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14. ABSTRACT The overall aim of this proposal was 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) and to compare longitudinal patterns of change within and between patients who are managed with the CADS system for differing durations. This comparison was intended to 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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INTRODUCTION

Diabetes mellitus (DM) affects more than 29 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 and quality of life years by 11 to 23 years in adults 65 years of age and older. The estimated total economic cost of diagnosed diabetes in 2012 was \$245 billion, a 41% increase from the previous estimate of \$174 billion (in 2007 dollars) with direct costs at \$177 billion and indirect at more than \$68 billion. People with diagnosed diabetes incur average medical expenditures of about \$13,700 per year, of which about \$7,900 is attributed to diabetes. Their average medical expenditures are approximately 2.3 times higher than their expenditures would be in the absence of diabetes. Hospital inpatient care comprises 43% of the total medical cost (1).

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 (2-4). 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%) (5), 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] (6). 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 (7-8).

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 (9). 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 (9--13). Similarly, the UKPDS showed a 13% reduction in microvascular complications for every 10 mmHg reduction in systolic pressure. This finding was confirmed and extended to DM patients who were “normotensive” (3). Gaede et al. showed the marked benefit of aggressive blood pressure, lipid, and blood glucose management achieved through multifactorial intervention (14). There also appears to be a legacy effect of blood pressure control in Type 2 diabetes as recently shown by Holman et al. (15).

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 Centers for Disease Control (CDC) estimates that approximately 48% of patients with DM have A1Cs over 7% (16). 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. In 2009, data from the Walter Reed Health Care System (WRHCS) indicated that 51% had an A1C above 7%. 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 mmHg.

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 (17), 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 thus creating 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 fifteen 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 (18-21). Only a few studies have shown that using the web and/or e-mail improves glycemic control (22-24) or can reduce the number of clinic visits (23) while others have not been able to show such an effect (24-25).

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 (26-29). We and our colleague (Berger) have previously developed methods to automatically select regimens and doses of insulin for patients with T1DM (30). 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 (31). 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 (32) and Chiarelli (33) 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 (34). 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 (35). Recently, the IDEATel consortium study showed that a telemedicine application improved A1C, BP and lipids in an older, ethnically diverse and underserved population (36). Salzsieder and colleagues used their Diabetiva® program to apply continuous glucose monitoring (CGM) data to a DSS to improve A1C (37). Decision support systems that been used in blood pressure management have shown conflicting results (38-39).

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, the presence or absence of certain co-morbidities, and current relevant laboratory data – and then making a recommendation based on established consensus algorithms (40).

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 and permits 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), delayed our ability to implement the extension study. An overview of the original study and the challenges that have prevented us from completing the first study are detailed in the 2013 Annual Report. This report summarizes the activity relevant to the continuation of the original study.

KEY RESEARCH ACCOMPLISHMENTS

1. Enrollment during Period of Performance

The Project Officer (PO) completed enrollment of 18 Primary Care Providers (PCPs) and 76 patients before closing enrollment on 30 September 2014. Three providers were enrolled during this PoP for a total of 18; two providers have withdrawn. Twenty two patients were enrolled for a total of 76 patients. With the revised study design and sample size we have enrolled 100% of the providers and 78% of the subjects. Enrolled patients per provider are:

- a. One provider enrolled 13 patients (prior to change in study design)
- b. Three provider enrolled 6 patients
- c. Two providers enrolled 5 patients
- d. Six providers enrolled 4 patients
- e. One provider enrolled 3 patients ,
- f. Four providers enrolled 1 patient
- g. One provider enrolled 1 patient

2. Progress of Patients in the Study:

- a. Completed the study (6 visits): 15 patients/1 provider
- b. Completed Visit 5: 2 patients completed
- c. Completed Visit 4: 7 patients completed; 2 patients missed visit
- d. Completed Visit 3: 8 patients; 6 patients missed visit
- e. Completed Visit 2: 30 patients (visit 2 marks the beginning of the intervention part of the study; it is after this visit that patients are asked to upload their glucometers before each quarterly visit with their PCPs and follow protocol instructions for SMBG frequency).

3. Withdrawn from Study: 2 Providers; 25 Patients

- a. Reason for provider withdrawal
 1. One left practice
 2. One was a contractor and research involvement was not in his contract
- b. Reasons for patient withdrawals
 1. Too busy: 1
 2. Diabetes care transferred from PCP to diabetes NP or endocrinologist: 8
 3. Too much difficulty uploading glucometer data: 1

4. Personal issues: 1
5. Well controlled and doesn't want to change treatment plan: 1
6. Too many fingerstick blood glucose tests required: 1
7. Initiation of dialysis: 1
8. Initiation of prandial insulin: 2
9. Left area: 1
10. No reason or other: 5
11. Lost to follow-up: 3

4. Provider Access to CDMP and CADS:

- a. Providers can access CADS from their desktop computers
- b. Initial access has usually required the assistance of the PO
- c. Once providers are familiar with CADS, access is straightforward and generally without difficulty, although the PO has often been available during patient visits to trouble shoot, offer moral support, or help the PCP get another user name or password.
- d. We revised the CADS study manual to provide step-by-step guidance to accessing and using CADS.

5. Study challenges

- a. After Numera terminated the contract to provide glucometer download support Estenda activated the patient portal, Diabetes Mellitus Everywhere (DME), in CDMP and the AI successfully downloaded loaded glucose data from several glucometers into CDMP.
- b. Study progress was delayed until we received Roche USBs and adaptors to give to the patients to upload glucometer data from home.
- c. Uploading glucose data has been problematic for several patients. Problem areas include having to download JAVA with first upload and accessing the DME portal.
- d. PO has downloaded glucose data for several patients (n=9) who were challenged by the technology into our study laptop and uploaded to CDMP prior to visits with their PCPs. Number of patients generally able to upload without difficulty is 8.
- e. Difficulties with patient enrollment also required us to close enrollment before reaching patient enrollment goal in order to maximize use of funds and try to complete study.

6. Adherence to Study Protocol and Timelines

The PO has worked extremely hard to adhere to study timeline for visits and protocol requirements, but many patients have been delinquent in adhering to study timeline for visits, self-monitoring blood glucose (SMBG) levels 4 times daily once weekly and 8 times daily once monthly. This has resulted in the generation of multiple protocol deviation reports for the WRNMMC IRB.

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. Activity that occurred during this PoP include:

- Submission of all of the documents required by the WRNMMC Information Assurance Office for DIACAP approval in January 2014.
- Additional questions posed by IA have been answered and the CDMP approval process has been elevated to a slightly higher priority level by the WRNMMC IA office.
- The DI Technical Advisor has been on medical leave since early May and the WRNMMC Dept of Information Management/Information Assurance has not had the manpower to support maintaining security on the CDMP server. We will address this when CDMP has completed the DIACAP approval process. The server has not been in use since 2011 when we moved from WRAMC to WRNMMC.

Task 2. Estenda has maintained all of the third-party infrastructure components required to versions that have documented support. These infrastructure components include. Oracle Database Server, Weblogic Application Server,

MIRTH Integration Engine, Struts Java Framework, etc) during the last quarter of 2012. The completed solution was tested and migrated to production in mid 2013.

Task 3. In support of the research team's clinical data capture and management Estenda has maintained significant upgrades to the platform's existing Survey and Study Management sub-modules. These modifications supported efficient, accurate and auditable data collection across the study's lifecycle: Specific improvements included during the previous PoP were detailed in the last annual report. :

Task 4 The core diabetes data management platform of which CADS is a module requires modification in order to fully support its research mission. Estenda completed the modifications which continue to support a range of current, common web browsers.

8. CDM and CADS Maintenance and Enhancements: Additional Accomplishments

a. Completion of the CADS User Manual

The original CADS User Manual was completed in 2012 and revised in 2013. Additional revisions were approved by the WRNMMC IRB in 2014.

b. Completion of Study Manager and the Study Manager User Manual

The CADS PO has entered all study related data into Study Manager. Although it is an organized and comprehensive approach to documenting all study-related data, it has been cumbersome to use. We will continue to use it to complete the CADS study, but may not use it going forward for other studies. Given that it is not likely that we will use Study Manager in the future we have not revised the user manual as originally intended during this PoP.

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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