported, which was made and published as planned. We now plan for an early analysis to take place shortly before data is fully completed with adjudicated outcomes and locked. There is to prepare to submit an important presentation in time to take place at the American Diabetes Association (ADA) 2018 which is planned to be made in conjunction with publication of the corresponding manuscript. Below we provide the full justification for this analysis.

A major concern about an early analysis of clinical trials is that it can potentially bias investigators involved in the study protocol and thus integrity of reported data. However, this concern does not apply to this proposed early VADT-F analysis. As active intervention ceased 10 years ago at the conclusion of the VADT, and there are no longer research personnel that have clinical contact with the study subjects, there is no way for investigators to influence patient care or outcomes. The outcomes are being collected through database search and surveys. In addition, the investigators will be still blinded to the individual treatment level data, which will become available for analyses before the final presentation. Thus, the potential for bias is not a threat to the VADT-F.

On the other hand, there will be substantial benefit to the diabetes community as we present in a timely manner this important study about whether or not there is a delayed effect of the intensive treatment, and all presentations and papers will use fully completed and locked data.

We therefore believe that the benefits of an early analysis provide substantial benefit to the diabetes community and do so at essentially no risk to the integrity of the VADT-F.

Other Analysis Considerations *Interaction (Subgroup) Effects*

The improved statistical power of the VADT-FS allows us more freedom to examine interaction effects (subject baseline attributes that modify the treatment effect) than is possible in the VADT. However, our only *a priori* hypotheses regarding biological factors that may modify the treatment effect relate to patient attributes that affect the likelihood of the outcomes. As has been recently reported, in such instances it is preferable to combine risk factors into a risk score whenever feasible (which will generally dramatically improve statistical power as well as diminish problems inherent in multiple comparisons)(Brookes, 2004; Hayward, 2005). Therefore, rather than look at cardiovascular risk factors in isolation, we will combine these risk factors into the Framingham risk score (Hayward, 2006). As reported by Brookes et al, statistical power for such interaction effects is further improved if these interaction effects are examined as continuous variables using Cox proportional hazard modeling, rather than subdividing the risk score into categories.(Brookes, 2001) Consequently, we will examine whether the treatment effect is modified by a subject's 10-year risk of CV events (as predicted by a subject's baseline Framingham score), which will test whether the hazard ratio varies conditional on baseline overall CV risk.(Wilson, 1998) Similarly, we will conduct regression analyses examining for interaction effects between treatment arm and a study subject's risk of major microvascular complications, using the prediction model discussed above (Vijan, 1997).

Evaluation of Mechanisms of Action

In addition to examining interaction effects (factors that modify the intervention's effect), we will examine factors that are hypothesized to mediate the interaction effect. Whereas interaction effects are part of the experimental analysis (examining baseline [pre-randomization] subject attributes that identify individuals or groups who will benefit more or less than average), examination of potential mediating factors are observational analyses (examining factors post-treatment but prior to the occurrence of an outcome trying to better understand the treatment's mechanism(s) of action).(Hayward, 2006) There are two principle hypothesized mechanisms of action for why improved metabolic control may reduce CV events: 1) direct effects of hyper-glycemia on blood vessels and atherosclerotic disease, and 2) decreasing the prevalence of diabetic nephropathy and proteinuria (microvascular complications known to increase with hyperglycemia), which in turn reduces risk of CV events. We will examine these two factors following the methods used in the DCCT/EDIC.(Nathan, 2005) The variable examining direct hyperglycemic effects will be based upon the log of cumulative average A1c (previous observational analyses have consistently reported a log-linear association between A1c and adverse outcomes), which will be updated annually for all subjects who have not yet reached the endpoint. Markers for diabetic nephropathy previously reported to be associated with CV risk, include presence of proteinuria and estimated GFR. In addition to the log of cumulative average A1c, proteinuria and GFR, this analysis will control for a subject's other CV risk factors. (Fleiss, 1986) Cox proportional hazards regression will be used for these analyses, except for the visual impairment outcome which was not collected during the original VADT. Since time of the event is not available, logistic regression will be used for this outcome.

Missing Data

In longitudinal studies relying on survey or tests ordered in routine clinical practice, problems of missing data will almost always increase. Fortunately, our primary outcome and three of our four secondary outcomes do not rely on these data sources. However, our

analysis of health related quality of life will be limited to those subjects who have answered the survey. For those analyses of interaction effects and potential mechanisms of action, outlined above, standard multiple imputation techniques will be utilized so as to prevent diminished sample size and potential response bias due to dropping subjects with missing data on covariates. (King, 2001; Revicki, 2001; Carroll, 1995) Imputed values for a given covariate will be informed by an individual's values for all other observed covariates to be used in the regression model, as well as temporal trends in the study population and previous values for that covariate in the individual. Multiple imputation is preferable in such instances, since it accounts for the degree of precision in imputed values and therefore provides better variance estimates for all regression coefficients. (King, 2001; Clayton, 1991; Carroll, 1995; Gatsonis, 1995; Oppenheimer, 1999)

Updates

There are no anticipated changes in the planned analyses, other than the addition of the new composite secondary endpoint, "Major Microvascular & Macrovascular Events" (see Endpoints Section) except severe visual impairment, which will be analyzed independently from other outcomes using only data collected through self-administered survey questionnaire during this follow-up period since 2009.

Study Significance.

The proposed extension of the VADT Follow-up Study (VADT-FS) would capitalize on a unique opportunity to examine factors that are associated with long-term complications and mortality for people with one of the most important conditions in modern medicine, a disease that will continue to grow dramatically if current epidemiological trends continue. Given the results of the UKPDS Follow-up Study and the DCCT-EDIC study, the objectives of the VADT-FS are important to answer in order to better assess possible multiplicative temporal effects and to obtain adequate statistical power to assess mortality benefits directly. It will also provide an opportunity to assess the long-term impact of tight glycemic control on vision and renal insufficiency when tight blood pressure control is achieved, a question unanswered by previous studies.

References:

- Abraira C, Colwell JA, Nuttall F, Emanuele N, Comstock J, Levin S, Sawin C, Silbert C. A Critical issue. Intensive insulin treatment and macrovascular disease. *Diabetes Care* 1998 Apr; 21(4):669-71.
- Abraira C, Colwell J, Nuttall F, Sawin CT, Henderson W, Comstock JP, Emanuele NV, Levin SR, Pacold I, Lee HS, and the Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes. Cardiovascular events and correlates in the Veterans diabetes feasibility trial. *Arch Intern Med* 1997 Jan 27; 157(2):181-188.
- Abraira C, Duckworth W, McCarren M, Emanuele N, Arca D, Reda D, Henderson W. Design of the cooperative study glycemic control and complications in diabetes mellitus Type 2 Veterans Affairs Diabetes Trial. *J Diabetes Complications* 2003 Nov-Dec; 17 (6):314-22.
- Abraira C, Duckworth W, Moritz T for the VADT group. Glycemic Separation and Risk Factor Control in the Veterans Affairs Diabetes Trial: An Interim Report. *Diabetes, Obesity and Metabolism*, 11: 150–156, 2009.
- ACCORD Study Group. (2008). Effects of Intensive Glucose Lowering in Type 2 Diabetes. *New England Journal of Medicine*, 358: 2545-2559.
- ACCORD Study Group and ACCORD Eye Study Group. (2010). Effects of medical therapies on retinopathy progression in type 2 diabetes. *New England Journal of Medicine*, 363: 233-244.
- Adler, A.I., Neil, H.A., Manley, S.E., Holman, R.R., Turner, R.C. (1999). Hyperglycemia and hyperinsulinemia at diagnosis of diabetes and their association with subsequent cardiovascular disease in the United Kingdom Prospective Diabetes Study (UKPDS 47). *Am Heart J*, 138:S353-9.
- ADVANCE Collaborative Group. (2008). Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. *New England Journal of Medicine*, 358: 2560-2572.
- Agrawal, L., Azad, N., Emanuele, N.V., Bahn, G.D., Kaufman, D.G., Moritz, T.E., Duckworth, W.C., Abraira, C. For the Veterans Affairs Diabetes Trial (VADT) Study Group. (2011). Observations on Renal Outcomes in the Veterans Affairs Diabetes Trial. *Diabetes Care*, 34: 2090-2094.
- Anderson, R.J., Bahn, G.D., Mortiz, T.E., Kaufman, D., Abraira, C., Duckworth, W. For the VADT Study Group. (2011). Blood Pressure and Cardiovascular Disease Risk in the Veterans Affairs Diabetes Trial. *Diabetes Care*, 34: 34-38.
- Asch SM, McGlynn EA, Hogan MM, Hayward RA, Shekelle P, Rubenstein L, Keesey J, Adams J, Kerr EA. Comparison of quality of care for patients in the Veterans Health Administration and patients in a national sample. *Ann Intern Med* 2004; 141(12):398- 45.
- Azad, N., Agrawal, L., Emanuele, N., Klein, R., Bahn, G., Kaufmann, D., Moritz, T., Duckworth, W., Abraira, C. for the Veterans Affairs VADT Study Group (2011). Ocular Outcomes in the Veterans Affairs Diabetes Trial. Annual Meeting of the American Diabetes Association.

- Barnett PG: Review of methods to determine VA health care costs. *Med Care* 1999;37:AS9-AS17
- Barnett PG, Rodgers JH: Use of the decision support system for VA cost-effectiveness research. *Med Care* 1999;37:AS63-AS70
- Barnett PG. Determination of VA health care costs. *Medical Care Research and Review* 2003; 60(Supplement to #3): 124S-141S.
- Beulens, J.W.J., Patel, A., Vingerling, J.R., Cruickshank, J.K., Huges, A.D., Stanton, A., Lu, J., McGThom, S.A., Grobbee, D.E., Stock, R.P. on behalf of the AdRem project team and ADVANCE management committee. (2009). Effect of blood pressure lowering and intensive glucose control on the incidence and progression of retinopathy in patients with type 2 diabetes mellitus: a randomized controlled trial. *Diabetologia*, 52: 2027-20-36.
- Boussageon, R., Bejan-Angoulvant, T., Saadatian-Elahi, M., Lafont, S., Bergeonneau, C., Kassai, B., Erpeldinger, S., Wright, J., Gueyffier, F., & Cornu, C. (2011). Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes; meta-analysis of randomized controlled trials. *BMJ*2011; 343:d4169.
- Brookes ST, Whitley E, Peters TJ, et al: Subgroup analyses in randomized controlled trials: Quantifying the risks of false-positives and false-negatives. *Health Technol Assess* 5:1-56, 2001.
- Brookes ST, Whitely E, Egger M, et al: Subgroup analyses in randomized trials: Risks of subgroup-specific analyses; power and sample size for the interaction test. *J Clin Epidemiol* 57:229-236, 2004
- Camacho P, Pitale S, Abaira C. Beneficial and detrimental effects of intensive glycemic control, with emphasis on type 2 diabetes mellitus. *Drugs Aging* 2000 Dec; 17(6):463- 76.
- Caroll RJ, Ruppert D, Stefanski LA. *Measurement Error in Nonlinear Models*. London: Chapman and Hall; 1995.
- CDC Diabetes Cost-effectiveness Group. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. *JAMA* 2002 May15; 287(19):2542-51.
- Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2005. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2005.
- [Chan PS, Nallamothu BK, Gurm HS, Hayward RA, Vijan S.](#) Incremental benefit and cost-effectiveness of high-dose statin therapy in high-risk patients with coronary artery disease. *Circulation*. 2007 May 8; 115(1 8):2398-409.
- Clayton DG. Models for the analysis of cohort and case control studies with inaccurately measured exposures. *Statistical Models for Longitudinal Studies in Health*. New York: Oxford University Press; 1991.

Concato J, Feinstein AR. Monte Carlo methods in clinical research: applications in multivariable analysis. *J Investig Med*. 1997; 45:394-400.

The DCCT Research Group. Reliability and validity of diabetes quality-of-life measure for the Diabetes Control and Complications Trial (DCCT). *Diabetes Care* 1988; 11:725-732.

Dillman DA. Mail and Internet Surveys: The Tailored Design Method 2007 Update (Second Edition). John Wiley & Sons, Hoboken, New Jersey, 2007.

Dominitz JA, et al. Assessment of vital status in Department of Veterans Affairs national databases. comparison with state death certificates. *Ann Epidemiol*. 2001; 11:286-291

Druss BG, Marcus SC, Olfson M, Pincus HA. The most expensive medical conditions in America. *Health Aff (Millwood)* 2002; 21(4):105-11.

[Duckworth WC, Saudek CD, Giobbie-Hurder A, et al.](#) The Veterans Affairs Implantable Insulin Pump Study: effect on cardiovascular risk factors. *Diabetes Care*. 1998 Oct;21(10): 1596-602.

Duckworth WC, McCarren M, Abaira C, VADT Investigators. Control of cardiovascular risk factors in the Veterans Affairs Diabetes Trial in advanced type 2 diabetes. *Endocr Pract* 2006 Jan-Feb; 12 Suppl 1:85-8

Duckworth WC, McCarren M, Abaira C. Glucose control and cardiovascular complications: the VA Diabetes Trial. *Diabetes Care* 2001 May; 24(5):942-5.

Duckworth, W., Abaira, C., Mortiz, T., Reda, D., Emanuele, N., Reaven, P.D., Zieve, F.J., Marks, J., Davis, S.N., Hayward R, Warren, S.R., Goldman, S., McCarren, M., Vitek, M.E., Henderson, W.G., Huang, G.D. for the Veterans Affairs Diabetes Trial. (2009). Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes: an analysis of the Veterans Affairs Diabetes Trial (VADT). *N Engl J Med*, 360:129-139.

Duckworth, W.C., Abaira, C., Mortiz, T., Davis, S.N., Emanuele, N., Goldman, S., Hayward, R., Huang, G.D., Marks, J.B., Reaven, P.D., Reda, D.J., Wareen, S.R., Zieve, F.J., for the Investigators of the VADT. (2011). The Duration of Diabetes Affects the Response to Intensive Glucose Control in Type 2 Subjects: The VA Diabetes Trial. Accepted for publication, *Journal of Diabetes and Its Complications*.

Eastman RC, Javitt JC, Herman WH, Dasbach EJ, Copley-Merriman C, Maier W, et al. Model of complications of NIDDM. II. Analysis of the health benefits and cost-effectiveness of treating NIDDM with the goal of normoglycemia. *Diabetes Care* 1997; 20:735-44.

Eastman RC, Javitt JC, Herman WH, Dasbach EJ, Zbrozek AS, Dong F, et al. Model of complications of NIDDM. I. Model construction and assumptions. *Diabetes Care* 1997; 20:725-34.

Emanuele, N., Sacks, J., Klein, R., Reda, D., Anderson, R., Duckworth, W., & Abaira, C. For the Veterans Affairs Diabetes Trial Group. (2005). Ethnicity, Race, and Baseline Retinopathy Correlates in the Veterans Affairs Diabetes Trial. *Diabetes Care*, 28:8.

Emanuele, N., Moritz, T., Klein, R., Davis, M.D., Glander, K., Khanna, A., Thottapurathu, L., Bahn, G., Duckworth, W., Abaira, C., and the VADT Study Group. (2009a). Ethnicity, race and clinically significant macular edema in the Veterans Affairs Diabetes Trial (VADT). *Diabetes Research and*

Clinical Practice, 86: 104-110.

Emanuele, N., Klein, R., Mortiz, T., Davis, M.D., Glander, K., Anderson, R., Reda, D., Duckworth, W., Abairra, C. For the VADT Study Group. (2009b). Comparison of dilated fundus examinations iwht seven-field stereo fundus photographs in the Veterans Affairs Diabetes Trial. *Journal of Diabetes and Its Complications*, 23: 323-329.

Engelgau M, Geiss L, Saaddine JB, Boyle JP, Benjamin SM, Gregg EW, Tierney EF, Burrows- Rios N, Mokdad AH, Ford ES, Imperatore G, Narayan V. The evolving diabetes burden in the United States. *Ann Intern Med* 2004 Jun 1; 140(1 1):945-50.

Feldt-Rasmussen, B., Mathiesen, E.R., Jensen, T., Laurtzen, T., Deckert, T. (1991). Effect of improved metabolic control on loss of kidney function in type 1 (insulin-dependent) diabetic patients: an update of the Steno studies. *Diabetologia*, 34:164-170.

Fisher SG, et al. Mortality ascertainment in the veteran population: alternatives to the National Death Index. *Am JEpidemiol.* 1995; 141:242-250

Fleiss JL. *The Design and Analysis of Clinical Experiments*, Wiley, New York, NY, 1986.

Gatsonis CA, Epstein AM, Newhouse JP, Normand SL, McNeil BJ. Variations in the Utilization of coronary angiography for elderly patients with an acute myocardial infarction An analysis using hierarchical logistic regression. *Med Care* 1995; 33:625- 42.

Goldman S, Holman W, Sethi G, Lee K. Radial Artery vs Saphenous Vein Grafts In Coronary Artery Bypass Surgery. Cooperative Studies Program #474 August 30, 2006.

Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. *Ann Intern Med* 1993; 118:622-629.

Haffner SM, Lehto S, Ronnema T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998; 339:229-34.

Halpern J, Brown BW. Designing clinical trials with arbitrary specification of Survival functions and for the log rank of generalized Wilcoxon test. *Controlled Clinical Trials* 1987; 12:304-313.

Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with Hypertension: principal results of the Hypertension Optimal Treatment (HOT) Randomized trial. HOT Study Group. *Lancet* 1998; 351:1755.

Hayward RA. All-or-Nothing Treatment Targets Make Bad performance measure. *Am J Manag Care* 2007 Mar; 13(3):126-8

Henderson, W.G., Fisher, S.G., Weber, L., Hammermeister, K.E., Sethi, G. (1991). Conditional Power for arbitrary survival curves to decide whether to extend a clinical trial. *Controlled Clinical Trials*,12:304-313.

Hayward RA, Hofer TP, Vijan S. Narrative review: lack of evidence for recommended low-density

lipoprotein treatment targets: a solvable problem. *Ann Intern Med* 2006; 145(7):520-30.

Hayward RA, Kent DM, Vijan S, Hofer TP. Reporting clinical trial results to inform clinical providers, payers and consumers: The need to examine benefits for lower vs. higher risk patients. *Health Affairs* 2005; 24(6):1571-81.

Hayward RA, Kerr EA, Krein S and Hofer TP. Quality improvement initiatives: Issues in moving from diabetes guidelines to policy. *Diabetes Care* 2004; 27(S2):B54-60.

Hendricks AM, Bradham DD. Estimating VA Treatment Costs: Methods and Applications. *Medical Care Research and Review* 2003; 60(Supplement to #3): 1S-175S.

[Herman WH, Hoerger TJ, Brandle M, et al. & the Diabetes Prevention Program Research Group.](#) The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med.* 2005 Mar 1; 142(5):323-32.

Hogan P, Dall T, Nikolov P. Economic costs of diabetes in the US in 2002. *Diabetes Care* 2003; 26(3):917-32.

Honeycutt AA, Boyle JP, Broglio KR, Thompson TJ, Hoerger TJ, Geiss LS, Narayan KM. A dynamic Markov model for forecasting diabetes prevalence in the United States through 2050. *Health Care Manag Sci* 2003; 6(3):155-64.

[Kerr EA, Heisler M, Krein SL, Kabeto M, Langa KM, Weir D, Piette JD.](#) Beyond Comorbidity Counts: How Do Comorbidity Type and Severity Influence Diabetes Patients' Treatment Priorities and Self-Management? *J Gen Intern Med.* 2007 Jul 24;

[Kerr EA, Gerzoff RB, Krein SL, et al.](#) Diabetes care quality in the Veterans Affairs Health Care System and commercial managed care: the TRIAD study. *Ann Intern Med.* 2004 Aug 17;141(4):272-81.

King G, Honaker J, Joseph A, Scheve J. Analyzing Incomplete Political Science Data: An Alternative Algorithm for Multiple Imputation, *American Political Science Review*, Vol. 95, No. 1 (March, 2001): Pp. 49-69.

Klein BE, Klein R, Wang Q, Moss SE. Older-onset diabetes and lens opacities. The Beaver Dam Eye Study. *Ophthalmic Epidemiol* 1995; 2:49-55.

Klein R, Klein BE, Moss SE. Visual impairment in diabetes. *Ophthalmology* 1984; 91:1-9.

Kirkman MS, McCarren Madeline, Shah J, Duckworth, Abaira C, The VADT Study Group. The association between metabolic control and prevalent macrovascular disease in Type 2 diabetes: The VA Cooperative Study in diabetes. *J. Diabetes Complications* 2006 Mar-Apr; 20(2):75-80.

Kiyota, Y., Schneeweiss, S., Glynn, R.J., Cannuscio, C.C., Avorn, J., Solomon, D.H. (2004). Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. *American Heart Journal.* Jul;148(1):99-104.

Kroc Collaborative Study Group. (1984). Blood glucose control and the evolution of diabetic retinopathy and albuminuria: a preliminary multicenter trial. *N Engl J Med*, 311: 365-372.

Kupersmith, J, Francis J, Kerr E, Krein S, Pogach L, Kolodner RM, Perlin JB. Advancing Evidence – Based Care For Diabetes: Lessons From The Veterans Health Administration. *Health Aff (Millwood)* 2007 Mar-Apr; 26(2):w1 56-68.

Levin, S.R., Coburn, J.W., Abaira, C. et al. (2000). Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes Feasibility Trial. Effect of intensive glycemic control on microalbuminuria in type 2 diabetes. *N Engl J Med*, 359:1577-1589.

Maciejewski ML, Maynard C. Diabetes-Related Utilization and Costs for Inpatient and outpatient Services in the Veterans Administration. *Diabetes Care* May 2004;27 (Supplemental 2); B69-B73.

Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD. National Eye Institute Visual Function Questionnaire Field Test Investigators. Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol* 2001 Jul; 119(7):1050-8.

Meigs JB, Singer DE, Sullivan LM, Dukes KA, D'Agostino RB, Nathan DM, et al. Metabolic control and prevalent cardiovascular disease in non-insulin-independent diabetes mellitus (NIDDM): The NIDDM Patient Outcome Research Team. *Am J Med* 1997; 102:38-47.

Meyers CD, McCarren M, Wong ND, Abaira C, Duckworth WC, Kashyap ML. VADT Investigators. Baseline achievement of lipid goals and usage of lipid medications in patients with diabetes mellitus (from the Veterans Affairs Diabetes Trial). *Am J Cardiol* 2006 Jul 1; 98(1):63-5. Epub 2006 May 4.

Miller DR, Safford MM, Pogach LM. Who has diabetes? Best estimates of diabetes prevalence in the Department of Veterans Affairs based on computerized patient data. *Diabetes Care* 2004 May; 27(Supplement)2:B10-21.

Naeim A, Keeler EB, Gutierrez PR, Wilson MR, Reuben D, Mangione CM. Is cataract surgery cost-effective among older patients with a low predicted probability for improvement in reported visual functioning? *Med Care* 2006 Nov; 44(11):982-9.

[Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B.](#) Diabetes Control and Complications Trial/Epidemiology of Diabetes. *N Engl J Med*. 2005 Dec 22;353(25):2643-53.

Oppenheimer L and Kher U. The impact of measurement error on comparison of two treatments using a responder analysis. *Statist Med* 1999; 18:2177-2188.

Petersen, L.A., Wright, S., Normand, S.L., Daley, J. (1999). Positive predictive value of the diagnosis of acute myocardial infarction in an administrative database. *Journal of General Internal Medicine*. Sep;14(9):555-558.

Phibbs CS, Bhandari A, Yu W, Barnett PG. Estimating the costs of VA ambulatory care. *Medical Care Research and Review* 2003; 60(Supplement to #3): 54S-73 S.

Pogach LM, Rajan M, Aron DC. Comparison of weighted performance measurement and dichotomous

thresholds for glycemic control in the Veterans Health Administration. *Diabetes Care* 2006; 29(2):24 1-6.

Pogach LM, Tiwari A, Maney M, Rajan M, Miller DR, Aron D. Should mitigating comorbidities be considered in assessing healthcare plan performance in achieving optimal glycemic control. *Am J Manag Care* 2007; 13:133-140.

Raphael BA, Galetta KM, Jacobs DA, Markowitz CE, Liu GT, Nano-Schiavi ML, Galetta SL, Maguire MG, Mangione CM, Globe DR, Balcer LJ. Validation and test characteristics Of a 10 neuro-ophthalmic supplement to the NEI-VFQ-25. *Am J Ophthalmol* 2006 Dec; 142(6):1026-35.

Ray, K., Seshasai, S.R.K., Wijesuriya, S., Sivakumaran, R., Nethcott, S., Preiss, D., Erqou, S., Sattar, N. (2009). Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomized controlled trials. *Lancet* 373, 1765-1772.

Reaven PD, Sacks J, Investigators for the VADT. Coronary artery and abdominal aortic calcification are associated with cardiovascular disease in type 2 diabetes. *Diabetologia* 2005 Feb; 48(2):379-85.

Reaven, P., Moritz, T., Schwenke, D., Anderson, R., Criqui M., Detrano, R., Emanuele, N., Kayshap, M., Marks, J., Mudaliar, S., Rao, R.H., Shah, J., Goldman, S., Reda, D., McCarren, M., Abaira, C. Duckworth, W., for the VADT. (2009). Intensive Glucose Lowering Therapy Reduces Cardiovascular Disease Events in Those with Lower Calcified Coronary Atherosclerosis: A sub study of the Veterans Affairs Diabetes Trial (VADT). *Diabetes* 58: 2642-2648, 2009.

Reichard, P., Nilsson, B.Y., Rosenqvist, U. (1993). The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med*, 329: 304-309.

Revicki DA, Gold K, Buckman D, et al. Imputing Physical Health Status Scores Missing Owing to Mortality: Results of a Simulation Comparing Multiple Techniques. *Medical Care*, Vol. 39, No. 1 (Jan., 2001), pp. 61-71.

Riche DM, McClendon KS. Role of statins for the primary prevention of cardiovascular disease inpatients with type 2 diabetes mellitus. *AM J Health Syst Pharm* 2007 Aug 1; 64(15):1603-10.

Ryerson B, Tierney EF, Thompson TJ, Engलगau MM, Wang J, Greg EW, et al. Excess physical limitations among adults with diabetes in the U.S. population, 1997-1999. *Diabetes Care* 2003; 26:206-10.

[Saudek CD, Duckworth WC, Giobbie-Hurder A, et al.](#) Implantable insulin pump vs multiple-dose insulin for non-insulin-dependent diabetes mellitus: a randomized clinical trial. Department of Veterans Affairs Implantable Insulin Pump Study Group. *JAMA*. 1996 Oct 23-30;276(16):1322-7.

Saydah S, Fradkin J, Cowie C. Poor control of risk factors for vascular disease among Adults with previously diagnosed diabetes. *JAMA* 2004; 291:335-342.

[Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH.](#) Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004;141:421-431.

Shaughnessy AF, Slawson DC. What happened to the valid POEMs? A survey of review articles on the

- treatment of type 2 diabetes. *BMJ* 2003; 327(7409):266.
- Shichiri, M., Kishikawa, H., Ohkubo, Y., Wake, N. (2000). Study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care*, 23 (Suppl. 2): B21-B29.
- Smith MW, Barnett PG. Direct measurement of health care costs. *Medical Care Research and Review* 2003; 60(Supplement to #3): 74S-91S.
- Smith MW, Joseph GJ. Pharmacy data in the VA Health Care System. *Medical Care Research and Review* 2003; 60(Supplement to #3): 92S-123S.
- Smith MW, Joseph GJ. Pharmacy data in the VA Health Care System. *Medical Care Research and Review* 2003; 60(Supplement to #3): 92S-123S.
- Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes(UKPDS): prospective observational study. *BMJ* 2000; 321:405-12.
- The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *NEJM* 1993; 329(14):977-86.
- Turnbull, F.M., Abraira, C., Anderson, R.J., Byington, R.P., Chalmers, J.P., Duckworth, W.C., Evans, G.W., Gerstein, H.C., Holman, Mortiz, T.E., Neal, B.C., Ninomiya, T., Patel, A.A., Paul, S.K., Travert, F., Woodward, M. (2009). Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia*, 52:2288-2298.
- UK Prospective Diabetes Study Group (UKPDS). Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; 352(9131):854-865.
- UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing Risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ* 1998; 3 17:713-720.
- UK Prospective Diabetes Study Group (UKPDS). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352:837-53.
- UK Prospective Diabetes Study Group. Tight blood pressure control and risk of Macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998; 3 17:703-13
- VA achievements in diabetes care (2006). <http://www.diabetesmonitor.com/other/press-releases/pr25.htm>.
- Vijan S, Hayward RA. Treatment of hypertension in type 2 diabetes: Blood pressure goals, choice of agents, and setting priorities in diabetes care. *Annals of Internal Medicine* 2003 Apr 1; 138(7):593-602.
- Vijan S, Hayward RA. Pharmacologic Lipid-Lowering Therapy in Type 2 Diabetes Mellitus:

Background Paper for the American College of Physicians. *Ann Intern Med* 2004; 140:650-658.

Vijan S, Hofer T, Hayward RA. Estimated benefits of glycemic control in microvascular complications in Type 2 diabetes. *Annals of Internal Medicine* 1997; 127(9):788-795.

Vijan S., Kent DM, Hayward RA. Are randomized controlled trials sufficient evidence to guide clinical practice in type 2 (non-insulin dependent) diabetes mellitus? *Diabetologia* 2000 Jan; 43(1): 125-130.

Wagner TH, Chen S, Barnett PG. Using average cost methods to estimate encounter-level costs for medical-surgical stays in the VA. *Medical Care Research and Review* 2003; 60(Supplement to #3): 15S-36S.

Weinstein RS, Hawley G, Repke D, Feuerstein BI, Sawin CT, Pogach LM. Pharmacy Costs and Glycemic Control in the Department of Veterans Affairs. *Diabetes Care* May 2004;27(Supplement 2); B74-B81.

Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Sibershatz H, Kannel WB. Prediction of Coronary Heart Disease Using Risk Factor Categories. *Circulation* 1998; 97:1837-1847.

Yu W, Barnett PG. Reconciliation of DSS encounter-level national data extracts and the VA national patient care database: FY2001-FY2002. Menlo Park, CA: VA Health Economics Resource Center, December 2, 2003. Technical Report #9.

Zimring, M.B., Anderson, R.J., Luo, P., Moritz, T.E., & the Investigators for the Veterans Affairs Diabetes Trial. (2008). Plasma basic fibroblast growth factor is correlated with plasminogen activator inhibitor-1 concentration in adults from the Veterans Affairs Diabetes Trial. *Journal of Metabolism*, 57:1563-1569.

Zimring, M.B., Anderson, R.J., Mortiz, T.E., Ge, L., & Investigators for the VADT. (2009). Endothelial cell inhibitory autoantibodies are associated with laser photocoagulation in adults from the Veterans Affairs Diabetes Trial. *Journal of Metabolism*, 58: 882-88.

Zimring, M.B., Anderson, R.J., Ling, G., Mortiz, T. (2011). Increased plasma basic fibroblast growth factor is associated with coronary heart disease in adult type 2 diabetes mellitus. *Journal of Metabolism*, 60: 284-291.

Appendix A

Published Manuscripts for VADT

- Abraira C: Tight control of Blood Glucose for Cardiovascular Risk Reduction? - Syllabus, 3rd Annual National VA Diabetes Symposium, Alexandria, VA (Sierra Military Health Services, Baltimore, MD) 2001 (Also abstracted in Veterans Health Journal 6:14-21, 2001).
- Duckworth W, McCarren M, Abraira C: The Department of Veterans Affairs Diabetes Trial., *Diabetes Care* 24: 942-945, 2001.
- Abraira C, Duckworth W. The Need for Glycemic Trials in type 2 Diabetes (Featured article). *Clinical Diabetes*, 21: 107-111, 2003.
- Abraira C, Duckworth W, McCarren M, Emanuele N, Arca D, Reda D, Anderson W for the participants of the VA Cooperative Study of Glycemic Control and Complications In Diabetes Mellitus Type 2. Design of the Cooperative Study on glycemic control and complications in Diabetes Mellitus type 2: the VADT. *Journal of Diabetes and its Complications*, 17: 314-322, 2003.
- Reaven PD, Sacks J and VADT investigators. Reduced Coronary and abdominal Artery Calcification in Hispanics with type 2 Diabetes. *Diabetes Care* 27:1115-1120, 2004.
- J. Shah, S. Kirkman, C. Wendell, McCarren M., W. Duckworth, C. Abraira and the VADT group. Baseline Macrovascular Disease Correlates in Older Type 2 Diabetic Patients in US Veterans Affairs Diabetes Trial (VADT). Proceedings, 12th International Congress of Endocrinology- Lisbon. :Medimond, Bologna-Italy, 2004, pp 653-658.
- C. Abraira, J. Sacks, N. Emanuele, R. Klein, W. Duckworth and the VADT Group. Retinopathy Associations in the V.A. Diabetes Trial. Proceedings, 12th International Congress of Endocrinology- Lisbon. Medimond, Bologna, 2004, pp. 435-439.
- C. Abraira, contributor. CADRE: Type 2 Diabetes Outcomes Trials on the Horizon. Reprint Lecture Kit, Volume 3. (<http://www.cadre-diabetes.org>) Council for the Advancement of Diabetes Research and Education. New York, 2004.
- Emanuele N, Sacks G, Klein R, Duckworth W, Abraira C (corresponding author) and VADT Group. Ethnicity, Race and Basal Retinopathy Correlates in the Veterans Diabetes Trial. *Diabetes Care*. 28: 1954-1958, 2005.
- Reaven PD, Sacks J, Investigators for the VADT Coronary artery and abdominal aortic calcification are associated with cardiovascular disease in type 2 diabetes. *Diabetologia*, 48:379-385, 2005.
- Duckworth W, McCarren M, Abraira C., VADT investigators, Control of Cardiovascular Risk Factors in the A Diabetes Trial in Advanced type 2 Diabetes. *Endocrine Practice*, 12 (Suppl. 1), 85-88, 2006.
- Kirkman MS, McCarren M, Shah J, Duckworth W, Abraira C, The association between metabolic control and prevalent cardiovascular disease in type 2 Diabetes. The VA Cooperative Study in Diabetes. *J Diab Compl*, 20: 75-80, 2006.
- Meyers CD, McCarren M, Wong ND, Abraira C, Duckworth W, Kashyap M, VADT Group. Baseline achievement of lipid goals and usage of lipid medications in the VA diabetes trial. *Am. J. Cardiology*, 98:63-65, 2006.
- Abraira, C: The VA Diabetes Trial, Design and Update. In, Alan J. Garber, Hertz C. Gerstein, Steven M. Haffner, MD and Carlos Abraira: What Impact Will Major Clinical Trials Have on Type 2 Diabetes? Satellite Symposium to ADA meeting, Washington DC, 2006. Medscape- Diabetes and Endocrinology, August 1, 2006. www.medscape.com/viewprogram/5528?rss (accessed October23, 2006).

- Reaven P, Emanuele N, Moritz T, Klein R, Davis M, Glander K, Duckworth W, Abairra C. Proliferative Diabetic Retinopathy is Strongly Related to Coronary Artery Calcium in the Veterans Affairs Diabetes Trial (VADT). *Diabetes Care*, 31:952-957, 2008.
- Zimering M, Anderson RJ, Luo P, Moritz TE and VADT Investigators .Increased plasma basic fibroblast growth factor immunoreactivity in adults In the Veterans Affairs Diabetes Trial: correlation with plasminogen activator inhibitor-1. *Metabolism* 57: 1487-1624, 2008.
- Saremi A, Anderson RJ, Luo P, Moritz TE, Schwenke DC, Allison M, Reaven PD; for the VADT Association between IL-6 and the extent of coronary atherosclerosis in the veterans affairs diabetes trial (VADT). *Atherosclerosis*. 2009 Apr;203(2):610-4.
- Emanuele N, Klein R, Moritz M, Davis M, Glander K, Anderson R, Reda D, Duckworth W, Abairra C (corresponding author) for the VADT group. Comparison of Dilated Fundus Examinations with 7-Field Stereo Photographs in VA Diabetes Trial. *J Diab. Comp.* 23:323-329,2009.
- Abairra C, Duckworth W, Moritz T for the VADT group. Glycemic Separation and Risk Factor Control in the Veterans Affairs Diabetes Trial: An Interim Report. *Diabetes, Obesity and Metabolism*, 11: 150–156, 2009.
- Duckworth W, Abairra C, Moritz T, Reda D, Emanuele N et al., VADT investigators: Glucose Control and Complications in the VA Diabetes Trial (VADT). *N Eng J of Med* 360:129-139, 2009.
- Zimering M, Anderson R, Moritz T, Ge L, Investigators for the VADT :Low plasma basic fibroblast growth factor is associated with laser photocoagulation treatment in adult type 2 diabetes mellitus from the Veterans Affairs Diabetes Trial. *Metabolism* 58: 393-400, 2009.
- Duckworth W, Moritz T and Abairra C: Glucose control and vascular complications in Type 2 diabetes. Reply to readers comments, *New Eng J of Med* 360: 2032, 2009.
- Zimering M, Pan Z : Autoantibodies in Type 2 Diabetes induce stress fiber formation and apoptosis in endothelial cells in VADT. *J Clin Endocrinol Metab*, 94(6): 2171-2177, 2009.
- Reaven P, Moritz T, Schwenke D, Anderson R, Criqui M, Detrano R, Emanuele N, Kayshap M, Marks J, Mudaliar S, Rao R, Shah J, Goldman S, Reda D, McCarren M, Abairra C, Duckworth W, for the VADT. Intensive Glucose Lowering Therapy Reduces Cardiovascular Disease Events in Those with Lower Calcified Coronary Atherosclerosis: A sub study of the Veterans Affairs Diabetes Trial (VADT). *Diabetes*, 58: 2642-2648, 2009.
- Zimering MB, Anderson RJ, Moritz TE, Ge L, investigators for VADT2009. Endothelial cell inhibitory antibodies are associated with laser coagulation in adults from the Veterans Affairs Diabetes Trial, *Metabolism*, 58:882-87, 2009.
- Emanuele N, Moritz T, Klein, R, Davis M, Glander K, Khanna A, Duckworth W, Abairra C_(Corresponding Author). Clinically Significant Macular Edema Is Associated With Ethnicity and Hemodynamic-Vascular.Factors at Baseline in the Veterans Affairs Diabetes Trial (VADT). *Diabetes Res and Clin. Practice*, 86: 104-110, 2009.
- Moritz T, Duckworth W, Abairra C. Veterans Affairs Diabetes Trial—Corrections, *N Eng J of Med*, 361:1024-1025, 2009 (Additional corrections in Page 1028, same issue).
- Turnbull FM, Abairra C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, Evans GW, Gerstein HC, Holman RR, Moritz TE, Neal BC, Ninomiya T, Patel AA, Paul SK, Travers F, Woodward M. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia*, 52 (Nov):2288-2298, 2009.
- Andreas Liebl, Guy Rutten, Carlos Abairra: “Treat early, treat appropriately”, *Primary Care Diabetes* 4, suppl. 1 (2010) S3–S10.

- Saremi A, Allison M, Ditomasso D, Moritz T, Ge L, Anderson R, Duckworth W, Abaira C, Reaven P, for the VADT. Hepatic Fat and Inflammation in Type 2 Diabetes. *Metabolism*. Mar;59(3):430-2, 2010
- Nicholas Emanuele, MD, Thomas Moritz, MS, Ronald Klein, MD, Matthew D. Davis, MD, Kathleen Glander, Anuradha Khanna, Lizy Thottapurathu, MS, Gideon Bahn, MS, William Duckworth, MD, Carlos Abaira, MD, and the VADT Study Group, (2009) Ethnicity, Race, and Clinically Significant Macular Edema in the Veterans Affairs Diabetes Trial (VADT) *Diabetes Research and Clinical Practice*
- Saremi, Aramesh; Moritz, Thomas; Anderson, Robert J.; Abaira, Carlos; Duckworth, William C.; Reaven, Peter D.; on behalf of the Veterans Affairs Diabetes Trial (VADT). Rates and Determinants of Coronary and Abdominal Aortic Artery Calcium Progression in the Veterans Affairs Diabetes Trial (VADT). *Diabetes Care* (2010) Dec;33(12): 2642-2647.
- Anderson, Robert J.; Bahn, Gideon; Kaufman, Derrick; Moritz, Thomas; Abaira, Carlos; Duckworth, William. Letters to the Editor/Observations - Blood Pressure and Cardiovascular Disease Risk in the Veterans Affairs Diabetes Trial (VADT). *Diabetes Care*, 34:34-38, 2011.
- Agrawal,L, Azad, N, Emanuele, N., Bahn, G., Kaufman, D., Moritz, T., Duckworth, W., Abaira, C., and the VADT Study Group. Observation on Renal Outcomes in the Veterans Affairs Diabetes Trial. *Diabetes Care* 34: 1-5, 2011.
- Duckworth, W. C., Abaira, C., Moritz, T. E., Davis, S. N., Emanuele, N., Goldman, S., & Zieve, F. J. (2011). The duration of diabetes affects the response to intensive glucose control in type 2 subjects: the VA Diabetes Trial. *Journal of Diabetes & Its Complications*, 25(6), 355-361.
- Azad N, Agrawal L, Emanuele NV, Klein R, Bahn GD, McCarren M, Reaven P, Hayward R, Duckworth W and the VADT Study Group. "Association of PAI-1 and Fibrinogen with Diabetic Retinopathy in the Veterans Affairs Diabetes Trial (VADT) *Diabetes Care*. (Published online before print October 7, 2013, doi: 10.2337/dc13-1193)
- Mark B. Zimring, Robert J. Anderson, Ling Ge, Thomas E. Moritz, and Investigators for the VADT: Increased plasma basic fibroblast growth factor is associated with coronary heart disease in adult type 2 diabetes. *Metabolism Clinical and Experimental* 60(2): 284-291, 2011.
- Nalruporn, C. Ability of Indices of Cardiovascular Disease (CVD) Risk and Comorbidity To Predict CVD Outcomes with Intensive Glucose Control in the VADT. Abstract presented at 71st Scientific Sessions on 06/25/2011.
- Aramesh Saremi, MD¹, Gideon Bahn, PhD², Peter D, Reaven, MD¹ for VADT investigators. Progression of Vascular Calcification Is Increased With Statin Use in the Veterans Affairs Diabetes Trial (VADT). [Diabetes Care 35.11](#) (Nov 2012): 2390-2.
- Lopes-Virella MF, Hunt KJ, Baker NL, Virella G, Moritz T; VADT Investigators. The levels of MDA-LDL in circulating immune complexes predict myocardial infarction in the VADT study. *Atherosclerosis*. 2012 Oct;224(2):526-31.
- Koska J, Saremi A, Bahn G, Yamashita S, Reaven PD for the VADT Investigators. The Effect of Intensive Glucose Lowering on Lipoprotein Particle Profiles and Inflammatory Markers in the Veterans Affairs Diabetes Trial (VADT). *Diabetes Care*. 2013 *published ahead of print March 27, 2013*, doi:10.2337/dc12-2082.
- Mark B. Zimring, Thomas E. Moritz, Robert J. Donnelly. Anti-Neurotrophic Effects from Autoantibodies in Adult Diabetes Having Primary Open Angle Glaucoma or Dementia. *Front Endocrinol (Lausanne)*. 2013; 4: 58.
- Bhensdadia NM, Hunt KJ, Lopes-Virella MF, Michael Tucker J, Mataria MR, Alge JL, Neely BA, Janech MG, Arthur JM. Urine haptoglobin levels predict early renal functional decline in patients with type 2 diabetes. *Kidney Int*. 2013 Jun;83(6):1136-43.

- Alele JD, Luttrell LM, Hollis BW, Luttrell DK, Hunt KJ; VADT Study Group. Relationship between vitamin D status and incidence of vascular events in the Veterans Affairs Diabetes Trial. *Atherosclerosis*. 2013 Jun;228(2):502-7.
- Madona Azar, Timothy J. Lyons, Petar Alaupovic, Julie A. Stoner, Carmen Quiroga, Derrick G. Kaufman, Maria Lopes-Virella, Richard L. Klein, Alicia J. Jenkins, VADT Study Group. Apolipoprotein-defined and NMR lipoprotein subclasses in the veterans affairs diabetes trial. *J Diabetes Complications*. 2013 Aug 1. doi:pii: S1056-8727(13)00113-X. 10.1016/j.jdiacomp.2013.05.005. [Epub ahead of print]
- Azad N, Agrawal L, Emanuele NV, Klein R, Bahn GD, Reaven P; VADT Study Group. Association of Blood - Jenkins, A.J., Fu, D., Azar, M., Stoner, J.A., Kaufman, D.G., Zhang, S.X., Klein, R.L., Lopes-Virella, M.F., Ma, J.X. & Lyons, T.J. Clinical Correlates of Serum Pigment Epithelium-Derived Factor in Type 2 Diabetes Patients. *J. J Diabetes Complications*. 2014 May-Jun;28(3):353-9. doi: 10.1016/j.jdiacomp.2014.01.008. Epub 2014 Jan 17.
- Glucose Control and Pancreatic Reserve with Diabetic Retinopathy in Veterans Affairs Diabetes Trial (VADT). *D Diabetologia*. 2014 Jun;57(6):1124-31. doi: 10.1007/s00125-014-3199-7. Epub 2014 Mar 6.
- Anderson, R.J., Bahn, G.D., Emanuele, N.V., Marks, J.B., Duckworth, W.C., for the VADT Study Group. Blood Pressure and Pulse Pressure Effects on Renal Outcomes in the Veterans Affairs Diabetes Trial (VADT). *Diabetes Care*. 2014 Oct;37(10):2782-8. doi: 10.2337/dc14-0284. Epub 2014 Jul 21.
- Saremi A, Schwenke DC, Bahn G, Ge L, Emanuele N, Reaven PD; VADT Investigators. The effect of intensive glucose lowering therapy among major racial/ethnic groups in the Veterans Affairs Diabetes Trial (VADT). *Metabolism* . 2015 Feb;64(2):218-25. doi: 10.1016/j.metabol.2014.10.010. Epub 2014 Oct 17.
- Florez H, Reaven P, Bahn G, Moritz T, Warren S, Marks J, Reda D, Duckworth W, Abaira C, Hayward R, Emanuele N, from VADT Research Group. Rosiglitazone Treatment and Cardiovascular Disease in the Veterans Affairs Diabetes Trial. *PubMed – NCBI Diabetes Obesity and Metabolism*. 2015 Oct;17(10):949-55. doi: 10.1111/dom.12487. Epub 2015 Jun 17.
- Hayward, R., Reaven, P., Wiitala, W., Bahn, G., Reda, R., Ge, L., McCarren, M., Duckworth, W., and Emanuele, N., for the VADT Investigators. Follow-up of Glycemic Control and Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine*. 2015 June;372(23):2197-2206. doi: 10.1056/NEJMoa1414266. Erratum in: *N Engl J Med*. 2015 Jul 9;373(2):198.
- Hayward, R., Reaven, P., and Emanuele, N., for the VADT Investigators. Follow-up of Glycemic Control and Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine*. 2015 Sep 3;373(10):978. DOI: 0.1056/NEJMc1508386
- Zimering MB, Behnke JA, Thakker-Varia S, Alder J (2015) Autoantibodies in Human Diabetic Depression Inhibit Adult Neural Progenitor Cells In vitro and Induce Depressive-Like Behavior in Rodents. *J Endocrinol Diab* 2(2): 11. 2015, April 25.
- Zimering, MB, Jeffrey, K, Ge, L, Bahn, G, and VADT Investigators (2016). Predictors of cognitive decline in older adult type 2 diabetes from the Veterans Affairs Diabetes Trial. *Front. Endocrinol.* 7:123. doi: 10.3389/fendo.2016.00123
- Azad N, Bahn G, Emanuele N, Agrawal L, Ge L, Reda D, Klein R, Reaven P, Hayward R and the VADT Study Group. Association of Blood Glucose Control and Lipids with Diabetic Retinopathy in the Veterans Affairs Diabetes Trail (VADT). *Diabetes Care*, 39: 816-822, 2016
- Saremi A, Bahn G, Reaven PD; A Link Between Hypoglycemia and Progression of Athrerosclerosis in the Veterans Affairs Diabetes Trial (VADT). *Diabetes care*, *Diabetes Care*, 39: 448-54, 2016
- Maria F Lopes-Virella, M.D., Ph.D., Kelly J Hunt, Ph.D., Nathaniel L Baker, M.S., Gabriel Virella, M.D., Ph.D., and the VADT Group of Investigators. High Levels of AGE-LDL, and of IgG Antibodies reacting with MDA-lysine epitopes expressed by oxLDL and MDA-LDL in Circulating Immune Complexes Predict Macroalbuminuria in Patients with Type 2 Diabetes. *Journal of Diabetes and Its Complications*. 2016 May-June;30(4): 693-699.

- Aramesh Saremi, Scott Howell, Dawn C. Schwenke, Gideon Bahn, Paul J. Beisswenger, Peter D. Reaven (2017) Advanced Glycation End Products, Oxidation Products, and the Extent of Atherosclerosis During the VA Diabetes Trial and Follow-up Study Diabetes Care 2017 Feb; dc161875. <https://doi.org/10.2337/dc16-1875>
- Herrington WG, Preiss D. Tightening our understanding of intensive glycaemic control. Lancet Diabetes Endocrinol 2017 Jun;5(6):405-407. doi: 10.1016/S2213-8587(17)30095-5. Epub 2017 Mar 30.
- Zoungas S, Arima H, Gerstein HC, Holman RR, Woodward M, Reaven P, Hayward RA, Craven T, Coleman RL, Chalmers J; Collaborators on Trials of Lowering Glucose (CONTROL) group. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. Lancet Diabetes Endocrinol 2017 Jun;5(6):431-437. doi: 10.1016/S2213-8587(17)30104-3. Epub 2017 Mar 30.

Appendix B

VADT Endpoint Definitions

CSP #465 (VADT) Endpoint Definitions

PRIMARY ENDPOINTS

1. MYOCARDIAL INFARCTION

Myocardial infarctions will be determined based on the algorithm supplied at the end of this appendix. All suspected MI will be evaluated in detail by the Endpoints Committee. All supporting documentation, i.e., ECGs, hospital records, laboratory values, etc. needed to confirm or rule out the presence or absence of an MI will be obtained by personnel at the ECG Laboratory.

2. CONGESTIVE HEART FAILURE – also see revised definition below:

Diagnosis of new congestive heart failure (CHF) can be made in the presence of at least two major manifestations of CHF or one major and at least two minor manifestations or new onset of pulmonary congestion requiring treatment. Treatment with diuretic, digitalis glycoside, ACE inhibitor, or hospitalization for management of symptoms of CHF would be appropriate.

Major Criteria:

- 1) paroxysmal nocturnal dyspnea
- 2) distended neck veins
- 3) cardiomegaly and pulmonary hilar congestion on X-ray, or increased heart size
- 4) acute pulmonary edema
- 5) increased venous pressure
- 6) hepatojugular reflux
- 7) documented 10% or greater decrease in ejection fraction to less than 40%.

Minor Criteria:

- 1) bilateral ankle edema
- 2) night cough
- 3) dyspnea on normal exertion
- 4) hepatomegaly
- 5) pleural effusion

Diagnosis of worsening CHF, for patients entering the Study with NYHA Class I or II CHF, will be made if there is a 10% (absolute) decrease in LVEF. Baseline assessment of LVEF must be made within the six months prior to randomization.

REVISED CHF DEFINITION: meets all criteria shown above with the additional requirement that the patient will have been hospitalized or had an urgent care visit associated with aggressive treatment for CHF as part of the event. Aggressive treatment today (2003) primarily includes intravenous treatment with diuretics and/or inotropic agents. However, as the study progresses, this list may be expanded to include newer oral agents. The aim of this additional condition is to ensure that the visit was accompanied by, if not precipitated by, moderate to severe CHF symptoms.”

3. STROKE

Occurrence and documentation (with copies of any hospital admissions) of cerebrovascular accident, subject to evaluation by the Endpoints Committee, will be counted as a primary endpoint.

Non-hemorrhagic stroke is defined as the sudden onset of localizing neurologic defect (e.g. hemiparesis, aphasia, homonymous hemianopsia) persisting for > 24 hours.

Intracranial hemorrhage is indicated by headache, change in consciousness, and signs of meningeal irritation with a bloody spinal fluid under increased pressure, with or without a localizing neurologic defect. Embolic stroke is indicated by the presence of an embolic source (e.g. atrial fibrillation, mitral stenosis, recent myocardial infarction, endocarditis), a consistent clinical course (e.g., rapid onset and clearing, localized defect, possibly bloody spinal fluid) and/or other peripheral emboli.

Results of imaging procedures, accompanied by a summary of a neurologist's examination or hospitalization work-up are to be included in the endpoint evaluation. No other disease process or event such as a brain tumor, trauma, subdural hematoma, subarachnoid hemorrhage, inflammatory disease, metabolic disorder, or peripheral lesion that could cause localized neurological deficit or course will be considered as an endpoint.

4. AMPUTATION

Amputation due to ischemic gangrene will be counted, with pathological report confirming the diagnosis.

5. CARDIOVASCULAR DEATH

Cardiovascular death is classified by the Endpoint Committee. An autopsy will be performed whenever possible. Major categories are sudden death, coronary heart disease, cerebrovascular accident, and other cardiovascular events (e.g. cardiomyopathy). The definition of sudden death will be used from the Framingham Study: death within one hour from the onset of symptoms, and if the cause of death could not be attributed to some potentially lethal disease other than coronary heart disease. Sudden death will be further classified as unexpected if the patient did not have a previous history of cardiovascular heart disease.

New York Heart Association Functional Classification

- | | |
|-----------|--|
| CLASS I | No limitation of physical activity. No dyspnea, fatigue, or palpitations with ordinary physical activity. |
| CLASS II | Slight limitation of physical activity. These patients have fatigue, palpitations, and dyspnea with ordinary physical activity, but are comfortable at rest. |
| CLASS III | Marked limitation of activity. Less than ordinary physical activity results
In symptoms but patients are comfortable at rest. |
| CLASS IV | Symptoms are present at rest and any physical exertion exacerbates the symptoms. |

Canadian Heart Classification

The Canadian Heart Classification is most often used to characterize a patient's limitation from angina pectoris. It is modified slightly from the New York Heart Association functional class.

- | | |
|-----------|--|
| CLASS I | Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina occurs with strenuous, rapid or prolonged exertion during work or recreational activity. |
| CLASS II | Slight limitations of ordinary activity by angina. Angina pectoris occur
when walking or stair climbing, after meals, or in cold, or I wind, or under emotional stress, or only during the few hours after awakening. Angina pectoris may also occur when walking more than ? blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions. |
| CLASS III | Marked limitation of ordinary physical activity. Angina pectoris occurs when walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace. |
| CLASS IV | Inability to carry on any physical activity without anginal discomfort.
Angina may be present at rest. |

Reference: Campeau, L: Grading of angina pectoris. Circulation 1976; 54:522-3.

Appendix C

Human Subjects



Subject Name: _____

Date: _____

Title of Study: **VA Diabetes Follow-up Study (VADT-FS)**Principal Investigator: **Nicholas Emanuele, M.D.**VAMC: **VAH Hines, IL****DESCRIPTION OF RESEARCH BY INVESTIGATOR**

PRINCIPLES CONCERNING RESEARCH: You are being asked to take part in a research project. It is important that you read and understand these principles that apply to all individuals who agree to participate in the research project below:

1. Taking part in the research is entirely voluntary.
2. You may not personally benefit from taking part in the research but the knowledge obtained may help the health professionals caring for you better understand the disease/condition and how to treat it.
3. You may withdraw from the study at any time without anyone objecting and without penalty or loss of any benefits to which you are otherwise entitled.
4. The purpose of the research, how it will be done, and what your part in the research will be, is described below. Also described are the risks, inconveniences, discomforts, and other important information, which you need to make a decision about whether or not you wish to participate. You are urged to discuss any questions you have about this research with the staff members.

SUBJECT'S IDENTIFICATION (*Social security number, give name-last, first, middle,*)

PURPOSE:

Version date: 08/01/2012
Study VA Promise # **0030**
In lieu of VA FORM 10-1086
IRB consent form Rev: 8-2009



Subject Name: _____

Date: _____

Title of Study: **VA Diabetes Follow-up Study (VADT-FS)**Principal Investigator: **Nicholas Emanuele, M.D.**VAMC: **VAH Hines, IL**

All patients who participated in CSP #465, "Glycemic Control and Complications in Diabetes Mellitus Type 2", are being asked to participate in a long-term follow-up study. The Long Term Follow-up Study will allow the investigators to determine the long term effects of tight and standard glycemic control on the progression of illness associated with diabetes, i.e., coronary artery (heart disease) and peripheral vascular disease (stroke, claudication or leg pain), kidney disease, vision loss and mortality. Although the main CSP #465 study which you participated in provided considerable information on the benefits and risks of tight and standard glycemic control, many of the potential health problems related to diabetes take years to develop. Through your continued participation in this research project we hope to learn about the long lasting benefits (if any) of the two types of treatment (tight and standard glycemic control).

The Long Term Follow-up study plans to follow all of the CSP #465 patients who agree to participate for 9 additional years from the end of the main trial in May, 2008. The Long-Term Follow-up Study began in June 2008 and will go through the end of May 2017. If you agree to participate in this Follow-up Study, you will be asked to authorize the researchers to perform computerized searches of centralized medical databases to collect information on health care services you receive from the end of your participation in the main trial till the end of this follow-up study. Both VA and non-VA computer files will be searched to obtain information about your health care. Examples of the non-VA databases to be searched include Medicare and Medicaid computer files, national death files, and any other databases that maintain national health care information that may be developed while the Long-Term Follow-up study is being conducted. The study will also attempt to evaluate the health care costs that are associated with treatments, care, and testing you have received for your diabetes and related illnesses. In addition, you will be asked on several occasions to complete questionnaires about your quality of life and respond to questions about health care you received from VA and non-VA providers.

The study is being funded by the Department of Veterans Affairs Cooperative Studies Program and may be funded by other agencies in the future and **will be coordinated at two VA centers: 1) the Hines VA Cooperative Studies Coordinating Center** and 2) the Clinical Data Collection Center, in the VA Health Services Research and Development Service at the Ann Arbor VA Medical Center. Both the Hines and Ann Arbor Centers have extensive experience in conducting observational studies similar to the CSP #465 Long Term Follow-up Study. You are approximately one of 1350-1500 patients that are eligible nationally.

PROCEDURES:

Version date: 08/01/2012

Study VA Promise # 0030

In lieu of VA FORM 10-1086

IRB consent form Rev: 8-2009



Subject Name: _____

Date: _____

Title of Study: **VA Diabetes Follow-up Study (VADT-FS)**Principal Investigator: **Nicholas Emanuele, M.D.**VAMC: **VAH Hines, IL**

You will be contacted once yearly during the study by mail and asked to complete questionnaires about your quality of life and any health care you have received during the previous year. The forms are easy to complete, should only take about 30 minutes of your time to complete and are similar to those that you may have completed during the active phase of CSP #465. You will be provided a Business Reply Envelope for your use in returning the completed questionnaires to the researchers.

If you do not respond to the study mailings or if you prefer, we will make telephone contact with you to encourage you to submit the questionnaires or provide the information during the telephone call. You will also be asked to provide the name and contact information of someone who will always know your whereabouts and who would be able to provide authorization for release of medical information if you should be unable to do so. This contact person would only be contacted if we were unable to reach you or if you were incapacitated.

If you have received health care in a non-VA facility and you do not have Medicare or Medicaid coverage, we will ask for your written authorization to obtain copies of these health care records.

Since your participation is very important to the success of this project, we will ask for updated address and telephone information in the annual questionnaires and we will provide you with information as to who to notify if you should move or change your telephone number.

Health Care Use/Database Searches

Periodically during the study the researchers will perform searches of VA and non-VA computer databases to determine your vital status and whether you have had any health events associated with diabetes. The study will also use these databases to help obtain costs of services information that would be associated with the type of medical care you may have received. The study will use your Social Security Number (SSN) to search these computer files; by signing this consent document you authorized the use of your SSN for this purpose. Because this study is expected to last for a total of 9 years, the database searches will continue through the end of the study to 2017. The medical information recorded between your local site study closure and today's date will also be sought.

Version date: 08/01/2012
Study VA Promise # 0030
In lieu of VA FORM 10-1086
IRB consent form Rev: 8-2009



Subject Name: _____

Date: _____

Title of Study: **VA Diabetes Follow-up Study (VADT-FS)**Principal Investigator: **Nicholas Emanuele, M.D.**VAMC: **VAH Hines, IL****RISKS:**

Since this study does not include any intervention or treatment, your participation should not put your physical health at risk. There are risks associated with your privacy and from completing the research questionnaires, these risks are explained below and also under "Confidentiality".

Health Information and Social Security Number:

By participating in this study you are granting the researchers access to your private health information (PHI). There are potential risks associated with sharing PHI and allowing the use of your Social Security Number, which include loss of confidentiality, privacy and even the possibility of identity theft. However, every precaution will be taken to safeguard your privacy, your Social Security Number and any other information collected as part of this study. The VA has established stringent policies and procedures regarding data security and patient privacy and these policies and procedures will be strictly adhered to by the study personnel. You will be asked to sign a HIPAA authorization.

Questionnaires:

Potential risks of completing the questionnaires may be that you will recognize changes in your daily functioning or quality of life that can be associated with aging and/or your health conditions.

Other Risks:

Participation in this research may also involve risks that are currently unforeseeable.

Potential risks involve experiencing negative mood states from being asked to recall unpleasant memories.

You may experience discomfort due to the types of questions being asked. You do not have to answer all the questions.

Note: sometimes the risk is the loss of confidentiality or privacy

BENEFITS: You may not directly benefit from this study. However, the knowledge gained from this study may help others in the future and will be of value to the medical community.

Version date: 08/01/2012

Study VA Promise # 0030

In lieu of VA FORM 10-1086

IRB consent form Rev: 8-2009



Subject Name: _____

Date: _____

Title of Study: **VA Diabetes Follow-up Study (VADT-FS)**Principal Investigator: **Nicholas Emanuele, M.D.**VAMC: **VAH Hines, IL****STUDY WITHDRAWAL:**

You do not have to take part in this study and refusal to participate will involve no penalty or loss of rights to which you are entitled. You may withdraw from this study at any time without consequences or loss of VA benefits.

If you choose to withdraw from this study you should send written notification to the investigator, Nicholas Emanuele, M.D. at 5000 S. 5th Ave, Mail route 111A, Hines, IL 60141.

The study may be stopped at any time for administrative or funding reasons at which time your participation the study would end, but you would be notified in writing that the study has been concluded.

CONFIDENTIALITY:

Any information obtained about you in this study will be treated as confidential and will be safeguarded in accordance with the Privacy Act of 1974. Information published or presented about the results of the study will be in a form that does not identify any particular participant. In order to comply with federal regulations, records identifying you may be reviewed by the members of the research team, the representatives of the sponsor or sponsor (the Veterans Health Administration) of this study, authorized representatives of the IRB, VA, Federal agencies such as the Food and Drug Administration (FDA), the Office for Human Research Protection (OHRP) and the Government Accounting Office (GAO). The FDA may choose to inspect research records that include the subject's individual medical records. By signing this document, you consent to such inspection.

FINANCIAL COMPENSATION:

You will receive a \$10 gift card for a retail store for every questionnaire that you complete.

RESEARCH SUBJECT COSTS: You will not be required to pay for medical care or services received as a participant in a VA research project except as follows: some veterans are required to pay co-payments for medical care and services provided by VA. These co-payment requirements will continue to apply to medical care and services provided by VA that are not part of this study. However, there are no medical costs that are part of this study.

Version date: 08/01/2012

Study VA Promise # 0030

In lieu of VA FORM 10-1086

IRB consent form Rev: 8-2009



Subject Name: _____

Date: _____

Title of Study: **VA Diabetes Follow-up Study (VADT-FS)**Principal Investigator: **Nicholas Emanuele, M.D.**VAMC: **VAH Hines, IL****RESEARCH-RELATED INJURIES:**

You are not expected to experience any research-related injuries by participating in this study. However, in the extremely rare event that you sustain an injury or illness as a result of your participation in this VA approved research study, all medical treatment (emergency as well as medical treatment beyond emergency care) will be provided by the VA. You will be treated for the injury at no cost to you. However, no additional compensation has been set aside.

According to the federal regulations, (Title 38 Code of Federal Regulations (CFR) 17.85), The VA will provide necessary medical treatment to you as a research subject if you are injured by participation in this research project. Except in limited circumstances, this care will be provided at this VA facility. This requirement does not apply to treatment for injuries that result from non-compliance by you with study procedures. The Department of Veterans Affairs does not normally provide any other form of compensation for injury. You have not released this institution or sponsor from liability for negligence.

RESEARCH SUBJECT'S RIGHTS: You have read, or have had read to you all of the above information. National study staff explained the study to you and has answered all your questions. The risks or discomforts and possible benefits and the alternatives of the study have been explained to you.

The results of this study may be published but your identity and records will not be revealed unless required by law.

If you have any complaints, concerns, or if you have questions about the research, you can call Dr. Nicholas Emanuele at 708-202-8387 during the day, or 708-202-3800 after hours.

Additionally, if you have any questions about the research, your rights as a research subject, want to discuss problems with the research process, offer input or have other concerns, you can contact the Chair of the Institutional Review Board or Research Staff at 708/202-5701."



Subject Name: _____ Date: _____

Title of Study: **VA Diabetes Follow-up Study (VADT-FS)**Principal Investigator: **Nicholas Emanuele, M.D.** VAMC: **VAH Hines, IL****STATEMENT OF CONSENT:**

I voluntarily consent to participate in this study. This research study and my rights as a research participant have been explained to me.

I will receive a copy of this consent form and a copy will be placed in my medical chart and additional copies will be filed in the Research Office.

Subject's Signature

Subject's Telephone Number_____
Date_____
Signature of Investigator_____
Date_____
Signature of Person Obtaining Consent_____
Date



DEPARTMENT OF VETERANS AFFAIRS
EDWARD HINES, JR. VA HOSPITAL
CAPT. JAMES A. LOVELL FEDERAL HEALTH CARE CENTER

INSTITUTIONAL REVIEW BOARD
Building 1, Room C334
PO Box 5000 (151)
Hines, IL 60141

Study Title: *VA Diabetes Trial Follow-up Study*

Principal Investigator: *Nicholas Emanuele, M.D.*

**Department of Veterans Affairs Authorization for
Release of Protected Health Information for Research Purposes**

You have been asked to be part of a research study under the direction of Dr. *Nicholas Emanuele* and his research team. The purpose of this study is to help determine allow the investigators to determine the long term effects of tight and standard glycemic control (diabetes management) on the progression of illness associated with diabetes, i.e., coronary artery (heart disease) and peripheral vascular disease (stroke, claudication or leg pain), kidney disease, vision loss and mortality.

By signing this document, you will authorize the Veterans Health Administration (VHA) to provide Dr. *Nicholas Emanuele* and his research team to use and/or disclose the following information about you.

- ☒ Demographic Information: e.g. Name, Address, Phone Number, Social Security Number, Date of Birth
- ☒ Medical Record: history and physical exam notes, progress notes, consultation reports, laboratory test results, operative reports
- ☐ *Photographs, videotapes, or digital or other radiographic images*
- ☐ *Tissue Samples (specify)*
- ☐ *Blood Samples (specify)*

The information that will be released may include information regarding the following conditions:

- ☐ Drug Abuse
- ☐ Alcoholism or Alcohol Abuse
- ☐ *Mental or Behavioral Health or Psychiatric Care*
- ☐ *Acquired Immunodeficiency Syndrome (AIDS) or Human Immunodeficiency Virus (HIV) Infection*
- ☐ *Sickle Cell Anemia*

The research team may also need to disclose the information to others as part of the study process. The others may include representatives of the Hines Cooperative Studies Program Coordinating Center and to the Ann Arbor VA Health Services Research & Development

Center of Excellence. The collected information will be maintained to the highest standards of confidentiality as required by VA research.

If you do not sign this authorization, you will not participate in the study.
This authorization to use your information has no expiration date.

While this study is being conducted, you will not be allowed to see research-related medical records about you that are created or obtained by the research team. You will be able to see them again when the study is completed. This will not affect your doctor's ability to see your records as part of your normal health care.

You can revoke this authorization, in writing, at any time. Your individually identifiable health information that is disclosed in accordance with this authorization may no longer be protected by Federal laws or regulations and may be subject to re-disclosure by the non-VA recipient. To revoke your authorization, you must write to the Release of Information Office at this facility or you can ask a member of the research team to give you a form to revoke the authorization. Your request will be valid when the Release of Information Office receives it. If you revoke this authorization, you will not be able to continue to participate in the study. This will not affect your right as a VHA patient to treatment or benefits outside the study. If you revoke this authorization, Dr. Nicholas Emanuele and his research team can continue to use information about you that was collected before receipt of the revocation. The research team will not collect information about you after you revoke the authorization.

The VHA complies with the requirements of the Health Insurance Portability and Accountability Act of 1996 and its privacy regulations and all other applicable laws that protect your privacy. We will protect your information according to these laws. Our Notice of Privacy Practices (a separate document) provides more information on how we protect your information. If you do not have a copy of the Notice, the research team will provide one to you.

I have read this authorization form and have been given the opportunity to ask questions. If I have questions later, I understand I can contact Dr. Nicholas Emanuele at 708-202-8387 Ext 4533. I will be given a signed copy of this authorization form for my records. I authorize the use of my identifiable information as described in this form.

Signature of Participant or Person Authorized
to Sign for Participant
(Attach authority to sign, e.g., Power of Attorney)

Date

Print Participant Name

Participants SSN (VHA 1605.1 b. 1(a))

Instructions to Investigator: VHA Handbook 1605.1 14 (d)

- When Signed, a copy of the signed authorization is required to be given to the individual

Written authorization for release of information is valid when signed by:

- The individual
- Court appointed guardian (NOT federal fiduciary monetary benefits)
- Person legally authorized in writing by the individual (or the individual's legal guardian (i.e. POA)
- If deceased, then the Executor of Estate

Appendix D

Survey Letter and Questionnaire

DEPARTMENT OF VETERANS AFFAIRS
HEALTH SERVICES RESEARCH & DEVELOPMENT CENTER OF EXCELLENCE
VA Medical Center
Ann Arbor, Michigan

In Reply Refer To: CSP #465-FS
#1234

June 1, 2011

Mr. John Doe
1234 Main Street
Any Town, MI 12345

Dear Mr. Doe:

Thank you for your ongoing participation in the VA Diabetes Trial (VADT, CSP #465). As you know, the clinic visits and examination portion of this important study ran from 2000-2008. We are very grateful that in 2008 you agreed to continue to participate in the VADT-Follow-up Study by completing an annual survey. Of course, your continued participation is completely voluntary and will not in any way affect your health care or your VA benefits. However, your ongoing participation is very important to the success of this study, and we hope that you will take the time to complete this brief annual survey to assist us in this important project. In order for this study to maintain the highest level of scientific accuracy, having information on each participant is extremely valuable and important. The information in this survey will provide useful information that could help us learn how to help veterans and other people with diabetes live longer and healthier lives. Your generous help with this study is much appreciated. As a small token of our thanks, we have enclosed a gift card with a value of \$10.

Please complete the enclosed survey and return it in the self-addressed, postage paid envelope provided. This survey is designed to take 10-20 minutes of your time. All responses to the questions will be strictly confidential and no information about any individual veteran will be released. If we do not hear from you within the next few weeks, we will contact you again. If you need assistance in completing the questionnaire or have any questions or concerns, you or a friend/family member should feel free to contact Douglas Bentley at (800) 753-3357. Alternatively, you can simply indicate on the cover of the questionnaire that you would like to answer the survey by phone, and return the uncompleted questionnaire to us in the envelope provided. We will then contact you by telephone to administer the questionnaire or respond to your questions.

We thank you for your time and assistance with the VADT Follow-up Study.

Sincerely,

Rodney A. Hayward, M.D.
Director
VA Ann Arbor Health Services Research
& Development Center of Excellence

Enclosures

The VA Diabetes Trial Follow-up Study
Annual Survey



Survey Instructions

- Please answer all questions as best you can
- All of your answers will be kept confidential
- Please return the completed questionnaire in the self-addressed, postage-paid envelope provided

Thank you so much for your time and assistance!

Would you prefer that we contact you by phone? ☐

If because of visual problems or any reason whatsoever, you would prefer to complete this survey by phone, please contact us at 1-800-753-3357 and ask for *Doug Bentley*.

Starts Approval Expires
12/16/13 IRB 10/06/14
Edward Hines, Jr. VAH/JALFHCC

CSP #465-F
VADT Long Term Follow-up Study

Form (70)
Annual Survey

I. General Health Questions:

1. In general, would you say your health is: **(Circle one)**

23 ☐ 1 Excellent ☐ 2 Very Good ☐ 3 Good ☐ 4 Fair ☐ 5 Poor

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? **(Circle one)**

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Moderate activities</u> such as moving a table, pushing a vacuum cleaner, bowling, playing golf: _ _ _ _	24 <input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
b. Climbing several flights of stairs: _ _ _ _ _	25 <input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health? **(Circle one)**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. <u>Accomplished</u> less than you would like? _ _ _ _ _	26 <input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
b. Were <u>limited</u> in the kind of work or other activities? _ _ _ _ _	27 <input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems? **(Circle one)**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. <u>Accomplished</u> less than you would like? _ _ _ _ _	28 <input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
b. Did work or other activities less carefully than usual? _ _ _ _ _	29 <input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4

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5. During the past 4 weeks, how much did pain interfere with your normal work, (including both work outside the home and housework)? (Circle one)

Not at all	A little bit	Moderately	Quite a bit	Extremely
30 <input type="text" value="1"/>	<input type="text" value="2"/>	<input type="text" value="3"/>	<input type="text" value="4"/>	<input type="text" value="5"/>

6. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)? (Circle one)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
31 <input type="text" value="0"/>	<input type="text" value="1"/>	<input type="text" value="2"/>	<input type="text" value="3"/>	<input type="text" value="4"/>

7. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks.... (Circle one)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful? 32	<input type="text" value="0"/>	<input type="text" value="1"/>	<input type="text" value="2"/>	<input type="text" value="3"/>	<input type="text" value="4"/>
b. Did you have a lot of energy? _ _ _ 33	<input type="text" value="0"/>	<input type="text" value="1"/>	<input type="text" value="2"/>	<input type="text" value="3"/>	<input type="text" value="4"/>
c. Have you felt downhearted and depressed? _ _ _ _ _ 34	<input type="text" value="0"/>	<input type="text" value="1"/>	<input type="text" value="2"/>	<input type="text" value="3"/>	<input type="text" value="4"/>

8. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is: (Circle one)

35 Excellent Good Fair Poor Very Poor Completely Blind

9. Is the VA your primary source for diabetes care? (Circle one)

36 No Yes

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II. Hospitalizations and Medical Procedures:

The following questions ask you about hospitalizations and medical procedures that you may have had since *June 1, 2013*.

10. Since *June 1, 2013*, have you had a heart attack, myocardial infarction ("MI") or coronary"? (Circle one)

37 ☐ No (If no, skip to question 11 on next page) ☐ Yes

If "yes", please list the hospital name, city, state, and admission date (including the year) for each hospitalization you had for a heart attack since *June 1, 2013*:

1st Admission:

Hospital Name: 40

City: 70 State: 90

Admitted: 92 / 94
Month Year

Is this a VA Hospital? 96 ☐ No ☐ Yes

Rec ☐ 2

2nd Admission:

Hospital Name: 22

City: 52 State: 72

Admitted: 74 / 76
Month Year

Is this a VA Hospital? 78 ☐ No ☐ Yes

3rd Admission:

Hospital Name: 22

City: 52 State: 72

Admitted: 74 / 76
Month Year

Is this a VA Hospital? 78 ☐ No ☐ Yes

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Rec **4**

11. Since *June 1, 2013*, have you had a stroke or “mini-stroke”? These are also called cerebrovascular accidents (“CVA”), blood clots in the brains, or transient ischemic attacks (“TIA”):
(Circle one)

21 ☐ **0** No (If no, skip to question 12 on next page) ☐ **1** Yes

If “yes”, please list the hospital name, city, state, and admission date (including the year) for each hospitalization you had for a stroke or mini-stroke since *June 1, 2013*:

1st Admission:

Hospital Name: 22

City: 52 State: 72

Admitted: 74 / 76
Month Year

Is this a VA Hospital? 78 ☐ **0** No ☐ **1** Yes

Rec **5**

2nd Admission:

Hospital Name: 22

City: 52 State: 72

Admitted: 74 / 76
Month Year

Is this a VA Hospital? 78 ☐ **0** No ☐ **1** Yes

3rd Admission:

Hospital Name: 22

City: 52 State: 72

Admitted: 74 / 76
Month Year

Is this a VA Hospital? 78 ☐ **0** No ☐ **1** Yes

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13. Since *June 1, 2013*, have you had any of the following procedures done? (Circle one)

	Yes	No	Unsure
a. Angioplasty or stent or balloon or bypass to unclog arteries to your heart ?	70 <input type="text" value="1"/>	<input type="text" value="0"/>	<input type="text" value="2"/>
b. Angioplasty or stent or balloon or bypass to unclog arteries to your brain ?	71 <input type="text" value="1"/>	<input type="text" value="0"/>	<input type="text" value="2"/>
c. Retina eye surgery (such as "laser" treatment or "vitrectomy")?	72 <input type="text" value="1"/>	<input type="text" value="0"/>	<input type="text" value="2"/>
d. Cataract eye surgery?	73 <input type="text" value="1"/>	<input type="text" value="0"/>	<input type="text" value="2"/>
e. Either dialysis or kidney transplant for kidney failure?	74 <input type="text" value="1"/>	<input type="text" value="0"/>	<input type="text" value="2"/>

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III. Diabetes & Your Health:

14. Directions: Read each statement carefully. Please indicate how satisfied or dissatisfied you currently are with the aspect of your life described in the statement. *CIRCLE* the number that corresponds to how satisfied or dissatisfied you feel. There are no right or wrong answers to these questions. We are interested in your opinion.

(Circle one number on each line)		Satisfied			Dissatisfied	
		Very	Moderately	Neither	Moderately	Very
75	a. How satisfied are you with the amount of time it takes to manage your diabetes?	1	2	3	4	5
76	b. How satisfied are you with the amount of time you spend getting checkups?	1	2	3	4	5
77	c. How satisfied are you with the time it takes to determine your sugar levels?	1	2	3	4	5
78	d. How satisfied are you with your current treatment?	1	2	3	4	5
79	e. How satisfied are you with the flexibility you have with your diet?	1	2	3	4	5
80	f. How satisfied are you with the burden your diabetes is placing on your family?	1	2	3	4	5
81	g. How satisfied are you with your knowledge about your diabetes?	1	2	3	4	5
82	h. How satisfied are you with your sleep?	1	2	3	4	5
83	i. How satisfied are you with your social relationships and friendships?	1	2	3	4	5

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III. Diabetes & Your Health: Continued

(Circle one number on each line)		Satisfied			Dissatisfied	
		Very	Moderately	Neither	Moderately	Very
84	j. How satisfied are you with your sex life?	1	2	3	4	5
85	k. How satisfied are you with your work, school, and household activities?	1	2	3	4	5
86	l. How satisfied are you with the appearance of your body?	1	2	3	4	5
87	m. How satisfied are you with the time you spend exercising?	1	2	3	4	5
88	n. How satisfied are you with your leisure time?	1	2	3	4	5
89	o. How satisfied are you with life in general?	1	2	3	4	5

15. Directions: Read each statement carefully. Please indicate how often the following events happen to you. *CIRCLE* the appropriate number. There are no right or wrong answers to these questions. We are interested in your opinion.

(Circle one number on each line)		Never	Very Seldom	Sometimes	Often	All of the Time
90	a. How often do you feel pain associated with the treatment of your diabetes?	1	2	3	4	5
91	b. How often are you embarrassed by having to deal with your diabetes in public?	1	2	3	4	5
92	c. How often do you have low blood sugar?	1	2	3	4	5
93	d. How often do you feel physically ill?	1	2	3	4	5
94	e. How often does your diabetes interfere with your family life?	1	2	3	4	5
95	f. How often do you have a bad night's sleep?	1	2	3	4	5

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III. Diabetes & Your Health: Continued

(Circle one number on each line)		Never	Very Seldom	Sometimes	Often	All of the Time
96	g. How often do you find your diabetes limiting your social relationships and friendships?	1	2	3	4	5
97	h. How often do you feel good about yourself?	1	2	3	4	5
98	i. How often do you feel restricted by your diet?	1	2	3	4	5
99	j. How often does your diabetes interfere with your sex life?	1	2	3	4	5
100	k. How often does your diabetes keep you from driving a car or using a machine (e.g., a typewriter)?	1	2	3	4	5
101	l. How often does your diabetes interfere with your exercising?	1	2	3	4	5
102	m. How often do you miss work, school, or household duties because of your diabetes?	1	2	3	4	5

Again, thank you very much for taking the time to complete this questionnaire.

Please return the completed questionnaire
in the self-addressed, postage-paid envelope provided.

Appendix E

Opt-in Letter and Opt-out Letter

DEPARTMENT OF VETERANS AFFAIRS

In Reply Refer To: CSP #465-FS
#1234

June 1, 2011

Mr. John Doe
1234 Main Street
Any Town, MI 12345

Dear Mr. Doe:

Thank you for your participation in the VA Diabetes Trial (VADT, CSP #465). As you know, the clinic visits and examination portion of this important study ended in 2008. The results of this study were very important and helped change the way diabetes is treated in the VA and around the world.

We are very grateful that you agreed to continue to participate in the VADT Follow-up Study, which only consists of tracking a few parts of your medical history using VA and other databases. This, therefore, requires no action on your part. There may also be an occasional voluntary survey to get your opinion on how your health is.

This letter is to inform you about a slight change in the Follow-up Study which will not in any way affect what you do to participate, or how you receive your local healthcare. Because the VADT Follow-up Study does not require local VA visits, it has been administratively closed at your VA hospital. However, the study will now be run centrally from the Hines VA Medical Center under direction of Dr. Nicholas Emanuele and Dr. Peter Reaven, who helped run the VADT. **We are asking that you continue to participate in this study by signing and returning two attached forms; HIPAA and Informed Consent (postage pre-paid).** Again, the only change is the central administration of the study by Hines and this point is highlighted in the attached documents.

Your ongoing participation is very important to the success of this study, and we hope that you will choose to sign and return the forms. Other medical studies have reported that some of the most important information comes during these follow-up periods. In order for this study to maintain the highest level of scientific accuracy, having information on each participant is extremely valuable and important, and we cannot continue to collect that information unless you sign and return the enclosed documents.

For questions about your rights as a research participant or to discuss problems, complaints or concerns about the study, contact the Hines IRB Office at 708-202-5701.

We thank you for your time and assistance with the VADT Follow-up Study and for returning the enclosed forms.

Sincerely,

Nicholas Emanuele, M.D.
Enclosures

DEPARTMENT OF VETERANS AFFAIRS

In Reply Refer To: CSP #465-FS
#1234

June 1, 2011

Mr. John Doe
1234 Main Street
Any Town, MI 12345

Dear Mr. Doe:

Thank you for your ongoing participation in the VA Diabetes Trial (VADT, CSP #465). As you know, the clinic visits and examination portion of this important study ended in 2008. We are very grateful that you have agreed to continue to participate in the VADT Follow-up Study. The Follow-up Study simply consists of tracking your medical history by study of several databases and requires no action on your part. In addition, there is a voluntary annual survey that is performed by mail.

This letter is to inform you about a very slight change in the Follow-up Study which will not in any way affect what you do to participate or how you receive your local healthcare. Since the active part of the VADT was completed in 2008, the study will now be run centrally from the Hines VA Medical Center under direction of Dr. Nicholas Emanuele and Dr. Peter Reaven. Although this change is very minimal and will not affect anything that you agreed to previously, we did want to give you a chance to 'opt out' of the Study. If you do **not** agree to continue participation (decide you no longer wish to continue), please sign the attached page and mail it back in the self-addressed envelope.

Your ongoing participation is very important to the success of this study, and we hope that you will choose to remain in the program. Other studies have reported that some of the most important information comes during these follow-up periods. In order for this study to maintain the highest level of scientific accuracy, having information on each participant is extremely valuable and important.

For questions about your rights as a research participant or to discuss problems, complaints or concerns about the study, contact the IRB Office at 708-202-5701.

If nothing is returned, we will assume that you wish to continue to allow us to track your medical information and receive the mailed questionnaires.

We thank you for your time and assistance with the VADT Follow-up Study.

Sincerely,

Nicholas Emanuele, M.D.
Enclosures

CSP 465-F
VA Diabetes Trial Follow-up
Opt Out

I _____ do not agree to continue to participation in the
(print Name)

CSP 465-F "VA Diabetes Trial Follow-up Study under the Hines IRB leadership.

(sign name)

(date)

(social security number)