Protocol

Young LA, Buse JB, Weaver MA, et al. Glucose monitoring in Non-Insulin Treated Type 2 Diabetes in Primary Care Settings: A Randomized Clinical Trial. JAMA.

Initial Protocol…………………………………...……………………...…………………………..……………page 1
Initial Statistical Analysis Plan........................................................................................................page 19
Final Protocol......................................................................................................................................page 25
Final Statistical Analysis Plan .............................................................................................................page 44

This supplementary material has been provided by the authors to give readers additional information about their work.
Effect of Glucose Monitoring on Patient and Provider Outcomes in Non-Insulin Treated Diabetes

THE MONITOR TRIAL

Original Study Protocol

Principal Investigators:
Katrina Donahue, MD, MPH
Laura Young, MD, PhD

Investigators:
John Buse, MD, PhD
Mark Weaver, PhD
Maihan Vu, PhD

Project Manager:
C. Madeline Mitchell, MURP

Prepared for:
Diane Bild, MD, MPH
Senior Program Officer
Patient-Centered Outcomes Research Institute (PCORI)
1828 L Street, NW 9th Floor,
Washington, DC 20036
# STUDY ABSTRACT

1

# INTRODUCTION

1.1 BACKGROUND .................................................. 2
1.2 SELF MONITORING PRACTICES ............................ 2
1.3 MODERN DIABETES SELF-MANAGEMENT TECHNOLOGIES ................................................... 5
1.4 TESTING APPROACHES ...................................... 5
1.5 RISK BENEFITS ............................................. 6

# STUDY OBJECTIVES

2

1.1 PRIMARY STUDY ENDPOINTS .............................. 7
1.2 SECONDARY STUDY ENDPOINTS ......................... 7
1.3 POTENTIAL MODERATING VARIABLES ................ 9

# STUDY DESIGN

3

# SUBJECT IDENTIFICATION AND WITHDRAWAL

4

4.1 INCLUSION CRITERIA ........................................ 11
4.2 EXCLUSION CRITERIA ....................................... 12
4.3 SUBJECT RECRUITMENT AND SCREENING .......... 12
4.4 WITHDRAWAL OF SUBJECTS .............................. 12

# STUDY GLUCOMETER

5

# STUDY PROCEDURES

6

6.1 METHOD FOR ASSIGNING SUBJECTS TO TREATMENT GROUPS .................................................. 13
6.2 BASELINE .................................................. 13
6.3 52-WEEK FOLLOW-UP ..................................... 13

# STATISTICAL PLAN

7

7.1 SAMPLE SIZE DETERMINATION .......................... 13
7.2 STATISTICAL METHODS ................................... 14

# DATA SAFETY AND MONITORING

8

# DATA HANDLING AND RECORD KEEPING

9

9.1 CONFIDENTIALITY .......................................... 16
9.2 SOURCE DOCUMENTS ..................................... 17

# DISSEMINATION PLAN

10

# STAKEHOLDERS

11

# REFERENCES

12

# ATTACHMENTS

13

---

2
BACKGROUND

For the nearly 75% of patients living with type 2 diabetes (T2DM) that do not use insulin, decisions regarding self-monitoring of blood glucose (SMBG) can be especially problematic. Considering the many burdens SMBG testing places on patients, it is a resource intensive activity without firmly established patient benefits. While in theory SMBG holds great promise for sparking favorable behavior change, the potential for no benefit or even patient harm must be acknowledged. Possible negative effects on patient quality of life must be more closely examined along with the speculative benefits of SMBG in non-insulin treated T2DM. Among studies examining this issue a general consensus is evolving; while SMBG may or may not be clinically useful, its value can only be fully appreciated when the SMBG results are provided to patients in a useful manner. Testing without feedback, a common clinical occurrence, holds little clinical promise.

OBJECTIVES

The overarching goal of this proposal is to assess the impact of three different SMBG testing approaches on patient-centered outcomes in patients with non-insulin treated T2DM within a community-based, clinic setting.

METHODS

This is a pragmatic trial of 450 patients randomized to one of the following three SMBG testing regimens: 1) no SMBG testing; 2) once daily SMBG testing with standard patient feedback consisting of glucose values being immediately reported to the patient through the glucose meter; and 3) once daily SMBG testing with enhanced patient feedback consisting of glucose values being immediately reported to the patient PLUS automated, tailored feedback messaging following each SMBG testing event delivered to the patient through the glucose meter.

The first two arms represent common SMBG testing approaches currently being used. The third arm is an enhanced, patient-centered approach to SMBG testing. SMBG values will be evaluated at routine clinic visits over 52 weeks. Patients’ health care providers will utilize the American Diabetes Association’s “patient-centered approach”, which focuses on individualization of patient care, to guide therapy modification. We will use a mixed methods approach. Quantitative patient assessments will occur at baseline and at 52 weeks. Qualitative assessments using patient and provider focus groups will occur at the conclusion of the intervention. We have actively engaged several stakeholders to inform the trial design, intervention and choice of outcomes.

PATIENT OUTCOMES

The following primary outcomes will be assessed: Quality of Life and Glycemic Control. We will assess differences across the following pre-specified subgroups: 1) prior experience using SMBG; 2) duration of T2DM; 3) baseline degree of glycemic control; 4) anti-hyperglycemic treatment; 5) age; 6) race/ethnicity; 7) health literacy; and 8) number of baseline comorbidities.

Secondary outcomes will include diabetes-related treatment satisfaction, self-efficacy, distress, self-care, hypoglycemia frequency and patient-provider communication.

1. Introduction

This document provides background information and a description of the overall study design for the Monitor Trial, a pragmatic clinical trial assessing three approaches for managing non-insulin treated type 2 diabetes (T2DM). This study has been approved by the University of North Carolina Institutional Review Board.

1.1 Background

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or generally both. At least 285 million people worldwide have DM. The estimated cost of the condition in the US alone top 174 billion annually. Now described as an epidemic, the global incidence of DM is expected to double over the next two decades, reaching 435 million cases by 2030. T2DM, closely linked to obesity, makes up around 90% of cases, with the remaining 10% being Type 1 and gestational. Recent Centers for Disease Control and Prevention (CDC) reporting shows alarming increases in T2DM in the US. The Southern states fare the worst, with rates of DM cases doubling in just 15 years. Complications from T2DM include heart disease, stroke, and diabetic retinopathy leading to visual impairment or blindness, kidney failure requiring dialysis or transplantation, and limb amputation. Other associations include higher risk of cognitive dysfunction, dementia, cancer, sexual dysfunction, and infection, plus increased rates of hospitalization and a shorter life expectancy. In the US, DM is the leading cause of kidney failure, non-traumatic lower-limb amputations, new onset blindness, and the seventh leading cause of death.

Given the devastating effects of DM, improving treatment for persons with DM is of obvious importance. DM is a chronic condition with no cure, thus disease management is the primary form of treatment. A main goal of management is to control blood glucose, which is evaluated primarily through blood levels of hemoglobin A1c (A1c). A1c relates closely to the average plasma glucose levels a patient experienced over ~3 months. According to the American Diabetes Association (ADA) guidelines, an A1c of 6.5% or above is a criterion for diagnosis. In addition to pharmaceuticals, self-monitoring of blood glucose (SMBG) through the use of strips and
glucose meters is a recommended method for maintaining better glucose regulation. The process entails using a lancing device to obtain a sample of capillary blood, which is then placed on a testing strip and read by a small handheld device. After several seconds, the current plasma glucose concentration is reported on the device. For patients with DM who are treated with insulin, SMBG is an accepted procedure for daily monitoring effects of insulin therapy. However, the majority of T2DM patients do not use insulin.

According to the CDC, 26% of people with DM use insulin, while the remainder uses oral medications only (58%) or no medications (16%). While control of A1c is equally important for persons with DM who are non-insulin treated (hereafter NIT DM), the value of SMBG testing for these patients is debatable. Proponents postulate that testing promotes better awareness of glucose levels, leading to improvements in diet and lifestyle. When test result are shared with health care providers, it is argued, there is also the potential for more timely treatment modifications. Competing arguments point to the costs of SMBG, both in terms of supplies (one-time use test strips currently cost around $1 each, with meters costing between $50-$100) and time, as well as the obvious discomfort involved (pricking the skin), all of which would be net harms if SMBG does not improve key outcomes for these patients.

Scientific examinations of SMBG in NIT DM have provided mixed results. An early epidemiological evaluation of the issue using a retrospective, longitudinal analysis showed that nonfatal micro- and macrovascular event rates along with fatal event rates were lower in individuals performing SMBG routinely as compared to those who were not. A multitude of clinical trials followed. Several showed a significant benefit from SMBG testing on improving glycemic control,15-18 while others found no evidence of benefit.9, 19-22 In fact, some studies even suggested harm from routine SMBG in patients with NIT DM, specifically, higher rates of depression and increased cost without accompanying benefits23, 24

Given these mixed results, a series of meta-analyses and systematic reviews were conducted to investigate the benefit or lack thereof of SMBG on glycemic lowering in patients with NIT DM. While meta-analyses can be a useful way to assess the clinical effectiveness of an intervention, they are limited by the quality and comparability of the clinical trials included in the analyses. Issues of sample size, duration/details of the intervention, and patient characteristics (e.g., newly diagnosed vs. longer duration of disease; baseline A1c level), varied considerably across the available studies. Given these critical differences, it is perhaps not surprising that the results of the meta-analyses have also shown conflicting results. However, the overall conclusion has been that SMBG is likely not cost effective for this population of patients.8, 9, 11

Perhaps most important to understanding these mixed results is the fact that the question being addressed by the studies is itself not consistent, falling generally into two camps: ‘simple’ SMBG and ‘enhanced’ SMBG. In studies testing simple SMBG, patients conducting SMBG were compared to patients who were not. In evaluations of ‘enhanced’ SMBG, intervention group patients and/or providers were given education or feedback such that they were better able to interpret SMBG results and use them in a meaningful way with regard to lifestyle changes and treatment modification. Among tests of ‘simple’ SMBG, A1c levels were reduced on average by 0.2%, an amount that was statistically significant in these studies, but of doubtful clinical significance.11, 12 Studies of ‘enhanced’ SMBG found A1c reductions closer to 0.5%.11, 18, 25, 26 As additional ‘enhanced’ intervention SMBG studies were added to the literature,25, 27 more recent reviews and meta-analyses have drawn conclusions more in favor of testing.11, 28 This pattern suggests that, for SMBG to be an effective self-management tool in NIT DM, the patient and the health care provider must both actively engage in performing, interpreting, and acting upon the SMBG values.

The effect of SMBG could impact patient quality of life (QOL) both positively and or negatively. Testing itself is a burden and could act as a constant reminder of one’s less than ideal health status. On the other hand, it could improve a patient’s sense of self-efficacy and hope for maximizing health and independence into the future. A recent Cochrane Review identified only a handful of studies that had examined health-related quality of life (HRQOL), well-being, or patient satisfaction.8 While these studies did not find clinically relevant differences in HRQOL for those who do or do not test, the review indicated future research was needed. In one study, HRQOL initially decreased, but follow-up qualitative interviews showed that patients in the testing groups experienced an increased awareness of illness.20 While both simple and ‘enhanced’ versions of SMBG were evaluated, the enhanced version included only training in the meaning of the results and encouragement to explore how lifestyle and dietary choices affect test values. Without more hands-on use of results (e.g., reports provided to the care provider), patients might have felt more ‘overwhelmed’ than empowered by the experience of testing. Future studies of HRQOL and other patient-centered aspects of SMBG must examine it within the context of patient’s having actionable knowledge and improved opportunities for provider/patient collaboration.

1.2 Self-monitoring practices
The lack of consensus around the benefits or lack thereof of employing SMBG for persons with NIT DM has led to virtually no standardization in SMBG recommendations worldwide. Guidelines range from clear recommendations for regular testing, to general statements about ensuring that testing is an available option to patients, to not recommending testing except in specific cases. The ADA suggests “SMBG results may be helpful to guide treatment decisions and/or patient self-management.”10 Mirroring the lack of research in this area, very few guidelines on diabetes care and management even touch upon quality of life issues. Without medical consensus, it is not surprising that there is little consistency in either reimbursement for or routine use of SMBG in patients with NIT DM.
While researchers and medical organizations debate the overall issue of the value of SMBG testing in NIT DM, patients and clinicians face this choice daily and without adequate information as to its clinical or psychological outcomes. For some patients, their decision on testing will mirror that of their care provider. Yet more and more, patients play an active role in managing their own health. To some degree this is a necessary trend, because providers simply do not have sufficient time to provide intensive ongoing and comprehensive education and decision-making around diabetes self-management. Then too, even providers are looking for additional guidance on this question, including how to present options to patients and incorporate test results into care.34 The fact that patients are taking a greater role in their healthcare is generally positive, because those who do so also improve their outcomes.35,36 Diabetes self-management, however, encompasses an increasingly complex set of services and supports, including glucose monitoring, medication management, nutrition counseling, physical activity promotion, social support networking and, when needed, psychotherapy.

While current SMBG testing rates have not been well documented, in a recently published study of over 500 patients with NIT DM, 14.1% reported never testing, 22.8% tested once a week or less, 22.3% tested once a day, and 54.7% tested more than twice a day.35 These results point to over 75% of patients currently performing regular SMBG testing. The wide range in SMBG testing frequency is likely at least in part dependent on the recommendations of the providers from whom the patients were receiving care. In preparation for this grant application, we conducted a survey of SMBG habits and attitudes among patients with NIT DM who are part of the UNC Diabetes Care Center Patient Registry, a group consented for participation in research projects. Among the 62 of patients who had NIT DM, we found lower SMBG testing rates. Only one third said that they test one or more times daily, while 15% tested never or less than once a month. The remainder tested several times per week (38%), several times per month (20%), or less than once per month (5%).

In addition to highlighting variability in testing rates, both the study by Wang and our pilot survey point to difficulties these patients encounter with regard to testing and using test results. Wang et al found that close to half (44.7%) reported missing or skipping blood sugar checks.35 In our UNC sample, despite the low testing rates, a full 87% felt SMBG is an important part of diabetes self-care, and 79% said it was important to their provider. Indeed, 43% admitted that they test less often than suggested by their provider. At the same time, a small but important minority said their provider never instructed them on how often to test. Finally, even within the sample of patients for whom over 75% test at least daily, most patients are not taking appropriate problem solving steps in response to high (hyperglycemia) or low (hypoglycemia) blood sugar levels.35

### 1.3 Modern diabetes self-management technologies

Increasingly, patients are turning to the Internet and other new means of electronic communication for information, connections and guidance.36,37 In a study of mobile health applications for SMBG that included English-language interfaces, over 900 were available for review.37 But of the 137 applications that were comprehensive enough to meet basic review criteria, only 7% included a module providing personalized education or feedback. This study highlights both the demand for and current unmet need among patients considering or currently participating in SMBG. Recognizing this, some are calling for greater use and development of such patient-centered medical options.38 Kaufman refers to these technologies as “a solution whose time has long since arrived” but argues that, to be most effective, they must be ‘clinically linked,’ that is, occurring within the context of a trusted therapeutic relationship and an effective medical care system.36 As he goes on to point out, internet and cell phone use is now so widespread and inexpensive that it is erasing geographic, economic and demographic barriers to obtaining health information and support. He argues that the medical system should take advantage of these facts to further incorporate information technology into patient care and support.

### 1.4 Testing approaches

In order to make informed patient choices, patients and their providers need accurate, generalizable and meaningful information about the merits or demerits of SMBG testing for persons with NIT DM. Because the existing research, though relatively extensive, has not yet met this important need, more research must be done on this issue. The Consensus Report of the Diabetes Technology Society provides a list of recommendations for future research relating to SMBG in NIT DM. In regard to the intervention itself, they recommend that it a) is linked to a structured program designed to facilitate behavior change, b) has A1c as a primary endpoint but include patient-centered endpoints, c) include encouragement and support, preferably in the form of personalized, automated feedback to patients in real time, d) takes advantage of telemedicine opportunities, and d) incorporate best practices guidelines and standards for physicians.28 Many of these recommendations overlap with others.28 In addition to these critical features, future research should be designed with a pragmatic eye, adhering as closely as possible to the real world setting in which SMBG would be carried out by patients and utilized by patients and health care providers collaboratively. To date, no large-scale, pragmatic RCT has evaluated the impact of SMBG testing in patients with NIT DM in which a multi-dimensional approach to SMBG value management has occurred. Performing another randomized clinical trial of efficacy would not help clarify this hotly debated topic. Also missing from current research is an examination of SMBG testing for selected patient groups.11 Racial and ethnic differences in A1c have been observed.3,39-41 Compared to non-Hispanic white adults, the risk of diagnosed DM is 66% higher among Hispanics/Latinos and 77% higher among non-Hispanic blacks.3 Persons from different racial or ethnic backgrounds might also respond differently to SMBG testing, as there may be differences in how individuals interact with providers, or the ease with which they are able to use and make use of a wireless glucometer.
While SMBG may or not be worthwhile, effective SMBG, if it exists for NIT DM, appears to require that it be embedded within the context of patient education around the use and interpretation of glucose readings, provider awareness of the results of repeated testing, and collaborative use of this information at medical visits. We would also argue for providing treatment algorithms to providers that are based on standard accepted guidelines (such as the ADA guidelines) linked to SMBG report results. This step facilitates the physician’s use of glucometer result reports and can be used by health care providers during clinic visits to better illustrate their concerns when talking to patients. Finally, we feel it is important to evaluate objectively and in a real world setting the possible additional benefits of personalized feedback for patients in the form of messages delivered via the glucometer based on patients’ current and recent SMBG patterns. By pointing out troubling patterns and rewarding results that are at goal, this aspect of the approach we are calling ‘enhanced feedback’ is akin to ‘mini consultations’ with a provider between routine clinic visits, which are generally 3-6 months apart. Patients are curious about these enhanced approaches as evidenced by 80% of our survey respondents reporting that they would perform SMBG as directed by their health care provider if they received instantaneous feedback on their glucose readings.

1.5 Risk/Benefits Associated with SMBG

Because there are currently no definitive clinical guidelines that describe how frequently a person with NIT DM should be monitoring their SMBG values, the randomized treatment provided in this proposed study represents variations in usual care. As an FDA approved glucose monitoring system will be utilized in conjunction with standard diabetes management by local providers, this study poses no greater than minimal risk.

Establishing the utility or lack thereof for SMBG monitoring in patients with NIT DM receiving care within a variety of primary care, clinical settings is a practical, contemporary issue, with far-reaching implications of value to numerous stakeholders including primary care providers, patients, academicians, insurance payers, and government regulatory agencies. A positive result will establish a standard of care. A negative result will reduce unnecessary burdens (time, effort and financial) for patients, providers and health care systems.

2. Study Objectives and Endpoints

The goal of this one-year randomized controlled trial is to evaluate SMBG testing for participants with NIT DM within a real world setting using patient-centered outcomes and incorporating new glucose meter technologies.

Objective 1: Assess SMBG effectiveness on two primary, patient-centered outcomes, glycemic control (A1c) and health related quality of life (HRQOL), over one year in 450 participants with NIT DM between the following three groups: 1) no SMBG testing, 2) once-daily SMBG testing with standard patient feedback consisting of glucose values immediately reported to the patient through the glucometer, and 3) once-daily SMBG testing with enhanced patient feedback consisting of glucose values immediately reported to the patient PLUS automated tailored messaging also delivered via the glucometer.

Sub-objective 1a. Assess differences in SMBG effectiveness across the following subgroups: 1) prior experience using SMBG; 2) duration of T2DM; 3) baseline glycemic control; 4) baseline anti-hyperglycemic treatment; 5) age; 6) race/ethnicity; 7) health literacy; and 8) number of baseline comorbidities.

Objective 2: Evaluate the impact of SMBG on secondary patient-centered, outcomes including: a) DM-related QOL, b) DM self-care, c) DM treatment satisfaction, d) DM self-efficacy, e) patient-provider communication, f) hypoglycemia frequency, g) health care utilization.

Objective 3: Conduct qualitative assessments of the patient participant and provider experience for all three intervention groups. This objective will support efficient translation of study findings to real world clinic settings by exploring such issues as patient/provider communications, the use of the glucose meter and accompanying reports, the utility of the treatment algorithm given to providers, and practice burden.

2.1 Primary endpoints

The two primary outcomes of the study are change in A1c and change in HRQOL. The A1c was chosen due to its use in prior studies and its standing as a measure on which: 1) providers evaluate patients; 2) payers evaluate providers; and 3) patients evaluate themselves and their providers. Though HRQOL is also critically important to patients, few studies have rigorously examined the impact of SMBG on HRQOL. Based on these facts and the recommendations of our stakeholder groups, HRQOL is a co-primary outcome for this pragmatic trial.

A1c. A1c will be measured at baseline and 52 weeks. A1c has long been accepted as the best indicator of recent (past 2-3 months) glucose control. It is the standard laboratory value upon which glycemic control is judged and treatment alterations are based. Baseline and 52-week A1c scores will be recorded by the study field coordinators. Because the 52-week time point may not align with
a scheduled primary care visit, we have defined this time point as 52 ± 6 weeks from the baseline visit. All other A1c values measured and recorded in the EHR during the study period will be captured passively and recorded in the dataset.

**General Quality of Life:** An important outcome for all patients with DM is their perception of how diabetes affects their physical, psychological, and social functioning. We will utilize the Short Form 36 (SF-36) to assess overall quality of life (QOL). It has been widely used and validated in medical studies generally and diabetes studies in particular. The SF-36 encompasses physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. Subscale scores range from 0 to 100, with high scores representing better HRQOL. We will use the physical component score (PCS) and the mental component score (MCS), with scores standardized to a normal distribution (mean = 50 and standard deviation [SD] = 10).

### 2.2 Secondary endpoints

The following secondary endpoints will be collected from patient participants at baseline and 52-weeks.

**Problem Areas in Diabetes (PAID).** Developed at the Joslin Diabetes Center, this scale is the most widely utilized tool to assess psychological and social stress associated with diabetes. This self-report measure contains 20-items with scores ranging from 0 (no distress) to 100 (high distress). It has been shown to have high internal reliability (Cronbach's alpha = 0.90), sensitivity to change (r=0.83), and clinical utility.

**Diabetes Symptom Checklist (DSC).** The DSC is a 34-item self-report measure of diabetes-related symptom frequency and perceived severity during the prior month covering six symptom categories: hyperglycemic, hypoglycemic, cardiac, neuropathic, psychological, and vision-related. Patients respond on a 5-point scale (1=symptom has not occurred or was not troublesome, to 5=symptom was extremely troublesome). The DSC is valid, reliable, and responsive to change. Higher scores are associated with poorer glycemic control and depression.

**Diabetes Self-Care.** To assess compliance with diabetes self-care, we will use the Summary of Diabetes Self Care Activities (SDCA) survey. This is a widely used, multidimensional measure of diabetes self-management activities with high internal and test-retest reliability. The SDCA assesses diet, exercise, blood glucose testing, foot-care, and smoking status. Supplementary questions are available, and we will include a question on medication adherence.

**Diabetes Treatment Satisfaction.** Treatment satisfaction is an inherently patient centered outcome. We will utilize the Diabetes Treatment Satisfaction Questionnaire (DTSQs) standard version to assess this variable. This 8-item survey has been widely used to assess patient satisfaction with their current treatment.

**Diabetes-Specific Self-Efficacy.** Diabetes-specific self-efficacy focuses on beliefs about one's ability to adhere to diet, exercise, SMBG, and medication regimens and is only moderately related to general self-efficacy. Higher diabetes-related self-efficacy is related to enhanced adherence to self-care activities. Study participants will complete the 8-item Diabetes Empowerment Scale Short Form (DES-SF). The DES-SF is highly reliable (Cronbach α = 0.85) and is responsive to change over time.

**Patient-Provider Communication.** A patient’s perceived connection with their health care provider significantly influences their sense of satisfaction and degree of concern about their health. Good patient–provider communication also predicts better diabetes self-care, improved adherence to treatment, and less diabetes-related morbidity. In general, patients prefer interactions that involve shared decision making. By providing shared and timely SMBG values, the new technology implemented in this study has the potential to strengthen the patient-provider relationship. We will use the Communication Assessment Tool (CAT) to measure patient-provider communication. The CAT is a 15-item survey that asks patients to rate different dimensions of the communication and interpersonal skills of their health care provider using a 5-point scale (1=poor, 2=fair, 3=good, 4=very good, 5=excellent). Overall scale reliability is high (Cronbach's alpha = 0.96).

**Hypoglycemia Frequency.** Downloaded SMBG values will be graded according to severity as Grade 1 (SMBG <70 mg/dl with or without mild or moderate symptoms), Grade 2 (SMBG<50 mg/dl with or without mild or moderate symptoms), Grade 3 (independent of SMBG, altered consciousness or inability to engage in self-care behaviors, which reverses promptly after administration of oral carbohydrate, presumed to be related to hypoglycemia but not requiring medical assistance), Grade 4 (similar to Grade 3, but reverses promptly after treatment (glucagon injection, intravenous glucose, emergency medical services provided at health care facility or in the field)), and Grade 5 (death or irreversible coma with circumstances suspicious for hypoglycemia). For study purposes, a hypoglycemic episode will be defined as Grade 3, 4, or 5 using self-report with additional queries as to whether the hypoglycemia might have been reversed without assistance. Events will be adjudicated by Drs. Buse, Donahue and Young without knowledge of treatment assignment. Narrative reports will be submitted to the IRB as serious adverse events potentially related to study procedures.
Health Care Utilization. Utilization outcomes will include inpatient, outpatient and emergency department utilization during the 52-week study period. UNC visits will be collected through the EHR while non UNC visits will be captured at the 52 week study visit via patient interview with the study coordinator.

Qualitative Assessment (Objective 3)

To gain a deeper understanding of patients’ and health care providers’ experiences with each of the SMBG testing approaches, including facilitators and barriers to dissemination, we will perform qualitative focus groups at the UNCPN practices.

Qualitative Assessment of Patient Outcomes. Five focus groups (one from each participating UNCPN practice) will be conducted by researchers skilled in qualitative data collection. Focus groups will be conducted once at least 80% of that practice’s enrolled study participants have completed their 52-week study visit. All participants will review and sign an additional IRB-approved informed consent document specific to the focus groups. Key topics will include: impressions of and experience with SMBG prior to and during the trial, including using a wireless glucometer and messaging system, and impressions of using the downloaded SMBG reports at clinic visits and how interactions with providers did/did not change per the intervention arm to which they were randomized.

Qualitative Assessment of Health Care Provider Outcomes. Five focus groups (one per practice) with 5-10 physicians and nursing staff will be conducted by researchers skilled in qualitative data collection. Groups will include 10 patients who have completed the study. They will occur at the practices once at least 80% of that practice’s enrolled study participants have completed their 52-week study visit. Key topics will include: impressions regarding the usefulness of SMBG summary reports and accompanying treatment algorithm; experience with recommending SMBG for patients with NIT DM prior to and during the trial (and for both enrolled and non-enrolled patients); and perceived benefits/problems arising from being a practice site for this study. All participants will review and sign IRB-approved informed consent documents prior to participation. We will also collect age, gender, race/ethnicity, full-time/part-time employment status, years in practice, and area of board certification for all participants.

2.3 Potential moderating variables

Based on their possible relationship to glycemic control and/or HRQOL, we will measure the following eight variables to be tested as possible modifiers of our primary outcomes. These include:

Prior experience using SMBG. Baseline use of blood glucose monitoring, including its frequency and the number of years of testing will be queried.

Duration of T2DM. Prior studies suggest that SMBG in NIT DM may be most beneficial for newly diagnosed patients and less beneficial for people with a longer duration of disease.

Baseline A1c. Some researchers have suggested that SMBG testing is most valuable for patients with higher baseline A1c results.

Anti-hyperglycemic treatment. Patients treated with insulin secretagogues (sulfonylureas and glinides) are at higher risk for hypoglycemia and may therefore be more likely to benefit from SMBG.

Age. A large meta-analytic study observed differences in the change in A1c level by age, with less change for older and younger patients. Age may also relate to comfort in using new technologies.

Race/ethnicity. A1c values are known to differ across racial and ethnic groups.

Health literacy. Low health literacy is associated with poorer diabetes knowledge, which could affect one’s ability to benefit from SMBG testing. Following consultation with the Health Literacy Core within the UNC Center for Diabetes Translational Research, we will use the Newest Vital Sign (NVS) screening tool to assess literacy and numeracy. This instrument has good internal consistency and reliability (Cronbach’s α > 0.76).

Number of comorbidities. Having additional illnesses might affect self-care behaviors. We will use a standard comorbidities list to obtain a count of comorbidities at baseline.

3. Study Design

Within the context of a controlled and randomized but pragmatic trial, we seek to answer the following question: Is SMBG testing sensible for people with NIT DM in terms of either A1c or QOL? We will also examine whether or not patients with different baseline characteristics might see different outcomes from SMBG testing. To achieve our goal of testing SMBG options in a ‘real world’ setting, the study has been designed to minimize as much as possible any interruptions in or alterations to standard daily patient care.
We will recruit 450 patients from five practices within the University of North Carolina Physicians Network (UNCPN). Patients will be randomized (see attachments) to one of the three study arms:

- Group 1) no SMBG testing;
- Group 2) once daily SMBG testing with standard patient feedback; and
- Group 3) once daily SMBG testing with enhanced patient feedback.

The first two study groups represent SMBG testing approaches commonly utilized in clinical practice. For all three groups, patients will receive information about maintaining normoglycemia. During routine clinic visits, their health care providers will be guided to modify therapies based on ADA guidelines, which focus on A1c values and SMBG values if available. Patients in groups 2 and 3 will also receive training in obtaining and interpreting SMBG values. These values will also be systematically evaluated at routine clinic visits. Finally, patients in group 3 will receive, through their glucose meters, wireless personalized immediate automated feedback about their testing values (see Figure 1).

### Subject Identification and Withdrawal

A multi-pronged approach will be utilized to identify study participants. First, patients who have NIT DM will be identified using the Carolina Data Warehouse (CDW) or by chart review in the participating practice. Patients will receive an invitation letter by mail, signed by their health care provider describing the study. Any patient not interested in participating will be able to opt out of further contact by returning a post card or calling a toll-free number. If no opt out call is made within one week of sending the letter, telephone contact will be attempted on up to three different occasions at three different times of day. The project Research Assistant will call each potentially eligible subject to confirm eligibility criteria. Second, we will place recruitment flyers within the participating practices that will be visible in waiting areas and exam rooms. Clinic staff will be encouraged to discuss the study with potentially eligible patients during routine clinic activities (i.e. while collecting vital signs and during check-in or check-out). The UNC field coordinators will communicate regularly with practice staff regularly regarding potentially eligible subjects.

#### 4.1 Inclusion criteria

Eligible patients will meet the following criteria:

1. T2DM diagnosed after age 30 (to reduce the likelihood of misclassification of T1DM) without clinical characteristics suggestive of type 1 diabetes (lack of obesity, unexplained weight loss)
2. An established patient at the participating UNCPN practice who identifies a UNCPN health care provider within that practice as their primary provider of diabetes care.
3. A1c ≥6.5% but ≤9.5% within the 6 months preceding the screening call/visit, as obtained from the electronic medical record. This range was chosen because patients with A1c above 9.5% should arguably be treated with insulin and check SMBG more frequently than once per day while patients with A1c below 6.5% are unlikely to get additional benefit from SMBG testing on one of the two primary outcomes (A1c) given their already excellent glycemic control.
4. Willing to comply with the results of random assignment into a study group.
4.2 Exclusion criteria

1. Currently sees or plans to see an endocrinologist or other diabetes specialist in the next year.
2. Is or plans to become pregnant in the next 12 months.
3. Plans to relocate in the next 12 months.
4. Has other conditions (e.g. renal or cardiovascular disease), factors (e.g. frailty) or comorbidities (e.g. cancer) that might put the patient at risk when following study protocols.
5. No history of significant issues with known or suspected hypoglycemia or any history of “severe” hypoglycemia (requiring assistance from a third party).

4.3 Subject recruitment and screening

All potentially eligible patients will be screened for eligibility by phone call. The call will take about 15 minutes, during which a member of the study team will describe the study, answer questions, and conduct a short set of simple screening questions to determine eligibility. Eligible patients who remain interested in participation will complete an assessment visit with a research coordinator. To decrease patient burden and further engage participating practices, assessment visits will occur at the patient’s primary care office. Assessments will be separate from their appointment with their primary care provider, and may or may not occur on the same day as a regularly scheduled clinic visit, though for patient convenience we will make every effort to coordinate the assessments with a regular clinic visits. During these assessments, the research coordinator will review the study details in greater depth, verify all inclusion and exclusion criteria, and obtain written informed consent.

4.4 Withdrawal of subjects

Once randomized, patients will not be discontinued from the study for any reason except patient request or withdrawal of consent.

5. Study Device: Telcare Glucometer

The Telcare glucometer is an FDA approved, cellurally-enabled device. The patient participants in the two testing arms will receive a Telcare glucometer to use during the 52-week study period. At the end of their participation, the participant will be allowed to keep the glucometer. The field coordinator enrolling the participant will register the meter with Telcare at www.telcare.com.

6. Study Procedures

6.1 Method for assigning subjects to treatment groups

After providing informed consent, baseline A1c, and completing the baseline study interview, participants will be randomized to one of the three treatment arms using sequentially numbered, opaque, sealed envelopes. The allocation sequence will be generated by an independent statistician who is not otherwise involved in the study using computer-generated randomly permuted blocks of random sizes. The randomization will be stratified by study practice. The research coordinator will then review the treatment assignment with the patient, using a standardized script, provide the initial training and supplies necessary for participation in that study and answer any remaining questions.

6.2 Baseline

Once written informed consent has been received, patient participants will:

- complete an interview that includes demographic, health history, and quality of life questions.
- have blood drawn for a hemoglobin A1c test. The blood sample will be sent to Quest Diagnostics and be processed using the National Glycohemoglobin Standardization Program (NGSP) certified High Performance Liquid Chromotography (HPLC) assay.

Upon completion of the interview and blood draw for hemoglobin A1c test, the field coordinator will randomize the patient to a treatment arm.

6.3 52-week follow-up

At the 52-week follow-up, patient participants will be asked to complete an interview that includes health history, health history, and quality of life questions. The patient’s blood will be drawn for a hemoglobin A1c test. The blood sample will be sent to Quest Diagnostics and will be processed in accordance with the procedures described under 6.2, Baseline.
7. Statistical Plan

7.1 Sample size determination

We desire high power for our primary between-arm comparison as well as reasonable power to detect an important effect modifier, should one exist. We will use an ANCOVA, controlling for baseline A1c and other baseline variables (See Sections 2.1-2.3) to compare mean change from baseline to 52-week A1c across the three intervention groups at the 0.05 significance level. In a recent Cochrane Review, the estimated mean 12-month differences between SMBG and control groups were -0.13% and -0.52%, respectively, for patients diagnosed more than and less than one year prior to the study. Assuming approximately equal enrollment of newly diagnosed and long term patients, this implies a mean difference of -0.325%. Based on results from one of the larger and better quality trials conducted to date, we assume the standard deviation for ΔA1c would be 0.8%. Assuming no more than 10% loss to follow-up. Given these assumptions, randomizing 150 patients per group would provide at least 90% power for the primary comparison for ΔA1c. This same sample size would provide at least 80% power for the primary comparison if the true standard deviation were as high as 1.0%. Under these same assumptions, this sample size would provide at least 70% power to detect an average interaction effect across the two SMBG groups compared to the no-SMBG group if the group means were similar to those for disease duration described above.

For comparing mean change in HRQOL between groups, we will use the physical and mental component scores of the SF-36, both of which range from 0 to 100. Because we are interested in two different aspects of QOL, we will apply a Bonferroni correction and assess each comparison at the 0.025 level. Based on observed results from the ZODIAC-17 SMBG study, we conservatively assume that the standard deviation for the change scores for either component will be 10 points. Under these assumptions, randomizing 150 patients per group with no more than 10% loss will provide at least 80% power to detect an overall difference between groups if the mean difference between the highest and lowest groups is at least 4 points. Power calculations were conducted using Procs GLMPower and POWER in SAS, V 9.2 (SAS Institute, Cary, NC).

7.2 Statistical methods

**OBJECTIVE 1: Quantitative Analysis of Patient Outcomes**

A detailed analysis plan will be developed by January 31, 2014 in accordance with the study contract. The following is a brief summary of the proposed plan. All comparisons will be made on an intention-to-treat basis, with patients analyzed according to their randomized group and regardless of the amount of intervention received. As the primary comparison of ΔA1c at 52 weeks across the 3 treatment groups (Objective 1), we will conduct an analysis of covariance (ANCOVA), controlling for prior use of SMBG, duration of T2DM, baseline A1c (A1c <8% vs. A1c>8%), baseline anti-hyperglycemic treatment (use of secretagogues vs. no use), age, race/ethnicity, health literacy, and baseline comorbidities at the 0.05 level. If the overall null hypothesis of no difference between groups is rejected, we will compare each SMBG group to the no-SMBG group separately using the Dunnett-Tamhane Step-Up procedure for multiple comparisons to control the family-wise error rate at 0.05; we will also conduct a contrast test comparing the average of the two SMBG groups to the no-SMBG group. Similar ANCOVA models will compare change in SF-36 physical and mental component scores between groups, controlling for the same baseline variables as for A1c. Because we are examining two aspects of HRQOL (physical and mental), we will apply a Bonferroni correction and assess each comparison at the 0.025 level. We will not adjust for multiple comparisons due to the co-primary endpoints of glycemic control and QOL.

Missing 52-week outcome data will be ignored for the primary model. As a sensitivity analysis that accommodates missing data and mistimed measurements, we will repeat the above analyses using linear mixed models that incorporate all observed A1c values, including those collected passively during interim months. This model will include fixed effects for time-since-randomization and time-by-treatment group interactions, and will include random intercepts and slopes for each patient.

We will assess the presence of effect modification for the baseline variables corresponding to the pre-specified subgroups of interest by adding appropriate interaction terms to the ANCOVA model one at a time. Each interaction term will be tested separately at the 0.05 significance level. Only if the associated interaction term is significant, similar contrasts to those described above will be assessed within the relevant subgroups.

**OBJECTIVE 2: Secondary outcomes**

Similar ANCOVA methods will be used to compare groups on each of the secondary outcomes (Objective 2). These tests will each be conducted at the 0.05 significance level with no adjustments for multiple comparisons.

**OBJECTIVE 3: Qualitative Assessment of Patient Outcomes**

Five patient focus groups (one from each participating UNCPN practice) will be conducted by researchers skilled in qualitative data collection. Groups will include 8-10 patients who have completed the study. They will occur at the practices once at least 80% of that practice’s enrolled study participants have completed their 52-week study visit. All participants will review and sign an additional IRB-approved informed consent document specific to the focus groups. Key topics will include: impressions of and experience with SMBG prior to and during the trial, including using a wireless glucometer and messaging system, and impressions of using the...
downloaded SMBG reports at clinic visits and how interactions with providers did/did not change per the intervention arm to which they were randomized. We will have previously collected all pertinent demographic information on patient focus group participants.

8. Data and Safety Monitoring Plan

Because there are currently no definitive clinical guidelines that describe how frequently a person with NIT DM should be monitoring their SMBG values, the randomized treatment provided in in this proposed study represents variations in usual care. As an FDA approved glucose monitoring system will be utilized in conjunction with standard diabetes management by local providers, this study poses no greater than minimal risk, and therefore a data safety and monitoring board is not required. Nevertheless, a data and safety monitoring plan is detailed below.

This study has been approved by the UNC Institutional Review Board. The project leadership team will meet weekly throughout study to review study milestone progress and adverse event reports.

Reporting Mechanisms:

Any reported adverse events will be categorized as related or not related to the study intervention by the investigators. These events will be reported in real time to the principal investigators for confirmation and review of grading. Regardless of causality, all unanticipated Serious Adverse Events or grade 3 or 4 glycemic events as defined in Section 2.2, will be reported to the IRB for review.

Any adverse events that occur will be discussed at team meetings with the project leadership team to make a decision regarding overall safety of the study, whether subject participation should be stopped, and plans for communicating safety concerns to the local providers.

Frequency of Monitoring Regarding Time or Number of Subjects:

Safety data will be reviewed by the project leadership team on an ongoing basis and will be summarized in quarterly reports by the Project Manager. In addition, the project leadership team will review subject accrual, adherence to study protocol and dropouts, and monitor data monthly.

Specific Data to be Monitored:

Adverse events and unexpected adverse events for all subjects, subject accrual, dropouts, and adherence to the study protocol will be monitored. Particular attention will be paid to psychological endpoints, infection at SMBG sites, hypoglycemia, and traumatic events.

Procedures for analysis and interpretation of the data:

Our study statistician will be blinded to subject randomization when analyzing the safety data.

Actions at Defined Events or End Points:

If 2 or more subjects experience Serious Adverse Events or Grade 3/4 adverse events related to the study intervention, enrollment will be held while the protocol undergoes review by the project leadership team and a decision can be made regarding the overall safety of the study. Clinicians will be counseled that presumed severe hypoglycemia (requiring assistance) would be an indication for SMBG monitoring and modification of the treatment plan unfettered by the protocol.

Procedures for Communication from the Data Monitor to the IRB and Other Sites:

All adverse events, whether serious or nonserious, will be reported from the time a signed and dated informed consent form is obtained until completion of the last study-related procedure. Any unanticipated or serious adverse events will be reported to the IRB within 7 days after occurrence by the site. Reports detailing unanticipated and serious adverse events will be reviewed weekly by the Clinical Site Coordination Team chaired by Dr. Donahue and appropriate reports sent to the IRB. All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject’s participation in the study, must be followed until: 1) the event resolves; 2) the event stabilizes; 3) the event returns to baseline, if a baseline value is available; 4) the event can be attributed to agents other than SMBG or to factors unrelated to study conduct; or 5) when it becomes unlikely that any additional information can be obtained.

Unanticipated Problems that are serious adverse events will be reported to the IRB within one (1) week of the investigator becoming aware of the event. Any other Unanticipated Problem will be reported to the IRB within two (2) weeks of the investigator becoming aware of the problem. Patients can contact the PIs and/or study coordinator should safety issues related to the study develop.
9. Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

Data collectors will be trained in the importance of protecting the confidentiality. Primary data, which contains identifiers, will be audio recordings and will be kept in locked storage cabinets and separate from consent forms. In addition, participant recruitment and scheduling logs will contain study ID numbers and participant names. Paper logs will be destroyed at the end of the study. Identifiers in the electronic logs will be removed at the end of the study. All audiotapes will be erased or destroyed at the end of the study. Data for analysis and reporting purposes will be stripped of all unique identifiers. Reports will not provide practice-specific or individual-specific identifiers.

9.2 Source Documents

Human research material and data collection: Several types of data will be collected during the course of this study. Recruitment and scheduling logs will be maintained by the study RA. Potential participant identifying information will be entered into the study data system log by the RA from the screening lists provided by the practices, the Carolina Data Warehouse, or retrieved from the electronic health record system in a practice. Field coordinators will update written recruitment logs with recruitment and data collection completion status and return to the study office. All logs will be stored in a locked filing cabinet until the end of the study. Research staff who collect data in person or by chart review will know the identity of the patient for whom the data is being collected; however, the patient’s name or medical record number will not be used on the data recording forms. Each category of data is outlined below.

Patient-Reported Demographic and Clinical Data: These data will include questionnaire assessments, patient reported outcomes, and diabetes disease related information.

Electronic Health Record (EHR) Data: EHR data will be obtained passively or by chart review by study staff from the electronic medical record for the following measures: capillary blood glucose values, capillary blood sample for A1c determination, new prescriptions for blood glucose testing strips, pharmacologic regimen changes, anti-hyperglycemic medication, and patient utilization of health care resources (clinic visits, ER visits, and hospitalizations).

Patient and Health Care Provider/Staff Impressions: For the qualitative assessments, research data sources include focus group interviews and paper surveys.

10. Dissemination Plan

The overall goal of involving various stakeholder groups (See Section 11) is to have key people with a variety of perspectives involved in planning, oversight, analysis and dissemination of this project. Groups interested in this research are varied and include patients, caregivers, providers, advocacy groups, glaucoma manufacturers, educators and policy makers.

Dissemination channels: At the state level, the NC Diabetes Advisory Council has several vehicles for dissemination, including newsletters, a website (http://www.ncdiabetes.org/), Twitter, and grass roots advocacy/lobbying groups. At the local level, the UNC Physicians network has biannual staff meetings and newsletters. UNC family medicine has newsletters and a radio show, blog and app on health that reaches 30,000 listeners and viewers weekly (http://yourhealthradio.org). At the national level, the American Diabetes Association and National Diabetes Education Program provide a vehicle for dissemination through conferences, web-sites, social media, newsletters, guidelines and a communications staff that engages, providers (physicians [primary care and multiple sub-specialties], nurses, dietitians, health educators, community health workers), industry, and state Diabetes Prevention and Control Programs.

Importance of literacy in dissemination: Our team includes the health literacy core, in the UNC Center for Diabetes Translation and Research. This core will work with us to ensure our messages, interviews, questionnaires and dissemination materials are appropriate to our audience.
11. Stakeholders

We have a diverse group of stakeholders and as noted above include industry representatives, patients, diabetes educators, providers, and advocacy groups.

Our stakeholders will meet 8 times in Years 1 and 3 of the project and 4 times in Year 2.
12. References


THE MONITOR TRIAL

Effect of Glucose Monitoring on Patient and Provider Outcomes in Non-Insulin Treated Diabetes

INITIAL STATISTICAL ANALYSIS PLAN

Principal Investigators:
Katrina Donahue, MD, MPH
Laura Young, MD, PhD

Investigators:
John Buse, MD, PhD
Mark Weaver, PhD
Maihan Vu, PhD

Project Manager:
C. Madeline Mitchell, MURP

Version date: 01/23/2014
# TABLE OF CONTENTS

1. STUDY OBJECTIVES .......................................................... 21
2. STUDY DESIGN ................................................................. 21
3. ANALYSIS POPULATIONS .................................................. 21
4. UNBLINDING PLAN ............................................................ 21
5. MISSING DATA ................................................................. 22
6. ANALYSIS OF SUBJECT FOLLOW-UP .................................... 22
7. ANALYSIS OF BASELINE DATA .......................................... 22
8. DESCRIPTIVE SUMMARY OF POST-RANDOMIZATION DATA .... 22
9. ANALYSIS OF PRIMARY OUTCOMES (OBJECTIVE 1) ........ 22
10. ANALYSIS OF SECONDARY OUTCOMES (OBJECTIVE 2) ...... 23
11. REFERENCES .................................................................... 24
This statistical analysis plan is an expanded version of the summary analysis plan included in the study protocol and supersedes the summary plan included in the study protocol. Any significant changes made to this analysis plan after study initiation will be documented herein.

**Study Objectives**

This randomized trial will assess the impact of three different self-monitoring of blood glucose (SMBG) testing approaches on patient-centered outcomes in patients with non-insulin treated type 2 diabetes (DM).

The objectives of this trial are as follows:

**Objective 1:** Assess SMBG effectiveness, with or without tailored messaging, on two primary, patient-centered outcomes, glycemic control (A1c) and health related quality of life (HRQOL), relative to the no testing arm over one year.

- **Sub-objective 1a:** Assess potential differences in SMBG effectiveness across the following subgroups: 1) prior experience using SMBG; 2) duration of DM; 3) baseline glycemic control; 4) baseline anti-hyperglycemic treatment; 5) age; 6) race/ethnicity; 7) health literacy; and 8) number of baseline comorbidities.

**Objective 2:** Evaluate the impact of SMBG on secondary patient-centered, outcomes including: a) DM-related QOL, b) DM self-care, c) DM treatment satisfaction, d) DM self-efficacy, e) patient-provider communication, f) hypoglycemia frequency, g) health care utilization.

**Objective 3:** Conduct qualitative assessments of the patient participant and provider experience for all three intervention groups.

This document describes the analyses planned for Objectives 1 and 2, and other supporting quantitative analyses. The qualitative approach to be applied for Objective 3 will be described elsewhere.

**Study Design**

This study is a multi-site, open-label, randomized controlled trial of 450 non-insulin treated diabetic patients followed over one year. Patients will be recruited from five practices within the University of North Carolina Physicians Network (UNCPN). Patients will be randomized to one of the three arms:

- Group 1) no SMBG testing;
- Group 2) once daily SMBG testing with standard patient feedback; and
- Group 3) once daily SMBG testing with enhanced patient feedback.

Patients will have two study contacts: enrollment at baseline and a 52-week follow-up visit. Additionally, daily SMBG values will be downloaded for patients assigned to Groups 2 and 3.

**Analysis Populations**

Two analysis populations will be defined for this study:

- **Intent-to-Treat (ITT) Population:** This population will include all subjects who were randomized (i.e., for whom a randomization envelope was opened), analyzed according to the group to which they were randomized. Nobody will be excluded.

- **Per Protocol Population:** This population will be a subset of the ITT population and will exclude all subjects who initiate insulin treatment or who become pregnant any time between randomization and their 52-week visit (defined as 52 weeks ± 6 weeks from their baseline visit). Additionally, this population will exclude subjects who do not adequately adhere to their assigned treatment arm, for whatever reason. For Group 1, this will exclude subjects who initiate SMBG testing at any point during the study. For Groups 2 and 3, this will exclude subjects who fail to perform SMBG testing on at least 80% of days between randomization and their 52-week visit or 365 days following randomization, whichever is earlier.

**Unblinding Plan**

As an open-label study, subjects, providers, and many study staff will know to which group individual subjects have been randomized. However, efforts will be made to keep the study statistician (Mark Weaver) blinded to randomization group during the course of the trial. Any key decisions regarding study outcomes, the appropriateness of test statistics or model assumptions, changes to this analysis.
Missing data

Missing 52-week (±6 weeks, or 323 days to 407 days post-randomization) outcome data will be ignored for the primary analyses. As a sensitivity analysis that accommodates missing data and mistimed measurements, we will repeat the analysis of A1c using linear mixed models that incorporate all observed A1c values, including those collected passively at interim clinical visits. As a further sensitivity analysis, we will repeat the A1c analysis using last observation carried forward (LOCF) to impute the 52-week value for any subjects who: do not provide a 52-week value, initiate insulin, or become pregnant. Data missing by design (i.e., due to a skip pattern in the data collection form) will be filled in logically where appropriate.

Analysis of Subject Follow-Up

We will present an account of the final disposition (completed, withdrew, lost, or died) of each subject in the ITT Population, including any admission violations and group assignment. The number and proportion of subjects in the ITT population who provided information for the analyses of the study objectives will be summarized by randomization group, both pooled across sites and separately by site. We will provide a CONSORT diagram showing the flow of subjects through the trial, indicating withdrawals by treatment arm with reasons, when provided.

Analysis of Baseline Data

We will summarize baseline data (i.e., pre-randomization data) for the ITT Population, by site and overall. Measures of central tendency and dispersion for continuous and certain discrete variables will include means, standard deviations, medians, minima, and maxima. Categorical data will be summarized with frequencies and percentages. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables. No inferential statistics (i.e., p-values and/or confidence intervals) for comparing data between groups will be presented.

Descriptive Summary of Post-Randomization Data

Descriptive statistics will be provided for all post-randomization study variables, by randomized group, including, for Groups 2 and 3, frequency of SMBG testing (weekly average) and descriptive statistics (mean, SD and range of SMBG values) by time of day and patient-noted circumstance via the wireless glucometer. Informative graphs will be used for descriptive purposes where appropriate.

Analysis of Primary Outcomes (Objective 1)

A1c

The primary analysis of change in A1c (ΔA1c) will use the ITT Population, and will be repeated secondarily using the Per Protocol Population. As the primary comparison of ΔA1c at 52 weeks (±6 weeks, or 323 days to 407 days post-randomization) across the 3 treatment groups, we will conduct an analysis of covariance (ANCOVA), controlling for baseline A1c, prior use of SMBG, duration of T2DM, baseline anti-hyperglycemic treatment (use of secretagogues vs no use), age, race/ethnicity, health literacy, and number of baseline comorbidities at the 0.05 significance level. If the overall null hypothesis of no difference between the three groups is rejected, we will compare each SMBG group (Groups 2 and 3) to the no testing group (Group 1) separately using the Dunnett-Tamhane Step-Up procedure for multiple comparisons to control the family-wise error rate at 0.05 (Dunnett and Tamhane, 1992). This multiple testing procedure is as follows:

- Compute the two pairwise comparison p-values for each SMBG group compared to the no testing group using appropriately specified contrasts in the ANCOVA model;
- Compare the largest of the pairwise comparison p-values to 0.05; if the p-value is less than 0.05, reject both null hypotheses and conclude both SMBG groups are more effective than no testing;
- If the largest p-value > 0.05, then compare the smaller of the two p-values to 0.0262 and, if smaller, reject only this null hypothesis and conclude that corresponding SMBG group is more effective than no testing.

We will also conduct a contrast test comparing the average of the two SMBG groups to the no-SMBG group at the 0.05 level.
As described in Section 5, we will conduct two sensitivity analyses to investigate sensitivity of our conclusions to certain data handling conventions. First, we will repeat the ANCOVA model using a linear mixed model that incorporates all observed A1c values, including those collected passively at interim clinical visits. This model will include fixed effects for time-since-randomization and time-by-treatment group interactions, and will include random intercepts and slopes for each patient. Second, we will repeat the primary ANCOVA using LOCF to impute 52-week A1c values for all subjects who either dropped out, initiated insulin, or became pregnant following randomization.

**HRQOL**

The primary analyses of change in HRQOL will use the ITT Population, and will be repeated secondarily using the Per Protocol Population. The physical and mental subscales of the SF-36 will be scored by the Sheps data management team using software provided by the scale developer, and the scores will be included in the dataset supplied to the statistician. Similar ANCOVA models to those described above will compare change in SF-36 physical and mental component scores between groups, controlling for the same baseline variables as for A1c in addition to the baseline values of the respective subscales. Because we are examining two aspects of HRQOL (physical and mental), we will apply a Bonferroni correction and assess each comparison at the 0.025 level. However, we will not adjust for multiple comparisons due to the co-primary endpoints of glycemic control and QOL.

**Sub-Objective 1a: Potential Effect Modifiers**

We will assess the presence of effect modification for the baseline variables corresponding to the pre-specified subgroups of interest by adding appropriate interaction terms to the respective ANCOVA models (for each of A1c and the physical and mental components of HRQOL) one at a time. Each interaction term will be tested separately at the 0.05 significance level. Only if the associated interaction term is significant, similar contrasts to those described above will be assessed within the relevant subgroups. The subgroups to be examined in this way are:

- prior experience using SMBG (any versus none);
- duration of DM (≤ 1 year prior to study versus > 1 year prior);
- baseline glycemic control (baseline A1c <8% vs A1c>8%);
- baseline anti-hyperglycemic treatment (use of secretagogues vs no use);
- age (< 65 vs. ≥ 65);
- race/ethnicity (non-Hispanic Caucasian, non-Hispanic African Americans, other);
- health literacy (<4 vs. ≥4);
- number of baseline comorbidities (low versus high, separated by the observed median score).

**Analysis of Secondary Outcomes (Objective 2)**

The ITT Population will be used in the primary analysis of all secondary outcomes. Similar ANCOVA methods to those described above for A1c will be used to compare groups on each of the secondary outcomes; for any scale measured at baseline, the corresponding ANCOVA will control for baseline value in addition to the variables noted above. These tests will each be conducted at the 0.05 significance level with no adjustments for multiple comparisons.

The secondary outcomes will be derived as follows:

**DM-Related QOL**

The Problem Areas in Diabetes (PAID) scale will be scored by summing the 20 items and multiplying by 1.25 for a resulting score between 0 and 100. Items with missing responses will be imputed using the mean of non-missing items if at least 75% of items are not missing.

The items on the Diabetes Symptoms Checklist (DSC) will be summed, both separately for each symptom category (hyperglycemic [items l, p, w, and ff], hypoglycemic [items h, s, and aa], psychological cognitive [items f, g, ee, and gg], psychological-fatigue [items a, d, q, and t], cardiovascular [items e, m, x, and dd], neurological pain [items b, o, u, y], neurological-sensory [items c, i, k, z, cc, and hh], and ophthalmologic [items j, n, r, v, and bb]) and overall. Symptoms that are indicated to have not occurred will be scored a 1, same as for symptoms that occurred but were “not at all” troublesome. For each symptom category, items with missing responses will be imputed using the mean of non-missing items if at least 75% of items are not missing.

**DM Self-Care**

The average of the items on the Summary of Diabetes Self Care Activities (SDCA) scales will be computed, both separately for each set of activities (diet, exercise, blood sugar testing, and foot care) as well as overall. For each set of activities, items with missing responses will be imputed using the mean of non-missing items if at least 75% of items are not missing.

**DM Treatment Satisfaction**

The sum of the items on the Diabetes Treatment Satisfaction Questionnaire (DTSQ) will be computed. Items with missing responses will be imputed using the mean of non-missing items if at least 75% of items are not missing.
DM Self-Efficacy
The average of the items on the Diabetes Empowerment Scale Short Form (DES-SF) will be computed. Items with missing responses will be imputed using the mean of non-missing items if at least 75% of items are not missing.

Patient-Provider Communication
The average of the items on the Communication Assessment Tool (CAT) will be computed. Items with missing responses will be imputed using the mean of non-missing items if at least 75% of items are not missing.

Hypoglycemia Frequency
For the ITT population, we will descriptively compare the self-reported frequency (captured at 52 weeks) of severe hypoglycemia across all three arms. Additionally, for the SMBG groups only (Groups 2 and 3), downloaded SMBG values will be graded according to severity as Grade 1 (SMBG <70 mg/dl) or Grade 2 (SMBG<50 mg/dl). The frequency of these events relative to the number of tests will be descriptively compared between the two arms.

Health Care Utilization
Patient reported frequency of visits to primary care provider, urgent care clinic, Emergency room, overnight hospitalizations, and EMS calls during the study year will be descriptively compared across the 3 groups.

Additionally, we will summarize use of glycaemia medications at baseline and 52 weeks, both overall and by group, and will descriptively compare change in medication use from baseline to 52 weeks between groups, except for use of insulin. We will compare groups for initiating use of insulin by calculating differences between groups, along with 95% confidence intervals, in participants who initiate insulin during the study.

References
THE MONITOR TRIAL

Effect of Glucose Monitoring on Patient and Provider Outcomes in Non-Insulin Treated Diabetes

FINAL STUDY PROTOCOL

Principal Investigators:
Katrina Donahue, MD, MPH
Laura Young, MD, PhD

Investigators:
John Buse, MD, PhD
Mark Weaver, PhD
Maihan Vu, PhD

Project Manager:
C. Madeline Mitchell, MURP

Prepared for:
Diane Bild, MD, MPH
Senior Program Officer
Patient-Centered Outcomes Research Institute (PCORI)
1828 L Street, NW 9th Floor,
Washington, DC 20036
BACKGROUND

For the nearly 75% of patients living with type 2 diabetes (T2DM) that do not use insulin, decisions regarding self-monitoring of blood glucose (SMBG) can be especially problematic. Considering the many burdens SMBG testing places on patients, it is a resource intensive activity without firmly established patient benefits. While in theory SMBG holds great promise for sparking favorable behavior change, the potential for no benefit or even patient harm must be acknowledged. Possible negative effects on patient quality of life must be more closely examined along with the speculative benefits of SMBG in non-insulin treated T2DM. Among studies examining this issue a general consensus is evolving; while SMBG may or may not be clinically useful, its value can only be fully appreciated when the SMBG results are provided to patients in a useful manner. Testing without feedback, a common clinical occurrence, holds little clinical promise.

OBJECTIVES

The overarching goal of this proposal is to assess the impact of three different SMBG testing approaches on patient-centered outcomes in patients with non-insulin treated T2DM within the real-world, clinic setting.

METHODS

This is a pragmatic trial of 450 patients randomized to one of the following three SMBG testing regimens: 1) no SMBG testing; 2) once daily SMBG testing with standard patient feedback consisting of glucose values being immediately reported to the patient through the glucose meter; and 3) once daily SMBG testing with enhanced patient feedback consisting of glucose values being immediately reported to the patient PLUS automated, tailored feedback messaging following each SMBG testing event delivered to the patient through the glucose meter.

The first two arms represent common SMBG testing approaches currently being used. The third arm is an enhanced, patient-centered approach to SMBG testing. SMBG values will be evaluated at routine clinic visits over 52 weeks. Patients’ health care providers will utilize the American Diabetes Association Guidelines, which focus on individualization of patient care, to guide therapy modification. We will use a mixed methods approach. Quantitative patient assessments will occur at baseline and at 52 weeks. Qualitative assessments using patient and provider focus groups will occur at the conclusion of the intervention. We have actively engaged several stakeholders to inform the trial design and choice of outcomes.

PATIENT OUTCOMES

The following primary outcomes will be assessed: Quality of Life and Glycemic Control. We will assess differences across the following pre-specified subgroups: 1) prior experience using SMBG; 2) duration of T2DM; 3) baseline degree of glycemic control; 4) anti-hyperglycemic treatment; 5) age; 6) race/ethnicity; 7) health literacy

Secondary outcomes will include diabetes-related treatment satisfaction, self-efficacy, distress, self-care, hypoglycemia frequency and patient-provider communication.

3. Introduction

This document provides background information and a description of the overall study design for the Monitor Trial, a pragmatic clinical trial assessing three approaches for managing non-insulin treated type 2 diabetes (T2DM). This study is to be conducted in accordance with the approved UNC Institutional Review Board study procedures.

1.1 Background

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or generally both. At least 285 million people worldwide have DM. The estimated costs of the condition in the US alone top 174 billion annually. Now described as an epidemic, the global incidence of DM is expected to double over the next two decades, reaching 435 million cases by 2030. T2DM, closely linked to obesity, makes up around 90% of cases, with the remaining 10% being Type 1 and gestational. Recent Centers for Disease Control and Prevention (CDC) reporting shows alarming increases in T2DM in the US. The southern states fare the worst, with rates of DM cases doubling in just 15 years. Complications from T2DM include heart disease, stroke, diabetic retinopathy leading to visual impairment or blindness, kidney failure requiring dialysis, and limb amputation. Other associations include higher risk of cognitive dysfunction, dementia, cancer, sexual dysfunction, and infection, plus increased rates of hospitalization and a shorter life expectancy. In the US, DM is the leading cause of kidney failure, non-traumatic lower-limb amputations, new onset blindness, and the seventh leading cause of death.

Given the devastating effects of DM, improving treatment for persons with DM is of obvious importance. DM is a chronic condition with no cure, thus disease management is the primary form of treatment. A main goal of management is to control blood glucose, which is evaluated primarily through blood levels of hemoglobin A1c (A1c). A1c relates closely to the average plasma glucose levels a patient experienced over ~3 months. According to the American Diabetes Association (ADA) guidelines, an A1c of 6.5% or above is
a criterion for diagnosis. In addition to pharmaceuticals, self-monitoring of blood glucose (SMBG) through the use of strips and

glucose meters is a recommended method for maintaining better glucose regulation. The process entails using a lancing device to

take a sample of capillary blood, which is then placed on a testing strip and read by a small handheld device. After several seconds,

current plasma glucose concentration is reported on the device. For patients with DM who are treated with insulin, SMBG is an

accepted procedure for daily monitoring effects of insulin therapy. However, the majority of T2DM patients do not use insulin.

According to the CDC, 26% of people with DM use insulin, while the remainder use oral medications only (58%) or no medications

(16%). While control of A1c is equally important for persons with DM who are non-insulin treated (hereafter NIT DM), the value of

SMBG testing for these patients is debatable. Proponents postulate that testing promotes better awareness of glucose levels,

leading to improvements in diet and lifestyle. When test result are shared with health care providers, it is argued, there is also the

potential for more timely treatment modifications. Competing arguments point to the costs of SMBG, both in terms of supplies (one-
time use test strips currently cost around $1 each, with meters costing between $50-$100) and time, as well as the obvious discomfort

involved (pricking the skin), all of which would be net harms if SMBG does not improve key outcomes for these patients.

Scientific examinations of SMBG in NIT DM have provided mixed results. An early epidemiological evaluation of the issue using a

retrospective, longitudinal analysis showed that nonfatal micro- and macrovascular event rates along with fatal event rates were lower

in individuals performing SMBG routinely as compared to those who were not. A multitude of clinical trials followed. Several

showed a significant benefit from SMBG testing on improving glycemic control, while others found no evidence of benefit.

In fact, some studies even suggested harm from routine SMBG in patients with NIT DM, specifically, higher rates of depression and

increased cost without accompanying benefits.

Given these mixed results, a series of meta-analyses and systematic reviews were conducted to investigate the benefit or lack thereof

of SMBG on glycemic lowering in patients with NIT DM. While meta-analyses can be a useful way to assess the clinical

effectiveness of an intervention, they are limited by the quality and comparability of the clinical trials included in the analyses. Issues

of sample size, duration/details of the intervention, and patient characteristics (e.g., newly diagnosed vs. longer duration of disease;

baseline A1c level), varied considerably across the available studies. Given these critical differences, it is perhaps not surprising that

the results of the meta-analyses have also shown conflicting results. However, the overall conclusion has been that SMBG is likely

not cost effective for this population of patients.

Perhaps most important to understanding these mixed results is the fact that the question being addressed by the studies is itself not

consistent, falling generally into two camps: ‘simple’ SMBG and ‘enhanced’ SMBG. In studies testing simple SMBG, patients

conducting SMBG were compared to patients who were not. In evaluations of ‘enhanced’ SMBG, intervention group patients and/or

providers were given education or feedback such that they were better able to interpret SMBG results and use them in a meaningful

way with regard to lifestyle changes and treatment modification. Among tests of ‘simple’ SMBG, A1c levels were reduced on average

by 0.2%, an amount that was statistically significant in these studies, but of doubtful clinical significance. Studies of ‘enhanced’

SMBG found A1c reductions closer to 0.5%. As additional ‘enhanced’ intervention SMBG studies were added to the literature,

more recent reviews and meta-analyses have drawn conclusions more in favor of testing. This pattern suggests that, for SMBG to be an effective self-management tool in NIT DM, the patient and the health care provider must both actively engage in

performing, interpreting, and acting upon the SMBG values.

The effect of SMBG could impact patient quality of life (QOL) both positively and negatively. Testing itself is a burden and could

act as a constant reminder of one’s less than ideal health status. On the other hand, testing may provide a sense of agency,

improving a patient’s sense of self-efficacy and hope for maximizing health and independence into the future. A recent Cochrane

Review identified only a handful of studies that had examined health-related quality of life (HRQOL), well-being, or patient

satisfaction. While these studies did not find clinically relevant differences in HRQOL for those who do or do not test, the review

indicated future research was needed. In one study, HRQOL initially decreased, but follow-up qualitative interviews showed that

patients in the testing groups experienced an increased awareness of illness. While both simple and ‘enhanced’ versions of SMBG

were evaluated, the enhanced version included only training in the meaning of the results and encouragement to explore how lifestyle

and dietary choices affect test values. Without more hands-on use of results (e.g., reports provided to the care provider), patients might

have felt more ‘overwhelmed’ than empowered by the experience of testing. Future studies of HRQOL and other patient-centered

aspects of SMBG must examine it within the context of patient’s having actionable knowledge and improved opportunities for

provider/patient collaboration.

1.3 Self-monitoring practices

The lack of consensus around the benefits or lack thereof of employing SMBG for persons with NIT DM has led to virtually no

standardization in SMBG recommendations worldwide. Guidelines range from clear recommendations for regular testing, to general

statements about ensuring that testing is an available option to patients, to not recommending testing except in specific cases. The

ADA suggests SMBG may be useful as a guide to the success of other therapies. Mirroring the lack of research in this area, very few

guidelines on diabetes care and management even touch upon quality of life issues. Without medical consensus, it is not surprising

that there is little consistency in either reimbursement for or routine use of SMBG in patients with NIT DM.
While researchers and medical organizations debate the overall issue of the value of SMBG testing in NIT DM, patients face this choice daily and without adequate information as to its clinical or psychological outcomes. For some patients, their decision on testing will mirror that of their care provider. Yet more and more, patients play an active role in managing their own health. To some degree this is a necessary trend, because providers simply do not have sufficient time to provide intensive ongoing and comprehensive education and decision-making around diabetes self-management. Then too, even providers are looking for additional guidance on this question, including how to present options to patients and incorporate test results into care. The fact that patients are taking a greater role in their health care is generally positive, because those who do so also improve their outcomes. Diabetes self-management, however, encompasses an increasingly complex set of services and supports, including glucose monitoring, medication management, nutrition counseling, physical activity promotion, social support networking and, when needed, psychotherapy.

While current SMBG testing rates have not been well documented, in a recently published study of over 500 patients with NIT DM, 14.1% reported never testing, 22.8 tested once a week or less, 22.3% tested once a day, and 54.7% tested more than twice a day. These results point to over 75% of patients currently performing regular SMBG testing. The wide range in SMBG testing frequency is likely dependent on the recommendations of the providers from whom the patients were receiving care. In preparation for this grant application, we conducted a survey of SMBG habits and attitudes among patients with NIT DM who are part of the UNC Diabetes Care Center Patient Registry, a group consented for participation in research projects. Among the 62 of patients who had NIT DM, we found lower SMBG testing rates. Only one third said that they test one or more times daily, while 15% tested never or less than once a month. The remainder tested several times per week (38%), several times per month (20%), or less than once per month (5%).

In addition to highlighting variability in testing rates, both the study by Wang and our pilot survey point to difficulties these patients encounter with regard to testing and using test results. Wang et al found that close to half (44.7%) reported missing or skipping blood sugar checks. In our UNC sample, despite the low testing rates, a full 87% felt SMBG is an important part of diabetes self-care, and 79% said it was important to their provider. Indeed, 43% admitted that they test less often than suggested by their provider. At the same time, a small but important minority said their provider never instructed them on how often to test. Finally, even within the sample of patients for whom over 75% test at least daily, most patients are not taking appropriate problem solving steps in response to high (hyperglycemia) or low (hypoglycemia) blood sugar levels.

### 1.3 Modern diabetes self-management technologies

Increasingly, patients are turning to the Internet and other new means of electronic communication for information, connections and guidance. In a study of mobile health applications for SMBG that included English-language interfaces, over 900 were available for review. But of the 137 applications that were comprehensive enough to meet basic review criteria, only 7% included a module providing personalized education or feedback. This study highlights both the demand for and current unmet need among patients considering or currently participating in SMBG. Recognizing this, some are calling for greater use and development of such patient-centered medical options. Kaufman refers to these technologies as “a solution whose time has long since arrived” but argues that, to be most effective, they must be ‘clinically linked,’ that is, occurring within the context of a trusted therapeutic relationship and an effective medical care system. As he goes on to point out, internet and cell phone use is now so widespread and inexpensive that it is erasing geographic, economic and demographic barriers to obtaining health information and support. He argues that the medical system should take advantage of these facts to further incorporate information technology into patient care and support.

### 1.4 Testing approaches

In order to make informed patient choices, patients and their providers need accurate, generalizable and meaningful information about the merits or demerits of SMBG testing for persons with NIT DM. Because the existing research, though relatively extensive, has not yet met this important need, more research must be done on this issue. The Consensus Report of the Diabetes Technology Society provides a list of recommendations for future research relating to SMBG in NIT DM. In regard to the intervention itself, they recommend that it a) is linked to a structured program designed to facilitate behavior change, b) has A1c as a primary endpoint but include patient-centered endpoints, c) include encouragement and support, preferably in the form of personalized, automated feedback to patients in real time, d) takes advantage of telemedicine opportunities, and d) incorporate best practices guidelines and standards for physicians. Many of these recommendations overlap with others. In addition to these critical features, future research should be designed with a pragmatic eye, adhering as closely as possible to the real world setting in which SMBG would be carried out by patients and utilized by patients and health care providers collaboratively. To date, no large-scale, pragmatic RCT has evaluated the impact of SMBG testing in patients with NIT DM in which a multi-dimensional approach to SMBG value management has occurred. Performing another randomized clinical trial of efficacy would not help clarify this hotly debated topic. Also missing from current research is an examination of SMBG testing for selected patient groups. Racial and ethnic differences in A1c have been observed. Compared to non-Hispanic white adults, the risk of diagnosed DM is 66% higher among Hispanics/Latinos and 77% higher among non-Hispanic blacks. Persons from different racial or ethnic backgrounds might also respond differently to SMBG testing, as there may be differences in how individuals interact with providers, or the ease with which they are able to use and make use of a wireless glucometer.
While SMBG may or not be worthwhile, effective SMBG, if it exists for NIT DM, appears to require that it be embedded within the context of patient education around the use and interpretation of glucose readings, provider awareness of the results of repeated testing, and collaborative use of this information at medical visits. We would also argue for providing treatment algorithms to providers that are based on standard and accepted guidelines (such as the ADA guidelines) linked to SMBG report results. This step facilitates the physician’s use of glucometer result reports and can be used by health care providers during clinic visits to better illustrate their concerns when talking to patients. Finally, we feel it is important to evaluate objectively and in a real world setting the possible additional benefits of personalized feedback for patients in the form of messages delivered via the glucometer based on patients’ current and recent SMBG patterns. By pointing out troubling patterns and rewarding results that are at goal, this aspect of the approach we are calling ‘enhanced feedback’ is akin to ‘mini consultations’ with a provider between routine clinic visits, which are generally 3-6 months apart. Patients are curious about these enhanced approaches as evidenced by 80% of our survey respondents reporting that they would perform SMBG as directed by their health care provider if they received instantaneous feedback on their glucose readings.

1.6 Risk/Benefits Associated with SMBG

Because there are currently no definitive clinical guidelines that describe how frequently a person with NIT DM should be monitoring their SMBG values, the randomized treatment provided in this proposed study represents variations in usual care. As an FDA approved glucose monitoring system will be utilized in conjunction with standard diabetes management by local providers, this study poses no greater than minimal risk.

Establishing the utility or lack thereof for SMBG monitoring in patients with NIT DM receiving care within a variety of primary care, clinical settings is a practical, contemporary issue, with far-reaching implications of value to numerous stakeholders including primary care providers, patients, academicians, insurance payers, and government regulatory agencies. A positive result will establish a standard of care. A negative result will reduce unnecessary burdens (time, effort and financial) for patients, providers and health care systems.

4. Study Objectives and Endpoints

The goal of this one-year randomized controlled trial is to evaluate SMBG testing for participants with NIT DM within a real world setting using patient-centered outcomes and incorporating new glucose meter technologies.

**Objective 1:** Assess SMBG effectiveness on two primary, patient-centered outcomes, glycemic control (A1C) and health related quality of life (HRQOL), over one year in 450 participants with NIT DM between the following three groups: 1) no SMBG testing, 2) once-daily SMBG testing with standard patient feedback consisting of glucose values immediately reported to the patient through the glucometer, and 3) once-daily SMBG testing with enhanced patient feedback consisting of glucose values immediately reported to the patient PLUS automated tailored messaging also delivered via the glucometer.

Sub-objective 1a. Assess differences in SMBG effectiveness across the following subgroups: 1) prior experience using SMBG; 2) duration of DM; 3) baseline glycemic control; 4) baseline anti-hyperglycemic treatment; 5) age; 6) race/ethnicity; 7) health literacy; and 8) number of baseline comorbidities.

**Objective 2:** Evaluate the impact of SMBG on secondary patient-centered, outcomes including: a) DM-related QOL, b) DM self-care, c) DM treatment satisfaction, d) DM self-efficacy, e) patient-provider communication, f) hypoglycemia frequency, g) health care utilization.

**Objective 3:** Conduct qualitative assessments of the patient participant and provider experience for all three intervention groups. This objective will support efficient translation of study findings to real world clinic settings by exploring such issues as patient/provider communications, the use of the glucose meter and accompanying reports, the utility of the treatment algorithm given to providers, and practice burden.

2.3 Primary endpoints

The two primary outcomes of the study are change in A1c and change in HRQOL. The A1c was chosen due to its use in prior studies and its standing as a measure on which: 1) providers evaluate patients; 2) payers evaluate providers; and 3) patients evaluate themselves and their providers. Though HRQOL is also critically important to patients, few studies have rigorously examined the impact of SMBG on HRQOL. Based on these facts and the recommendations of our stakeholder groups, HRQOL is a co-primary outcome for this pragmatic trial.

**A1c.** A1c will be measured at baseline and 52 weeks. A1c has long been accepted as the best indicator of recent (past 2-3 months) glucose control. It is the standard laboratory value upon which glycemic control is judged and treatment alterations are based.

Baseline and 52-week A1c scores will be collected by the study research coordinator. Because the 52-week time point may not align
with a scheduled primary care visit, we have defined this time point as 52 ± 6 weeks from the baseline visit. All other A1c values measured and recorded in the EHR during the study period will be captured passively and recorded in the dataset.

General Quality of Life. An important outcome for all patients with DM is their perception of how diabetes affects their physical, psychological and social functioning. We will utilize the Short Form 36 (SF-36) to assess overall quality of life (QOL). It has been widely used and validated in medical studies generally and diabetes studies in particular.65-68 The SF-36 encompasses physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. Subscale scores range from 0 to 100, with high scores representing better HRQOL. We will use the physical component score (PCS) and the mental component score (MCS), with scores standardized to a normal distribution (mean = 50 and standard deviation[SD] = 10).69

2.4 Secondary endpoints

The following secondary endpoints will be collected from patient participants at baseline and 52-weeks.

Problem Areas in Diabetes (PAID). Developed at the Joslin Diabetes Center, this scale is the most widely utilized tool to assess psychological and social stress associated with diabetes. This self-report measure contains 20-items with scores ranging from 0 (no distress) to 100 (high distress). It has been shown to have high internal reliability (Cronbach's alpha = 0.90), sensitivity to change (r=0.83), and clinical utility.55-57

Diabetes Symptom Checklist (DSC). The DSC is a 34-item self-report measure of diabetes-related symptom frequency and perceived severity during the prior month covering six symptom categories: hyperglycemic, hypoglycemic, cardiac, neuropathic, psychological, and vision-related.59 Patients respond on a 5-point scale (1=symptom has not occurred or was not troublesome, to 5=symptom was extremely troublesome). The DSC is valid, reliable, and responsive to change. Higher scores are associated with poorer glycemic control and depression.61, 62

Diabetes Self-Care. To assess compliance with diabetes self-care, we will use the Summary of Diabetes Self Care Activities (SDCA) survey. This is a widely used, multidimensional measure of diabetes self-management activities with high internal and test-retest reliability. The SDCA assesses diet, exercise, blood glucose testing, foot-care, and smoking status. Supplementary questions are available, and we will include a question on medication adherence. Treatment satisfaction is an inherently patient centered outcome. We will utilize the Diabetes Treatment Satisfaction Questionnaire (DTSQs) standard version to assess this variable at baseline. This 8-item survey has been widely used to assess patient satisfaction with their current treatment.64

Diabetes-Specific Self-Efficacy. Diabetes-specific self-efficacy focuses on beliefs about one’s ability to adhere to diet, exercise, SMBG, and medication regimens and is only moderately related to general self-efficacy.65 Higher diabetes-related self-efficacy is related to enhanced adherence to self-care activities.66, 69 Study participants will complete the 8-item Diabetes Empowerment Scale Short Form (DES-SF). The DES-SF is highly reliable (Cronbach α = 0.85) and is responsive to change over time.70

Patient-Provider Communication. A patient’s perceived connection with their health care provider significantly influences their sense of satisfaction and degree of concern about their health.71 Good patient–provider communication also predicts better diabetes self-care, improved adherence to treatment, and less diabetes-related morbidity.72, 74 In general, patients prefer interactions that involve shared decision making. By providing shared and timely SMBG values, the new technology implemented in this study has the potential to strengthen the patient-provider relationship. We will use the Communication Assessment Tool (CAT) to measure patient-provider communication. The CAT is a 15-item survey that asks patients to rate different dimensions of the communication and interpersonal skills of their health care provider using a 5-point scale (1=poor, 2=fair, 3=good, 4=very good, 5=excellent)75. Overall scale reliability is high (Cronbach’s alpha = 0.96).

Hypoglycemia Frequency. Downloaded SMBG values will be graded according to severity as Grade 1 (SMBG <70 mg/dl with or without mild or moderate symptoms), Grade 2 (SMBG<50 mg/dl with or without mild or moderate symptoms), Grade 3 (independent of SMBG, altered consciousness or inability to engage in self-care behaviors, which reverses promptly after administration of oral carbohydrate, presumed to be related to hypoglycemia but not requiring medical assistance), Grade 4 (similar to Grade 3, but reverses promptly after treatment (glucagon injection, intravenous glucose, emergency medical services provided at health care facility or in the field)), and Grade 5 (death or irreversible coma with circumstances suspicious for hypoglycemia). For study purposes, a hypoglycemic episode will be defined as Grade 3, 4, or 5 using self-report with additional queries as to whether the hypoglycemia might have been reversed without assistance. Events will be adjudicated by Drs. Buse, Donahue and Young without knowledge of treatment assignment. Narrative reports will be submitted to the IRB as serious adverse events potentially related to study procedures.

Health Care Utilization. Utilization outcomes will include inpatient, outpatient and emergency department utilization during the 52-week study period. UNC visits will be collected through the EHR while non UNC visits will be captured at the 52 week study visit via patient interview with the study coordinator.

Qualitative Assessment (Objective 3)

To gain a deeper understanding of patients’ and health care providers’ experiences with each of the SMBG testing approaches, including facilitators and barriers to dissemination, we will perform qualitative focus groups at the UNCPN practices.

Qualitative Assessment of Patient Outcomes. Five focus groups (one from each participating UNCPN practice) will be conducted by researchers skilled in qualitative data collection. Groups will include 10 patients who have completed the study. They will occur at the practices once at least 80% of that practice’s enrolled study participants have completed their 52-week study visit. All participants will review and sign an additional IRB-approved informed consent document specific to the focus groups. Key topics will include: impressions of and experience with SMBG prior to and during the trial, including using a wireless glucometer and messaging system,
and impressions of using the downloaded SMBG reports at clinic visits and how interactions with providers did/did not change per the intervention arm to which they were randomized.

Qualitative Assessment of Health Care Provider Outcomes. Five focus groups (one per practice) with 5-10 physicians and nursing staff will be conducted by researchers skilled in qualitative data collection. Focus groups will be conducted once at least 80% of the practice’s enrolled study participants will have completed their 52-week follow-up visit. Key topics will include: impressions regarding the usefulness of SMBG summary reports and accompanying treatment algorithm; experience with recommending SMBG for patients with NIT DM prior to and during the trial (and for both enrolled and non-enrolled patients); and perceived benefits/problems arising from being a practice site for this study. All participants will review and sign IRB-approved informed consent documents prior to participation. We will also collect age, gender, race/ethnicity, full-time/part-time employment status, years in practice, and area of board certification for all participants.

2.3 Potential moderating variables

Based on their possible relationship to glycemic control and/or HRQOL, we will measure the following eight variables to be tested as possible modifiers of our primary outcomes. These include:

Prior experience using SMBG. Baseline use of blood glucose monitoring, including its frequency and the number of years of testing will be queried.

Duration of T2DM. Prior studies suggest that SMBG in NIT DM may be most beneficial for newly diagnosed patients and less beneficial for people with a longer duration of disease 8.

Baseline A1c. Some researchers have suggested that SMBG testing is most valuable for patients with higher baseline A1c results 50.

Anti-hyperglycemic treatment. Patients treated with insulin secretagogues (sulfonylureas and glinides) are at higher risk for hypoglycemia and may therefore be more likely to benefit from SMBG.

Age. A large meta-analytic study observed differences in the change in A1c level by age, with less change for older and younger patients 12. Age may also relate to comfort in using new technologies.

Race/ethnicity. A1c values are known to differ across racial and ethnic groups 51.

Health literacy. Low health literacy is associated with poorer diabetes knowledge 52, which could affect one’s ability to benefit from SMBG testing. Following consultation with the Health Literacy Core within the UNC Center for Diabetes Translational Research, we will use the Newest Vital Sign (NVS) screening tool to assess literacy and numeracy. This instrument has good internal consistency and reliability (Cronbach’s α > 0.76) 53.

Number of comorbidities. Having additional illnesses might affect self-care behaviors. We will use a standard comorbidities list to obtain a count of comorbidities at baseline.

5. Study Design

Within the context of a controlled and randomized but pragmatic trial, we seek to answer the following question: does SMBG testing make sense for NIT DM patients in terms of either A1c values or QOL. We will also examine whether or not patients with different baseline characteristics might see different outcomes from SMBG testing. To achieve our goal of testing SMBG options in a “real world” setting, the study has been designed to minimize as much as possible any interruptions in or alterations to standard daily patient care.

We will recruit 450 patients from five practices within the University of North Carolina Physicians Network (UNCPN). Patients will be randomized (see attachments) to one of the three study arms:

- Group 1) no SMBG testing;
- Group 2) once daily SMBG testing with standard patient feedback; and
- Group 3) once daily SMBG testing with enhanced patient feedback.

Patients will be followed for one year. The first two study groups represent SMBG testing approaches commonly utilized in clinical practice, while the third incorporates cutting edge glucose monitoring tools now on the market. For all three groups, patients will receive information about maintaining normoglycemia. During routine clinic visits, their health care providers will be guided to modify therapies based on ADA guidelines, which focus on A1c values and SMBG values if available. Patients in groups 2 and 3 will also receive training in obtaining and interpreting SMBG values. These values will also be systematically evaluated at routine clinic visits. Finally, patients in Group 3 will receive, through their glucose meters, wireless personalized immediate automated feedback about their testing values (see Figure 1).

Figure 1
6. Subject Identification and Withdrawal

A multi-pronged approach will be utilized to identify study participants. First, patients who have NIT DM will be identified using the Carolina Data Warehouse (CDW) or by chart review in the participating practice. Patients will receive an invitation letter by mail, signed by their health care provider describing the study. Any patient not interested in participating will be able to opt out of further contact by returning a post card or calling a toll-free number. If no opt out call is made within one week of sending the letter, telephone contact will be attempted on up to three different occasions at three different times of day. The project Research Assistant will call each potentially eligible subject to confirm eligibility criteria. Second, we will place recruitment flyers within the participating practices that will be visible in waiting areas and exam rooms. Clinic staff will be encouraged to discuss the study with potentially eligible patients during routine clinic activities (i.e. while collecting vital signs and during check-in or check-out). The UNC field coordinators will communicate regularly with practice staff regularly regarding potentially eligible subjects.

4.1 Inclusion criteria

Eligible patients will meet the following criteria:

5. T2DM diagnosed after age 30 (to reduce the likelihood of misclassification of T1DM) without clinical characteristics suggestive of type 1 diabetes (lack of obesity, unexplained weight loss)

6. An established patient at the participating UNCPN practice who identifies a UNCPN health care provider within that practice as their primary provider of diabetes care.

7. A1c ≥6.5% but ≤9.5% within the 6 months preceding the screening call/visit, as obtained from the electronic medical record. This range was chosen because patients with A1c above 9.5% should arguably be treated with insulin and check SMBG more frequently than once per day while patients with A1c below 6.5% are unlikely to get additional benefit from SMBG testing on one of the two primary outcomes (A1c) given their already excellent glycemic control.

8. Willing to comply with the results of random assignment into a study group.

4.2 Exclusion criteria

2. Currently sees or plans to see an endocrinologist or other diabetes specialist in the next year.

7. Use of insulin.

8. Is or plans to become pregnant in the next 12 months.

9. Plans to relocate in the next 12 months.

10. Has other conditions (e.g. renal or cardiovascular disease), factors (e.g. frailty) or comorbidities (e.g. cancer) that might put the patient at risk when following study protocols.

11. No history of significant issues with known or suspected hypoglycemia or any history of “severe” hypoglycemia (requiring assistance from a third party).

4.3 Subject recruitment and screening

All potentially eligible patients will be screened for eligibility by phone call. The call will take about 15 minutes, during which a member of the study team will describe the study, answer questions, and conduct a short set of simple screening to determine. Eligible
patients who remain interested in participation will complete an assessment visit with a research coordinator. To decrease patient burden and further engage participating practices, assessment visits will occur at the patient’s primary care office. Assessments will be separate from their appointment with their primary care provider, and may or may not occur on the same day as a regularly scheduled clinic visit, though for patient convenience we will make every effort to coordinate the assessments with a regular clinic visits. During these assessments, the research coordinator will review the study details in greater depth, verify all inclusion and exclusion criteria, and obtain written informed consent.

4.4 Withdrawal of subjects

Once randomized, patients will not be discontinued from the study for any reason except patient request or withdrawal of consent.

5. Study Device: Telcare Glucometer

The Telcare glucometer is an FDA approved, cellurally-enabled device. The patient participants in the two testing arms will receive a Telcare glucometer to use during the 52-week study period. At the end of their participation, the participant will be allowed to keep the glucometer. The field coordinator enrolling the participant will register the meter with Telcare at www.telcare.com.

12. Study Procedures

6.4 Method for assigning subjects to treatment groups

After providing informed consent, baseline A1c, and completing the baseline study interview, participants will be randomized to one of the three treatment arms using sequentially numbered, opaque, sealed envelopes. The allocation sequence will be generated by an independent statistician who is not otherwise involved in the study using computer-generated randomly permuted blocks of random sizes. The randomization will be stratified by study practice. The research coordinator will then review the treatment assignment with the patient, using a standardized script, provide the initial training and supplies necessary for participation in that study and answer any remaining questions.

6.5 Baseline

Once written informed consent has been received, patient participants will:

- complete an interview that includes demographic, health history, health history, and quality of life questions.
- have blood drawn for a hemoglobin A1c test. The blood sample will be sent to Quest Laboratory and be assessed using immunoturbidimetry consistent with CLIA-based protocol.

Upon completion of the interview and blood draw for hemoglobin A1c test, the field coordinator will randomize the patient to a treatment arm.

6.6 52-week follow-up

At the 52-week follow-up, patient participants will be asked to complete an interview that includes health history, health history, and quality of life questions. The patient’s blood will be drawn for a hemoglobin A1c test. The blood sample will be sent to Quest Labs and will be processed in accordance with the procedures described under 6.2, Baseline.

7. Statistical Plan

7.1 Sample size determination

We desire high power for our primary between-arm comparison as well as reasonable power to detect an important effect modifier, should one exist. We will use an ANCOVA, controlling for baseline A1c and other baseline variables specified above, to compare mean change-from-baseline to 52-week A1c across the three intervention groups at the 0.05 significance level. In a recent Cochrane Review, the estimated mean 12-month differences between SMBG and control groups were -0.13% and -0.52%, respectively, for patients diagnosed more than and less than one year prior to the study. Assuming approximately equal enrollment of newly diagnosed and long term patients, this implies a mean difference of -0.325%. Based on results from one of the larger and better quality trials conducted to date, we assume the standard deviation for ΔA1c would be 0.8% \(^{20}\). We assume no more than 10% loss to follow-up. Given these assumptions, randomizing 150 patients per group would provide at least 90% power for the primary comparison for ΔA1c. This same sample size would provide at least 80% power for the primary comparison if the true standard deviation were as high as 1.0%. Under these same assumptions, this sample size would provide at least 70% power to detect an average interaction effect across the two SMBG groups compared to the no-SMBG group if the group means were similar to those for disease duration described above.

For comparing mean change in HRQOL between groups, we will use the physical and mental component scores of the SF-36, both of which range from 0 to 100. Because we are interested in two different aspects of QOL, we will apply a Bonferroni correction and assess each comparison at the 0.025 level. Based on observed results from the ZODIAC-17 SMBG study, we conservatively assume
that the standard deviation for the change scores for either component will be 10 points\textsuperscript{21}. Under these assumptions, randomizing 150 patients per group with no more than 10\% loss will provide at least 80\% power to detect an overall difference between groups if the mean difference between the highest and lowest groups is at least 4 points. Power calculations were conducted using Procs GLMPower and POWER in SAS, V 9.2 (SAS Institute, Cary, NC).

7.2 Statistical methods

OBJECTIVE 1: Quantitative Analysis of Patient Outcomes

A detailed analysis plan will be developed prior to initiating the study; the following is a brief summary of the proposed plan. All comparisons will be made on an intention-to-treat basis, with patients analyzed according to their randomized group and regardless of the amount of intervention received. As the primary comparison of ΔA1c at 52 weeks across the 3 treatment groups (Objective 1), we will conduct an analysis of covariance (ANCOVA), controlling for prior use of SMBG, duration of T2DM, baseline A1c (A1c <8\% vs A1c ≥8\%), whether baseline A1c was directly measured or calculated, baseline anti-hyperglycemic treatment (use of secretagogues vs no use), age, race/ethnicity, health literacy, and baseline comorbidities at the 0.05 level. If the overall null hypothesis of no difference between groups is rejected, we will compare each SMBG group to the no-SMBG group separately using the Dunnett-Tamhane Step-Up procedure for multiple comparisons to control the family-wise error rate at 0.05; we will also conduct a contrast test comparing the average of the two SMBG groups to the no-SMBG group\textsuperscript{76}. Similar ANCOVA models will compare change in SF-36 physical and mental component scores between groups, controlling for the same baseline variables as for A1c. Because we are examining two aspects of HRQOL (physical and mental), we will apply a Bonferroni correction and assess each comparison at the 0.025 level. We will not adjust for multiple comparisons due to the co-primary endpoints of glycemic control and QOL.

Missing 52-week outcome data will be ignored for the primary model. As a sensitivity analysis that accommodates missing data and mistimed measurements, we will repeat the above analyses using linear mixed models that incorporate all observed A1c values, including those collected passively during interim months. This model will include fixed effects for time-since-randomization and time-by-treatment group interactions, and will include random intercepts and slopes for each patient.

We will assess the presence of effect modification for the baseline variables corresponding to the pre-specified subgroups of interest by adding appropriate interaction terms to the ANCOVA model one at a time. Each interaction term will be tested separately at the 0.05 significance level. Only if the associated interaction term is significant, similar contrasts to those described above will be assessed within the relevant subgroups.

OBJECTIVE 2: Secondary outcomes

Similar ANCOVA methods will be used to compare groups on each of the secondary outcomes (Objective 2). These tests will each be conducted at the 0.05 significance level with no adjustments for multiple comparisons.

OBJECTIVE 3: Qualitative Assessment of Patient Outcomes

Five patient focus groups (one from each participating UNCPN practice) will be conducted by researchers skilled in qualitative data collection. Groups will include 8-10 patients who have completed the study. They will occur at the practices once at least 80\% of that practice’s enrolled study participants have completed their 52-week study visit. All participants will review and sign an additional IRB-approved informed consent document specific to the focus groups. Key topics will include: impressions of and experience with SMBG prior to and during the trial, including using a wireless glucometer and messaging system, and impressions of using the downloaded SMBG reports at clinic visits and how interactions with providers did/did not change per the intervention arm to which they were randomized. We will have previously collected all pertinent demographic information on patient focus group participants.

8. Data and Safety Monitoring Plan

Because there are currently no definitive clinical guidelines that describe how frequently a person with NIT DM should be monitoring their SMBG values, the randomized treatment provided in in this proposed study represents variations in usual care. As an FDA approved glucose monitoring system will be utilized in conjunction with standard diabetes management by local providers, this study poses no greater than minimal risk, and therefore a data safety and monitoring board is not required. However, a data and safety monitoring plan is in place.

This study has been approved by the UNC Institutional Review Board. The project leadership team will meet weekly throughout study to review study milestone progress and adverse event reports.

Reporting Mechanisms: Any reported adverse events will be categorized as related or not related to the study intervention by the investigators. These events will be reported in real time to the principal investigators for confirmation and review of grading.

Regardless of causality, all unanticipated Serious Adverse Events or grade 3 or 4, will be reported to the IRB for review. Any adverse events that occur will be discussed at team meetings with the project leadership team to make a decision regarding overall safety of the study, whether subject participation should be stopped, and plans for communicating safety concerns to the local providers.

Frequency of Monitoring Regarding Time or Number of Subjects:
Safety data will be reviewed by the project leadership team on an ongoing basis and will be summarized in quarterly reports by the Project Manager. In addition, the project leadership team will review subject accrual, adherence to study protocol and dropouts, and monitor data monthly.

Specific Data to be Monitored:
Adverse events and unexpected adverse events for all subjects, subject accrual, dropouts, and adherence to the study protocol will be monitored.

Procedures for analysis and interpretation of the data:
Our study statistician will be blinded to subject randomization when analyzing the safety data.

Actions at Defined Events or End Points:
If 2 or more subjects experience Serious Adverse Events or Grade 3/4 adverse events related to the study intervention, enrollment will be held while the protocol undergoes review by the project leadership team and a decision can be made regarding the overall safety of the study. Clinicians will be counseled that severe hypoglycemia (requiring assistance), which occurs without a cause that can be mitigated, would be an indication for increased monitoring and modification of the treatment plan. Similar two episodes of severe hypoglycemia independent of cause would be an indication for increased monitoring and modification of the treatment plan.

Procedures for Communication from the Data Monitor to the IRB and Other Sites:
All adverse events, whether serious or non-serious, will be reported from the time a signed and dated informed consent form is obtained until completion of the last study-related procedure. Any unanticipated or serious adverse events will be reported to the IRB within 7 days after occurrence by the site. Reports detailing unanticipated and serious adverse events will be reviewed weekly by the Clinical Site Coordination Team chaired by Dr. Donahue and appropriate reports sent to the IRB. All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject’s participation in the study, must be followed until: 1) the event resolves; 2) the event stabilizes; 3) the event returns to baseline, if a baseline value is available; 4) the event can be attributed to agents other than SMBG or to factors unrelated to study conduct; or 5) when it becomes unlikely that any additional information can be obtained.

Unanticipated Problems that are serious adverse events will be reported to the IRB within one (1) week of the investigator becoming aware of the event. Any other Unanticipated Problem will be reported to the IRB within two (2) weeks of the investigator becoming aware of the problem. Patients can contact the PIs and/or study coordinator should safety issues related to the study develop.

### 9. Data Handling and Record Keeping

#### 9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

Data collectors will be trained in the importance of protecting the confidentiality. Primary data, which contains identifiers, will be audio recordings and will be kept in locked storage cabinets and separate from consent forms. All audiotapes will be erased or destroyed at the end of the study. Data for analysis and reporting purposes will be stripped of all unique identifiers. Reports will not provide practice-specific or individual-specific identifiers.

#### 9.2 Source Documents

**Human research material and data collection:** Several types of data will be collected during the course of this study. Research staff who collect data in person or by chart review will know the identity of the patient for whom the data is being collected; however, the patient’s name or medical record number will not be used on the data recording forms. Each category of data is outlined below.

**Patient-Reported Demographic and Clinical Data:** These data will include questionnaire assessments, patient reported outcomes, and diabetes disease related information.

**Electronic Health Record (EHR) Data:** EHR data will be obtained passively or by chart review by study staff from the electronic medical record for the following measures: capillary blood glucose values, capillary blood sample for HgA1c determination, new prescriptions for blood glucose testing strips, pharmacologic regimen changes, anti-hyperglycemic medication, and patient utilization of health care resources (clinic visits, ER visits, and hospitalizations).
Patient and Health Care Provider/Staff Impressions: For the qualitative assessments, research data sources include focus group interviews and paper surveys.

10. Dissemination Plan

The overall goal of involving various stakeholder groups (See Section 11) is to have key people with a variety of perspectives involved in planning, oversight, analysis and dissemination of this project. Groups interested in this research are varied and include patients, caregivers, providers, advocacy groups, glucometer manufacturers, educators and policy makers.

Dissemination channels: At the state level, the NC Diabetes Advisory Council has several vehicles for dissemination, including newsletters, a website (http://www.ncdiabetes.org/), twitter, and grass roots advocacy/lobbying groups. At the local level, the UNC Physicians network has biannual staff meetings and newsletters. UNC family medicine has newsletters and a radio show, blog and app on health that reaches 30,000 listeners and viewers weekly (http://yourhealthradio.org). At the national level, the American Diabetes Association and National Diabetes Education Program provide a vehicle for dissemination through conferences, web-sites, newsletters, guidelines and a communications staff that engages, providers (physicians [primary care and multiple sub-specialties], nurses, dietitians, health educators, community health workers), industry, and state Diabetes Prevention and Control Programs.

Importance of literacy in dissemination: Our team includes the health literacy core, in the UNC Center for Diabetes Translation and Research. This core will work with us to ensure our messages, interviews, questionnaires and dissemination materials are appropriate to our audience.

11. Stakeholders

We have a diverse group of stakeholders and as noted above include industry representatives, patients, diabetes educators, providers, and advocacy groups.
Our stakeholders will meet 8 times in Years 1 and 3 of the project and 4 times in Year 2.

John Buse, MD, PhD, Stakeholder Engagement Leader
(National Diabetes Education Program Chair and Co-Investigator)

Key Stakeholder Groups
- NC Diabetes Advisory Council
- UNC Family Medicine Patient Advisory Board
- UNC Diabetes Care Center Patient Registry
- UNC Physicians Network
- Greensboro Community Advisory Board
- American Diabetes Association
- National Diabetes Education Program
- Glucometer Manufacturers
12. References


64. Schmidt WE, Christiansen JS, Hammer M, Zychma MJ, Buse JB. Patient-reported outcomes are superior in patients with type 2 diabetes treated with liraglutide as compared with exenatide, when added to metformin, sulphonylurea or both: Results from a randomized, open-label study. Diabetic Med. 2011;28(6):715-23.


THE MONITOR TRIAL

Effect of Glucose Monitoring on Patient and Provider Outcomes in Non-Insulin Treated Diabetes

FINAL STATISTICAL ANALYSIS PLAN

Principal Investigators:
Katrina Donahue, MD, MPH
Laura Young, MD, PhD

Investigators:
John Buse, MD, PhD
Mark Weaver, PhD
Maihan Vu, PhD

Project Manager:
C. Madeline Mitchell, MURP

Version date: 05/03/2016
TABLE OF CONTENTS

1. STUDY OBJECTIVES ................................................................. 21
2. STUDY DESIGN ................................................................. 21
3. ANALYSIS POPULATIONS .............................................. 21
4. UNBLINDING PLAN ............................................................. 21
5. MISSING DATA ................................................................. 22
6. ANALYSIS OF SUBJECT FOLLOW-UP .................................. 22
7. ANALYSIS OF BASELINE DATA ........................................ 22
8. DESCRIPTIVE SUMMARY OF POST-RANDOMIZATION DATA .................. 22
9. ANALYSIS OF PRIMARY OUTCOMES (OBJECTIVE 1) ................. 22
10. ANALYSIS OF SECONDARY OUTCOMES (OBJECTIVE 2) .......... 23
11. REFERENCES ................................................................. 24
This statistical analysis plan is an expanded version of the summary analysis plan included in the study protocol and supersedes the summary plan included in the study protocol. Any significant changes made to this analysis plan after study initiation will be documented herein.

**Study Objectives**

This randomized trial will assess the impact of three different self-monitoring of blood glucose (SMBG) testing approaches on patient-centered outcomes in patients with non-insulin treated type 2 diabetes (DM).

The objectives of this trial are as follows:

**Objective 1:** Assess SMBG effectiveness, with or without tailored messaging, on two primary, patient-centered outcomes, glycemic control (A1c) and health related quality of life (HRQOL), relative to the no testing arm over one year.

Sub-objective 1a. Assess potential differences in SMBG effectiveness across the following subgroups: 1) prior experience using SMBG; 2) duration of DM; 3) baseline glycemic control; 4) baseline anti-hyperglycemic treatment; 5) age; 6) race/ethnicity; 7) health literacy; and 8) number of baseline comorbidities.

**Objective 2:** Evaluate the impact of SMBG on secondary patient-centered outcomes including: a) DM-related QOL, b) DM self-care, c) DM treatment satisfaction, d) DM self-efficacy, e) patient-provider communication, f) hypoglycemia frequency, g) health care utilization.

**Objective 3:** Conduct qualitative assessments of the patient participant and provider experience for all three intervention groups.

This document describes the analyses planned for Objectives 1 and 2, and other supporting quantitative analyses. The qualitative approach to be applied for Objective 3 will be described elsewhere.

**Study Design**

This study is a multi-site, open-label, randomized controlled trial of 450 non-insulin treated diabetic patients followed over one year. Patients will be recruited from five practices within the University of North Carolina Physicians Network (UNCPN). Patients will be randomized to one of the three arms:

- Group 1) no SMBG testing;
- Group 2) once daily SMBG testing with standard patient feedback; and
- Group 3) once daily SMBG testing with enhanced patient feedback.

Patients will have two study contacts: enrollment at baseline and a 52-week follow-up visit. Additionally, daily SMBG values will be downloaded for patients assigned to Groups 2 and 3.

**Analysis Populations**

Two analysis populations will be defined for this study:

- **Intent-to-Treat (ITT) Population:** This population will include all subjects who were randomized (i.e., for whom a randomization envelope was opened), analyzed according to the group to which they were randomized. Nobody will be excluded.

- **Per Protocol Population:** This population will be a subset of the ITT population and will exclude all subjects who initiate insulin treatment or who become pregnant any time between randomization and their 52-week visit (defined as 52 weeks ± 6 weeks from their baseline visit). Additionally, this population will exclude subjects who do not adequately adhere to their assigned treatment arm, for whatever reason. For Group 1, this will exclude subjects who initiate SMBG testing at any point during the study. For Groups 2 and 3, this will exclude subjects who fail to perform SMBG testing on at least 80% of days between randomization and their 52-week visit or 365 days following randomization, whichever is earlier.
Unblinding Plan

As an open-label study, subjects, providers, and many study staff will know to which group individual subjects have been randomized. However, efforts will be made to keep the study statistician (Mark Weaver) blinded to randomization group during the course of the trial. Any key decisions regarding study outcomes, the appropriateness of test statistics or model assumptions, changes to this analysis plan, or any other statistical issues will be made in a masked review of the data (i.e., masked to the true randomization groups). Study randomization has been performed by a statistician not otherwise involved with the study and the generated allocation sequence is stored electronically in a password protected file. Datasets provided to the statistician by the Sheps data management team prior to unblinding will not include randomized treatment assignment. Primary analyses using the ITT population will be initially programmed using dummy (computer generated) treatment assignments. Unmasking with respect to the true randomization groups will only be done for the final interpretation of the results. Membership in the Per Protocol Population cannot be adjudicated without knowing actual group assignment.

Missing Data

Missing 52-week (±6 weeks, or 323 days to 407 days post-randomization) outcome data will be ignored for the primary analyses. As a sensitivity analysis that accommodates missing data and mistimed measurements, we will repeat the analysis of A1c using linear mixed models that incorporate all observed A1c values, including those collected passively at interim clinical visits. As a further sensitivity analysis, we will repeat the A1c analysis using last observation carried forward (LOCF) to impute the 52-week value for any subjects who: do not provide a 52-week value, initiate insulin, or become pregnant. Data missing by design (i.e., due to a skip pattern in the data collection form) will be filled in logically where appropriate.

Analysis of Subject Follow-Up

We will present an account of the final disposition (completed, withdrew, lost, or died) of each subject in the ITT Population, including any admission violations and group assignment. The number and proportion of subjects in the ITT population who provided information for the analyses of the study objectives will be summarized by randomization group, both pooled across sites and separately by site. We will provide a CONSORT diagram showing the flow of subjects through the trial, indicating withdrawals by treatment arm with reasons, when provided.

Analysis of Baseline Data

We will summarize baseline data (i.e., pre-randomization data) for the ITT Population, by site and overall. Measures of central tendency and dispersion for continuous and certain discrete variables will include means, standard deviations, medians, minima, and maxima. Categorical data will be summarized with frequencies and percentages. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables. No inferential statistics (i.e., p-values and/or confidence intervals) for comparing data between groups will be presented. Additionally, for a manuscript using only baseline data, we may do some exploratory modelling of baseline data.

Descriptive Summary of Post-Randomization Data

Descriptive statistics will be provided for all post-randomization study variables, by randomized group, including, for Groups 2 and 3, frequency of SMBG testing (weekly average) and descriptive statistics (mean, SD and range of SMBG values) by time of day and patient-noted circumstance via the wireless glucometer. Informative graphs will be used for descriptive purposes where appropriate.

Analysis of Primary Outcomes (Objective 1)

A1c

The primary analysis of change in A1c (ΔA1c) will use the ITT Population, and will be repeated secondarily using the Per Protocol Population. As the primary comparison of ΔA1c at 52 weeks (±6 weeks, or 323 days to 407 days post-randomization) across the 3 treatment groups, we will conduct an analysis of covariance (ANCOVA), controlling for site, baseline A1c, whether baseline A1c was directly measured or calculated¹, prior use of SMBG, duration of T2DM,

¹ Updated 01/26/2015: For the first 40 subjects enrolled, A1c was not directly measured at baseline; instead, for these subjects, baseline A1c was calculated based on glycosylated hemoglobin using a published formula. Controlling for how A1c was measured at baseline will account for any potential differences in these measurement methods.
baseline anti-hyperglycemic treatment (use of secretagogues vs no use), age, race/ethnicity, health literacy, and number
of baseline comorbidities at the 0.05 significance level. If the overall null hypothesis of no difference between the three
groups is rejected, we will compare each SMBG group (Groups 2 and 3) to the no testing group (Group 1) separately
using the Dunnett-Tamhane Step-Up procedure for multiple comparisons to control the family-wise error rate at 0.05
(Dunnett and Tamhane, 1992). This multiple testing procedure is as follows:

- Compute the two pairwise comparison p-values for each SMBG group compared to the no testing group using
  appropriately specified contrasts in the ANCOVA model;
- Compare the largest of the pairwise comparison p-values to 0.05; if the p-value is less than 0.05, reject both
  null hypotheses and conclude both SMBG groups are more effective than no testing;
- If the largest p-value > 0.05, then compare the smaller of the two p-values to 0.0262 and, if smaller, reject only
  this null hypothesis and conclude that corresponding SMBG group is more effective than no testing.

We will also conduct a contrast test comparing the average of the two SMBG groups to the no-SMBG group at the 0.05
level.

As described in Section 5, we will conduct two sensitivity analyses to investigate sensitivity of our conclusions to
certain data handling conventions. First, we will repeat the ANCOVA model using a linear mixed model that
incorporates all observed A1c values, including those collected passively at interim clinical visits. This model will
include fixed effects for time-since-randomization and time-by-treatment group interactions, and will include random
intercepts and slopes for each patient. Second, we will repeat the primary ANCOVA using LOCF to impute 52-week
A1c values for all subjects who either dropped out, initiated insulin, or became pregnant following randomization.

HRQOL

The primary analyses of change in HRQOL will use the ITT Population, and will be repeated secondarily using the Per
Protocol Population. The physical and mental subscales of the SF-36 will be scored by the Sheps data management
team using software provided by the scale developer, and the scores will be included in the dataset supplied to the
statistician. Similar ANCOVA models to those described above will compare change in SF-36 physical and mental
component scores between groups, controlling for the same baseline variables as for A1c in addition to the baseline
values of the respective subscales. Because we are examining two aspects of HRQOL (physical and mental), we will
apply a Bonferroni correction and assess each comparison at the 0.025 level. However, we will not adjust for multiple
comparisons due to the co-primary endpoints of glycemic control and QOL.

Sub-Objective 1a: Potential Effect Modifiers

We will assess the presence of effect modification for the baseline variables corresponding to the pre-specified
subgroups of interest by adding appropriate interaction terms to the respective ANCOVA models (for each of A1c and
the physical and mental components of HRQOL) one at a time. Each interaction term will be tested separately at the
0.05 significance level. Only if the associated interaction term is significant, similar contrasts to those described above
will be assessed within the relevant subgroups. The subgroups to be examined in this way are:

- prior experience using SMBG (any versus none);
- duration of DM (≤ 1 year prior to study versus > 1 year prior);
- baseline glycemic control (baseline A1c <8% vs A1c>8%);
- baseline anti-hyperglycemic treatment (use of secretagogues vs no use);
- age (< 65 vs. ≥ 65);
- race/ethnicity (non-Hispanic Caucasian, non-Hispanic African Americans, other);
- health literacy (<4 vs. ≥4);
- number of baseline comorbidities (low versus high, separated by the observed median score).

Analysis of Secondary Outcomes (Objective 2)

The ITT Population will be used in the primary analysis of all secondary outcomes. Similar ANCOVA methods to
those described above for A1c will be used to compare groups on each of the secondary outcomes; for any scale
measured at baseline, the corresponding ANCOVA will control for baseline value in addition to the variables noted
above. These tests will each be conducted at the 0.05 significance level with no adjustments for multiple comparisons.

The secondary outcomes will be derived as follows:

DM-Related QOL

The Problem Areas in Diabetes (PAID) scale will be scored by summing the 20 items and multiplying by 1.25 for a
resulting score between 0 and 100. Items with missing responses will be imputed using the mean of non-missing items
if at least 75% of items are not missing.
The items on the Diabetes Symptoms Checklist (DSC) will be summed, both separately for each symptom category (hyperglycemic [items l, p, w, and ff], hypoglycemic [items h, s, and aa], psychological cognitive [items f, g, ee, and gg], psychological-fatigue [items a, d, q, and t], cardiovascular [items e, m, x, and dd], neurological pain [items b, o, u, y], neurological-sensory [items c, i, k, z, cc, and hh], and ophthalmologic [items j, n, r, v, and bb]) and overall. Symptoms that are indicated to have not occurred will be scored a 0, as implied in the original paper. For each symptom category, items with missing responses will be imputed using the mean of non-missing items if at least 75% of items are not missing.

DM Self-Care
The average of the items on the Summary of Diabetes Self Care Activities (SDCA) scales will be computed, both separately for each set of activities (diet, exercise, blood sugar testing, and foot care) as well as overall. 3

DM Treatment Satisfaction
The sum of the items on the Diabetes Treatment Satisfaction Questionnaire (DTSQ) will be computed. Items with missing responses will be imputed using the mean of non-missing items if at least 75% of items are not missing.

DM Self-Efficacy
The average of the items on the Diabetes Empowerment Scale Short Form (DES-SF) will be computed. Items with missing responses will be imputed using the mean of non-missing items if at least 75% of items are not missing.

Patient-Provider Communication
The average of the items on the Communication Assessment Tool (CAT) will be computed. Items with missing responses will be imputed using the mean of non-missing items if at least 75% of items are not missing.

Hypoglycemia Frequency
For the ITT population, we will descriptively compare the self-reported frequency (captured at 52 weeks) of severe hypoglycemia across all three arms. Additionally, for the SMBG groups only (Groups 2 and 3), downloaded SMBG values will be graded according to severity as Grade 1 (SMBG < 70 mg/dl) or Grade 2 (SMBG < 50 mg/dl). The frequency of these events relative to the number of tests will be descriptively compared between the two arms.

Health Care Utilization
Patient reported frequency of visits to primary care provider, urgent care clinic, Emergency room, overnight hospitalizations, and EMS calls during the study year will be descriptively compared across the 3 groups.

Additionally, we will summarize use of glycaemia medications at baseline and 52 weeks, both overall and by group, and will descriptively compare change in medication use from baseline to 52 weeks between groups, except for use of insulin. We will compare groups for initiating use of insulin by calculating differences between groups, along with 95% confidence intervals, in participants who initiate insulin during the study.

References

---

2 Revised 04/28/2016 after reviewing the original paper in preparation for the final analysis. Original SAP indicated that these would be scored “same as for symptoms that occurred but were ‘not at all’ troublesome.
3 Updated 5/3/2016. Deleted sentence about imputing missing responses with mean of non-missing items for this scale since that would not apply to the subscales.