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PRINCIPAL INVESTIGATOR: Dr. Robert Vigersky

CONTRACTING ORGANIZATION: The Geneva Foundation
917 Pacific Ave., Ste. 600
Tacoma, WA 98402

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COL Robert Vigersky, MD

Email: Robert.a.vigersky.mil@health.mil

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14. ABSTRACT
The overall aim of this proposal is to test the clinical effects of a Computer Assisted Decision Support (CADS) System for the management of Type 2 diabetes (T2D) by primary care providers (PCPs). Moreover, the aims are to compare longitudinal patterns of change within and between patients who are managed with the CADS system for differing durations. This comparison will help us to understand the clinical utility of using the CADS system continuously or up to a certain threshold of patient improvement. To achieve these aims, we requested a second year of funding (first year funded through United States Army Medical Research Acquisition Activity [USAMRAA], contract number W81XWH-09-2-0196, for a prospective, cluster, randomized controlled trial (RCT). The ongoing project is a multi-site study including the Walter Reed National military Medical Center, Fort Belvoir Community Hospital (FBCH), and the Kimbrough Ambulatory Care Center.

The proposal herein is not duplicative of any current study but rather an extension of the already funded one. A detailed, technical explanation of the software and hardware elements of this study are included in reports for the original CADS study and available upon request.

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None provided.

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INTRODUCTION

Diabetes mellitus (DM) affects nearly 26 million people in the United States and is associated with devastating complications in both personal and financial terms. Diabetes is the leading cause of blindness, non-traumatic amputations, and renal failure in adults and reduces life expectancy by 5-10 years. The direct ($116 billion) and indirect ($68 billion) costs of DM care have dramatically increased along with the epidemic increase in the number of those with DM over the past 10 years. The cost of medical care per capita is approximately $10,000 per year compared with $2,700 per year for those without DM. The vast majority of these costs are related to hospitalizations resulting from the chronic complications of DM, with only about 15% of the costs attributable to professional visits and pharmaceuticals.

The Diabetes Control and Complications Trial (DCCT), the United Kingdom Prospective Diabetes Study (UKPDS), and the "Kumamoto" study conclusively proved that improved glycemic control is important in reducing microvascular complications (1-3). Together, these studies showed that for every 1% decrease in A1C, there is a 25% decrease in microvascular complications. Based on these studies, the American Diabetes Association (ADA) recommends that the goal for A1C should be below 7% (normal = 4 - 6.1%) (4), and the American Association of Clinical Endocrinologists (AACE) recommends that it should be below 6.5%, corresponding to an average blood glucose (BG) values of 150 and 135 mg/dL, respectively, [normal = 70 - 126 mg/dl] (5). Furthermore, years of improved glycemic control appear to have a legacy effect and not only reduce the future rate of microvascular complications but also decrease the incidence of macrovascular complications in both Type 1 and Type 2 diabetes (6-7).

Hypertension is one of the most common co-morbidities associated with DM and substantially contributes to the macrovascular disease that occurs in up to 80% of patients with DM (14). Several large randomized clinical trials (RCTs), including the UKPDS, demonstrated that, independent of the effects of glycemic control, improving blood pressure (BP) control significantly reduced macrovascular complications and cardiovascular-related deaths (14-17). Similarly, the UKPDS showed a 13 % reduction in microvascular complications for every 10 mmHg reduction in systolic pressure (18). This finding was confirmed and extended to DM patients who were "normotensive" (19). Gaede et al. showed the marked benefit of aggressive blood pressure, lipid, and blood glucose management achieved through multifactorial intervention (20). There also appears to be a legacy effect of blood pressure control in Type 2 diabetes as recently shown by Holman et al. (21).

Despite the well-documented benefits of glycemic and BP control, these are still sub-optimal in most patients. Although there is a trend toward improved glycemic control, the latest (2004) National Health and Nutrition Examination Survey (NHANES) data demonstrated that 42.3% of patients with DM have A1Cs over 7% (22). The military healthcare system (MHS) - where there is no cost to the patient for care and testing supplies - has similar results with hemoglobin A1C's over 7% in 42% and over 9.0% in 23.3% of all patients with diabetes. The data from the Walter Reed Health Care System (WRHCS) is similar with 51% having an A1C above 7% as of December, 2009. Furthermore, BP control in our patients is similar to the national average with 62% of our patients having either systolic over 140 mmHg and/or diastolic over 90 mmHg under current treatment. Recommended levels to reduce the risk of cardiovascular mortality and morbidity are less than 130/80 mm/Hg.

Reasons for Sub-optimal Achievement of Diabetes Control

The reasons why more patients do not reach appropriate goals for glycemic control are multiple and complex. First, due to an insufficient number of Endocrinologists and Certified Diabetes Educators in both military and civilian health care settings (23), the vast majority of patients with DM are managed by primary care providers (PCPs), including family practitioners, nurse generalists, nurse practitioners, and physicians' assistants, who are not necessarily equipped with the latest information and tools to provide optimum care nor have the time required to evaluate relevant data necessary to do so. The patient may bring his/her handwritten logbook and/or meter to the clinic where the data must be reviewed manually or the patient will bring his/her memory-equipped meter to the clinic, where it may be uploaded to the provider's computer and analyzed. Manual review of the records precludes any statistical and graphical analysis of the data and often limits the provider's ability to recognize patterns and trends. Moreover, this approach is a time-consuming and an inefficient use of both the provider's and patient's time. Uploading of the glucose data provides the requisite statistical and graphical analysis. However, all the major glucose meter manufacturers have their own proprietary software – none of which are integrated into the electronic medical record (EMR) - and each of the meters has its own unique connecting cable. Thus, the multiplicity of non-integrated programs and connecting cables prevent the provider from efficiently reviewing BG data and thus creates a significant barrier to using this technology.

Second, the introduction of new oral and parenteral agents has exponentially increased the complexity of the management of T2DM in the last 10-15 years. Prior to the introduction of metformin in 1995, the only available class of oral agents was

sulfonylureas. Now there are thirteen classes of oral medications, insulins, and non-insulin injectables. Recombinant human insulin and analog insulins have come into common use and the long-acting insulin analogs (insulin glargine and Detemir) have been incorporated into many regimens for type 2 diabetes either alone or in combination with oral agents. The enormous number of possible combinations of therapeutic agents makes it difficult for physicians to be familiar with all available approaches. Making matters more complex is that for each class there may be several options, e.g. for insulin secretagogues one can choose sulfonylureas like glipizide, glipizide-XL, or glyburide or a meglitinide such as nateglinide or repaglinide.

Third, self–monitoring of blood glucose (SMBG) on the part of the patient is an essential tool in achieving improved glycemic control. Several studies have shown that improved glycemic control is cost effective in both Type 1 and Type 2 DM (T1DM and T2DM) despite the increase in cost of supplies, a greater number of clinic visits, and more pharmaceuticals used. Yet, many patients do not monitor as recommended, in part because of the barriers noted above (e.g., they perceive that their providers cannot or do not review the SMBG results), a lack of understanding of how to use their glucose data to improve their glycemic control, as well as social and personal barriers.

The Case for Systematic, Rigorous Examination of a Computer Assisted Decision Support System for Diabetes Management

Although many studies have demonstrated the potential advantages of telemedicine, web-based, and/or web-assisted DM management, most have used the web for patient education, performance monitoring, risk stratification, and case management by nurses (24-26). Only a few studies have shown that using the web and/or e-mail improves glycemic control (27-29) or can reduce the number of clinic visits (30) while others have not been able to show such an effect (31-32).

Computer-assisted algorithms to provide decision support for interpretation of the glucose profile have been previously developed and published by the collaborators on this project as well as others (33-36). We and our colleague (Berger) have previously developed methods to automatically select regimens and doses of insulin for patients with T1DM (37). Lehmann has adopted and slightly modified the models of Rodbard and Bergman, and used it to develop "AIDA" – http://www.2aida.org – a program intended for education of health care providers and patients (38). This has not been employed therapeutically and no controlled trials have been performed.

There are only a few studies investigating decision support in the management of diabetes. Holman (36) and Chiarelli (39) reported that portable decision support devices used by patients with T1DM resulted in improved glycemic control. A web-based decision support system (DSS) improved compliance with generally recognized process measures of DM care (e.g. the number of A1C and low density lipoprotein [LDL] tests obtained) but did not improve the actual A1C level (40). Cleveringa et al. were unable to show that a DSS used by a practical nurse improved A1C in T2DM although it did improve cardiovascular risk factors (41). Recently, the IDEATel consortium study showed that a telemedicine application improved A1C, BP and lipids in an older, ethnically diverse and underserved population (42). Salzsieder and colleagues used their Diabetiva® program to apply continuous glucose monitoring (CGM) data to a DSS to improve A1C (43). Decision support systems that been used in blood pressure management have shown conflicting results (44-45).

Building on our prior experience in developing methods to select regimens and doses of insulin for patients with T1DM, we developed a CADS system for management of T2DM by PCPs to overcome many of the aforementioned barriers to the appropriate management of T2DM. The key feature of CADS is that it simplifies the work of the PCP by automatically integrating the essential factors necessary to make a recommendation for management - the patient's SMBG data from their uploads, current and previous medication, and current relevant laboratory data – and then making a recommendation based on established consensus algorithms (47).

BODY

The use of a computer assisted decision system (CADS) has been described in detail in the quarterly, annual, and final reports that have been submitted. The goal of the first study (Year 1 or Months 1-12) was to determine whether or not the use of CADS by PCPs, i.e. Internists, Family Practitioners, Nurse Practitioners, and Physician's Assistants, can improve glycemic and other outcomes in patients with poorly controlled T2DM over one year. The theoretic construct for establishing the hypotheses is that non-endocrinologist providers have neither the time nor expertise to address critical issues of management for patients with T2DM and that a CADS system will help them do so. Additionally, a CADS system will, because it saves time in the management of glycemic-related outcomes, will permit providers to give more attention to management of the important co-morbidities of T2DM. Finally, a patient with improved glycemic control and comorbidities will be more satisfied with their overall treatment.

This study entitled, "Extension of a Computer Assisted Decision Support (CADS-X) Study to Improve Outcomes in Patients with Type 2 DM Treated by Primary Care Providers" (CADS-X) was designed with two primary aims: (1) To provide those providers who were not assigned to the CADS arm in the initial study an opportunity to "cross-over" to CADS in a subsequent year provided that: a) CADS is shown to produce statistically significant improvements in A1C or other response variables (fasting plasma glucose {FPG}, post-prandial plasma glucose {PPG}, post prandial excursions, rate of hypoglycemia) and b) funding is available for continuation of the trial) and (2) to determine the legacy effect of CADS by providing primary care providers (PCPs) and their patients who were initially randomized to CADS an opportunity to use CADS for an additional year for a total of 2 years. However, significant challenges in the approval and implementation of the original study, "The Use of a Computer-Assisted Decision Support (CADS) System to Improve Outcomes in Patients with Type 2 Diabetes Who Are Treated by Primary Care Providers" (the CADS study), have delayed our ability to implement the extension study. The following provides a brief overview of the original study and the challenges that have prevented us from completing the first study.

The purpose of the original study, CADS, was to test the safety and efficacy of a computer assisted decision support (CADS) system in a multi-site, ethnically and geographically diverse study in a 12-month, open, prospective, cluster-randomized, controlled clinical trial. Specific aims included: (1) monitor the impact of the intervention on: a) measures of glycemic control, b) the number of diabetes–related hospitalizations and emergency room visits, c) the control of co-morbidities, hyperlipidemia and hypertension, d) the number of clinic visits, e) the change in the patients' quality of life as a result of the intervention; and (2) evaluate the PCPs' and patients' satisfaction with the technology. The progress of the CADS study as well as the challenges to the achievement of our specific aims has been described in detail in quarterly and annual reports submitted for the original study.

The following summarizes the challenges and our solutions to date. Challenges and solutions that occurred or persisted through this PoP are bolded:

1. The original CADS study included PIs and their research teams at Wilford Hall Ambulatory Surgery Center (WHASC) in San Antonio, TX, and the University of HI (UH) health care system in Honolulu, HI in addition to the lead PI and research team at WRNMMC. The following changes were made in March 2013 to maximize the effective use of the remaining funds and to determine the CADS' safety and effectiveness as a decision support tool :
    A. In March 2013, WHASC and UH were dropped as research sites for the following reasons:
        a. WHASC:
            I. Provider enrollment was progressing fairly well, but patient enrollment was very difficult despite 15 months of concerted effort screening a large database of patients. Primary reason for failure to enroll was that A1C levels were outside range.
            II. The Comprehensive Diabetes Management Program (CDMP), the electronic platform that supported CADS had been DIACAP'd for use at WH in 2010, but the license was expiring in the fall, 2013. Neither the Air Force Surgeon General's office nor the study had funds to support a new DIACAP process, the upgrades that would be required in CDMP, and personnel costs.
        b. UH: Enrollment was even more difficult at UH. Despite monthly conference calls among all the sites, numerous visits by the lead PI and project director, and the addition of patient and provider stipends. A total of 8 providers, two of whom withdrew, and even fewer patients were enrolled during 15 months of targeted effort. Recruitment was additionally challenged by distance between clinics and research staff, changes in staff and provider practices, reluctance of patients to participate in study, and reluctance of providers to

assist in patient recruitment

B. The study design was changed from a cluster-randomized control trial (RCT) to a proof of principal design involving up to 18 PCPs from WRNMMC, FBCH, and KACC who will each recruit at least 5 patients to test the efficacy of the CADS intervention. This study will be used to evaluate the CADS' safety and effectiveness as a decision support tool as an intervention in a small study to determine if the tool will be effective and safe prior to using it on a broader scale.

2. The DoD Information Assurance Certification and Accreditation Process (DIACAP) required of both CDMP and CADS.
   A. The DI began the DIACAP approximately 3 years ago when still at WRAMC
   B. Delay of DIACAP certification has impacted the study in two major ways:
      a. There is no exchange of relevant patient information between the existing EMR (AHLTA) at WRNMMC.
      b. Patients were unable to upload their glucometers into Diabetes Mellitus Everywhere (DME), the patient portal in CDMP.
   C. The following strategy has been utilized as a temporary strategy until CDMP/CADS has been DIACAP approved:
      a. The Project Officer (PO) or AI at WRNMMC manually enters into CDMP the information from the patient's EMR that is necessary to correctly run the CADS analysis. This information includes actual and target A1C levels, relevant laboratory values, current and past hypoglycemic medications, and co-morbid or co-existing diagnoses.
      b. Once the patients have uploaded their de-identified glucose data into a password-protected server, the PO or AI at WRNMMC will run the data through the CADS analysis and provide via email all the recommendation to the subjects' providers.
      c. The providers will select one of the recommendations which the PO will then select in the program.
      d. If the provider does not choose to follow any of the recommendations the PO will ask him/her for a reason and document the reason given.
      a. We have determined that the PCPS can access CADS from their WRNMMC, FBCH, or KACC computers, therefore providers will be given user names and passwords, 1:1 instruction to access and use CADS, and the CADS user manual.
3. The most recent challenge to the research being conducted at WRNMMC is the method patients will use to upload their glucometers in order run the CADS analysis:
   A. Numera, the manufacturer of iMetriLink, terminated their contract with us effective 31 August 2013.
   B. Our best option was to open DME, but the existing budget did not allow funding for Estenda, the software developers of CDMP and CADS, to activate DME
      a. A no cost extension (NCE) was submitted by Geneva in July.
      b. The revised SOW included funding for Estenda to open the DME portal
      c. We have asked Roche, manufacturers of the Aviva glucometer (glucometer being used by study subjects) to donate up to 96 USBs and adaptors.
         i. The USBs and adaptors will allow subjects to upload from home if they have a computer.
         ii. If Roche does not donate, then we will have to use study funds to purchase.
         iii. Until this issue is resolved, we are uploading glucometer data into our study laptop which is not on the WRNMMC network.
         iv. Use of a non-network laptop is necessary since WRNMMC IT does not allow the glucometer software on the network, a challenge that did not exist when we were at WRAMC.

KEY RESEARCH ACCOMPLISHMENTS

Enrollment during Period of Performance

WRNMMC: Four providers were enrolled during this PoP for a total of 15; two providers have withdrawn. Thirty six patients were enrolled for a total of 54 patients. With the revised study design and sample size we have enrolled 83% of the providers and 56% of the subjects. Three providers have reached their patient enrollment goals. One provider's patients were using the iMetrilink to upload glucometer data from home. Patients of the other two providers are uploading their glucometers at WRNMMC until the Roche USBs and adaptors are available. Estenda has activated the DME portal and the AI has successfully uploaded glucose data from several glucometers into CDMP.

CDMP AND CADS MAINTENANCE AND ENHANCEMENTS

Task 1

Delays in the DIACAP approval process have been explained in the quarterly reports and will not be repeated in this report. Mr. Anthony Hooker, together with R.J. Kedziora at Estenda continue to work with the JTF on renewed DIACAP certification so that the system can be reconnected to the central patient medical record via ICDB. Minor updates and maintenance was conducted on the CADS system as required.

Task 2

In support of continued DISA compliance over the project lifetime, Estenda will updated all of the third-party infrastructure components required to versions that have documented support. These infrastructure components include. Estenda completed major infrastructure updates (Oracle Database Server, Weblogic Application Server, MIRTH Integration Engine, Struts Java Framework, etc) during the last quarter of 2012. The completed solution has been tested and be migrated to production in mid 2013.

Task 3

In support of the research team's clinical data capture and management Estenda has made significant upgrades to the platform's existing Survey and Study Management sub-modules. These important modifications will help support efficient, accurate and auditable data collection across the study's lifecycle: Specific improvements included: The following tasks were accomplished during this PoP: (1) Addition of a user friendly tool for users to create their own subject data collection forms (completed in first quarter); (2) Improvement of navigation features based on feedback from use on prior Diabetes Institute research studies; (3) Addition of native support for additional study randomization schemes; Improvement in ability to correct site data entry errors through a managed workflow; and (4) Improvement in subject informed consent workflow.

Task 4

The core diabetes data management platform of which CADS is a module requires modification in order to fully support its research mission. Core improvements include: Adding functionality for authorized clinical staff to merge duplicate patients; supporting for a broader range of Web Browsers; Allowing users to customize the patient information "snapshot" to best meet their individual mission; improved graphing; and adding new support to capture for patient reported use of alternative medications. Estenda has completed modifications to support a range of current, common web browsers.

CDMP and CADS Maintenance and Enhancements: Additional Accomplishments

Completion of the CADS User Manual: The original CADS User Manual was completed in 2012. Changes to accommodate the activation of the DME portal will be completed first quarter, FY2014.

Completion of Study Manager and the Study Manager User Manual

Study Manager is a standalone component within the Comprehensive Diabetes Management Program (CDMP) that was designed to track subjects' progress through an entire study and has the capacity to be customized to every study. Study Manager includes alerts to remind the research coordinators/project officer of tasks and due dates. The Study Manager User Manual (Appendix B in the 2012 report)) was completed in June 2012. Study Manager is undergoing some additional changes and the user manual will be modified to reflect changes once they are complete.

REPORTABLE OUTCOMES
None to date

CONCLUSIONS
Diabetes mellitus is a significant cause of morbidity and mortality in the United States, and the leading cause of new blindness, chronic kidney disease, and non-traumatic amputation in the working-aged American population. Although the financial costs to individuals, communities, and health care systems are measurable, the devastating costs in terms of quality of life personal costs are not easily measured. A computer assisted decision support system that makes available the knowledge and expertise of endocrinologists to primary care providers who care for the majority of people with Type 2 diabetes has the potential to significantly improve the level of care provided to people with T2 DM, thus preventing or delaying the onset of and/or reducing the severity of diabetes-related complications. Reducing the risk and/or severity of complications promises to improve the quality of life for people with T2 diabetes and decrease the financial impact on the individual as well as both the military and civilian health care systems.

CADS is a web-based interactive application that enables primary care providers to aggressively and systematically use available medications to help their patients move increasingly and safely toward a level of glycemic control that minimizes their risk of developing diabetes-related complications and/or the severity of these complications. The extensive delays in and challenges to the implementation of the original study have made it impossible to begin the extension study as planned. The research staff at all three sites are making a consistent and concerted effort to meet enrollment goals. It is our hope that, once fully executed, the successes and lessons learned from this study can be applied to an even larger population of people with Type 1 and Type 2 diabetes, thus further mitigating the devastating financial and personal costs of poorly controlled diabetes mellitus.

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