# Effect of simplified insulin regimen on glycemic control and quality of life in an elderly population with type 2 diabetes

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1) **Protocol Title**

Effect of simplified insulin regimen on glycemic control and quality of life in an elderly population with type 2 diabetes

2) **IRB Review History***

Not applicable, the protocol has not been submitted for review by an external IRB.

3) **Objectives***

Primary objective of this study is to test the hypothesis that once daily basal insulin (BI) is non-inferior to multiple subcutaneous injections (MSI) of insulin for glycemic control (HbA1c) in elderly patients with T2DM. A secondary aim of this study is to test that BI is superior to MSI for lowering HbA1c and is associated with lower incidence of hypoglycemia.

4) **Background***

The prevalence of type 2 diabetes mellitus (T2DM) has been increasing over time, especially in the older age groups. According to the latest CDC data, 25.2% of the US population >65 years old has diabetes and it is expected to grow due to increase in life span as well as increase in incidence of T2DM [1, 2]. Many patients in this age group have other co-morbidities like heart disease, renal insufficiency, cognitive impairment, and lack of social support among others [3]. Elderly patients with T2DM are at an increased risk of hypoglycemia. Moreover, the benefits of tight glycemic control have not been established in this age group. Taking these factors into consideration, many professional organizations (American Diabetes Association, American Geriatrics Society) recommend relaxed glycemic goals (HbA1c ~8%) in the elderly population [4]. However, even for these relatively relaxed glycemic goals, insulin treatment is often necessary because due to associated comorbidities, many patients in this age group are poor candidates for non-insulin antidiabetic agents

[5]. Moreover, elderly patients with long standing T2DM may have decreased beta cell function and respond poorly to non-insulin antidiabetic agents [5].

Currently, basal-bolus insulin therapy that includes one injection of long acting insulin and three injections of meal-time short acting insulin is the most commonly used insulin regimen. However, many older patients find the basal-bolus insulin regimen hard to manage due to the need of multiple injections and frequent blood glucose testing, especially in the setting of impaired vision, poor physical function and cognitive impairment [7]. If unsupervised, there are more errors with this regimen that can lead to hypoglycemia and hospitalization. Moreover, basal-bolus insulin regimen is stressful and expensive for the elderly patients, as well as time consuming for their care-givers. Many experts have tried a simplified regimen of basal insulin alone in the elderly patients (unpublished). In our experience, this simplified regimen is associated with less errors, improved glycemic control and dramatic improvement in the quality of life for the patient as well as their care-givers, without compromising glycemic control. However, there are no systematic studies comparing simplified insulin regimen versus the basal-bolus insulin regimen. We propose a study comparing single injection of basal insulin versus the usual basal-bolus insulin regimen in elderly patients (age >65 years) with T2DM. We believe this study will help in improving clinical care of elderly patients with T2DM and save healthcare costs.

## 5) **Inclusion and Exclusion Criteria***

Inclusion Criteria

- Age >65 years
- Patient treated with an insulin regimen

Exclusion Criteria

- Unable to provide informed consent
- Enrollment in another research study
- History of hypoglycemia unawareness
- Pregnant women
- Prisoners

6) **Number of Subjects***

We plan to recruit a total of 44 subjects from the outpatient clinic of the University of Miami including Diabetes Research institute and the Lennar Foundation Medical Center. We also recruit patients from the clinics at the Jackson Health System.

7) **Study-Wide Recruitment Methods***

Subjects will be recruited from the outpatient clinics of the University of Miami and Jackson Health affiliated clinics. Treating providers must have provided permission to include their patients into the study. The treating physician will identify the potential subject by screening through the clinic records or during the clinic visit. The study will be first introduced to potentially eligible patients by their treating physicians. After the treating physician speaks to the patient and if the patient agrees to be part of the study, the treating physician will refer the patient to the study team via verbal contact, phone contact, secure email or HER message. A member of study team will then speak with the patient and explain the study. This will take place either during the patient's clinic visit or over the phone. If the patient remains interested, patient chart will be accessed to screen for inclusion / exclusion criteria. If the patient qualifies for the study, a copy of the informed consent will be given or mailed. The patients will be encouraged to discuss participation with their primary care providers. They will be asked to call back if they have any questions. The consent

form will be signed at the time of first study visit that would often coincide with the patient's clinic visit.

**Study Timelines**

Patients will be recruited over a period of one year, 09/01/2018 – 8/31/2022.
All patients will be followed for a period of 6 month. The estimated date to complete the primary analysis will be 06/2023.

8) **Study Endpoints***

Primary endpoint: Hemoglobin A1c (HbA1c) at 6 months after enrollment.

Secondary endpoint: 1. Average blood glucose levels (BG) during the study, 2. Incidence of hypoglycemia defined as any reported BG <70 mg/dl, 3. Incidence of severe hypoglycemia defined as any BG <54 mg/dl or patient requiring assistance to recover from hypoglycemia.

9) **Procedures Involved***

Subject Enrollment

Subjects will be recruited from the outpatient clinics of the University of Miami and Jackson Health ACC clinics. Treating providers will inform the patients about the study. If a patient shows interest in participation, the study staff will review patient's chart for inclusion / exclusion criteria and provide the patient with more information about the study. Those, eligible for study and willing to participate, will have to provide a written informed consent.

Study Plan

This will be a randomized controlled trial of elderly patients with T2DM currently inadequately controlled on an insulin regimen. After an informed consent, patients will be randomized in 1:1 ratio to either a control group (MSI) or a study group (BI). MSI group will receive four insulin injections per day that will include a long acting and a short acting insulin. BI group will receive only one injection of insulin glargine in the morning. The goal of treatment in both groups will be achieving an HbA1c <8% without any incidence of hypoglycemia. The study period after randomization will be 6 months.

Both groups will receive instructions about diet and exercise and all other treatments as per the current ADA standards. Patients will be advised to send their blood glucose data to the study team every 3-7 days. In addition, patients will be asked to complete the questionnaires for quality of life measures and patient satisfaction at baseline and after 6 months of treatment.

Insulin doses

The BI group will receive insulin glargine at a dose of 0.40 units/kg body weight once a day in the morning. If the total daily dose is more than 80 units, we will split the dose into two equal doses given morning and evening. The patient will be advised to monitor blood glucose (BG) four times daily: before meals and bedtime. The dose of insulin will be increased by 2 units every 3$^{rd}$ day to bring down the bedtime BG to <200 and fasting BG <130 mg/dL. Any BG <70 mg/dL or complaints of hypoglycemic symptoms at any time will lead to a decrease in insulin dose by 2 units or more.

The MSI group will receive insulin at a dose of 0.40 unit/kg body weight given 50% as insulin glargine at bedtime and 50% as rapid acting insulin divided into three doses before each major meal. The patient will be advised to monitor blood glucose (BG) four times daily: before meals and bedtime. The dose of insulin glargine will be adjusted every 3$^{rd}$ day to keep the fasting BG in 70-130 mg/dl range. The meal-time

rapid acting insulin doses will be adjusted to keep the pre-lunch and pre-dinner BGs <180 and bedtime BG <200 mg/dl.

10) **Data and Specimen Banking***

The data or specimens will not be banked.

11) **Data Management***

Statistical Analysis

Baseline characteristics will be summarized and compared to assure that the randomization algorithm resulted in comparable groups. Distributions will be evaluated and transformations to approximate normality will be considered if skewed. The main analysis will be an independent sample t-test or an analysis of covariance to allow for the inclusion of possible covariates such as age, baseline A1C, duration of diabetes, oral anti-diabetic medication use at baseline and number of comorbidities. 95% two-sided confidence interval (calculated on the basis of t-test or analysis of covariance) for the difference between BI and MSI treatment will be used for interpreting the results with regard to the non-inferiority margin. The main outcome variable will be the HbA1c after 6 months of treatment. Secondary outcomes will include mean glucose levels, hypoglycemic events, quality of life measures, patient satisfaction, and treatment failure.

The power calculation is based on the assumption that BI regimen will be non-inferior to MSI regimen for glycemic control. We anticipate that mean HbA1c in the control group (MSI group) at the end of treatment period will be 8.0% with standard deviation of 0.9. The study is designed to demonstrate a non-inferiority margin of 0.5, which is well within the margin of clinical relevance for this population. Group sample sizes of 18 in each group will achieve 95% power to detect non-inferiority using a two-sided, two-sample t-test with alpha 5%. Assuming a 20% drop-out rate, we plan to enroll 44 subjects into this study.

12) **Provisions to Monitor the Data to Ensure the Safety of Subjects***

Follow-up and Laboratory test

Patients will be required to send their BG data to the study team every 3 days while the insulin doses are being adjusted and then every 1-2 weeks. Communication will be arranged via secure patient portal emails, telephone or clinic visits. HbA1C will be obtained at randomization and every 3 months after enrollment into the study.

13) **Withdrawal of Subjects***

Subject withdrawal criteria

- Patient with severe hypoglycemia needing assistance or BG below 54 ng/dl after two insulin dose adjustments.
- Patient who develops hyperosmolar hyperglycemic syndrome.
- Patient with uncontrolled hyperglycemia >400 despite two insulin dose adjustments.
- Pregnancy during the study

14) **Risks to Subjects***

A relatively large dose of insulin glargine given in the morning may increase the risk of hypoglycemia. We will monitor patients closely and decrease the insulin dose as needed to prevent hypoglycemia. Any severe hypoglycemia in the BI group after two dose adjustments will lead to withdrawal from the study and conversion of insulin regimen to MSI.

There is also a risk of less tight glycemic control in the BI group as compared to the MSI group. However, a relatively high HbA1c is unlikely to cause any harm within the study period. Patients unable to achieve a lower HbA1c as compared to the baseline within first 3 months of the study will be withdrawn from the BI group and placed on MSI regimen.

15) **Potential Benefits to Subjects***

Glucose control is likely to improve in all patients participating in this study. The main research intervention in this study will be decreasing the number of insulin injection to once daily instead of multiple daily injections. The remaining outpatient care for diabetes will be as per the ADA guidelines. Knowledge gained from this study may help simplify treatment of diabetes for the elderly patients with T2DM

16) **Vulnerable Populations***

Children, incarcerated people and individuals with impaired decision-making capacity will be excluded from participating in the study. The study includes only the patients aged >65 years. Therefore, women of childbearing potential are excluded from this study. In spite of this, if a woman becomes pregnant, she will be immediately excluded from the study. However, we will follow them during the pregnancy for any potential complications that may be related to the study. Students and employees of the University of Miami are eligible for the study. Before they agree to participate, the students will be explained that their decision not to participate or to withdraw from the study will not affect their grades. Employees of the University of Miami will be explained that their decision not to participate or to withdraw from the study will not affect their employment at the University of Miami

17) **Sharing of Results with Subjects***

The results of the study will be published in a peer review journal. If the results show that the BI group has significantly better outcomes, patients in the MSI group will be informed and given the option of change in their insulin regimen.

18) **Setting**

The outpatient clinic of the University of Miami including Diabetes Research institute and the Lennar Foundation Medical Center and Jackson Health Clinics.

19) **Resources Available**

The diabetes clinics at the University of Miami are well equipped to recruit patients into clinical trials. All staff involved in this study have completed CITI training. The PI has extensive experience in clinical research. The PI has a furnished office with locked cabinets, a private phone-line and password protected computer with all the necessary software. The study will be conducted at the investigators' own time.

20) **Recruitment Methods**

Subjects will be recruited from the outpatient clinics of the University of Miami affiliated clinics. Treating providers must have provided permission to include their patients into the study. The inclusion/exclusion criteria will be applied to identify appropriate subjects. Either the treating physician will identify the potential subject or a member of the study team will identify the potential subject by screening through

the clinic schedule. The study will be first introduced to potentially eligible patients by their treating physicians. If they agree to obtain more information, a member of study team will speak with the patient and explain the study. If the patient shows willingness to participate, a copy of the informed consent will be given. The patients will be encouraged to discuss participation with their primary care providers. They will be asked to call back if they have any questions. The consent form is signed only at the time of first visit study visit that would often coincide with the patient's clinic visit.

21) **Local Number of Subjects**

We plan to recruit 44 subjects into this study.

22) **Confidentiality**

Each subject will be assigned a study ID, and all study-related measurements and information will be stripped of subject identifiers. Data will be used only in aggregate, and no identifying characteristics of individuals will be published or presented. Data will be stored for a period of seven years after completion of the study.

**Choose the statements below that are applicable to this research:**

(a). Will the research collect protected health information or personally identifiable information from the EMR or from subjects at UHealth and/or JHS?

☒ Yes (If checked go to 26(b))

☐ No (If checked, go to Section 27)

(b). Check the box next to the correct statement below

☒ Research Subjects will sign a HIPAA Authorization before the research will collect this data.

☐ Research Subjects will not sign a HIPAA Authorization for this data collection and the research is requesting a waiver of HIPAA authorization from the IRB.

(c). How will the research store the data?

☒ On a University of Miami electronic device (e.g. encrypted, password-protected computer)

☒ On a cloud-based storage system that is approved by the University of Miami

☒ On the secured JHS SharePoint environment

☐ Other, specify: Click here to enter text.

(d) Select one of the following:

☐ The Principal Investigator (and/or Study Team members) will record (e.g. write down, abstract) data acquired in a manner that does not include any indirect or direct identifiers (listed in the instructions for Section 26 of this protocol), and the recorded data will not be linked to the individual's' identity.

OR

☒ The Principal investigator (and/or Study Team members) will record (e.g. write down, abstract) the data collected in a manner that does not include any direct identifiers (see list in the instructions for Section 26 of this protocol) of any subject. Instead, the Principal Investigator and/or Study Team members shall will assign a code (that is not derived in whole or in part from any direct or indirect identifiers of the individual) to each study subject and link the code to the study subject's identity. The link to each subject's identity and/ or other identifiable information will be maintained on a document separate from the research data.

(e) Additional requirement for Jackson Health System Data:

☒ Not-applicable, no data will be acquired from JHS under a waiver of authorization.

☐ JHS data, including Protected Health Information (PHI) and/or Personally Identifiable Information (PII), acquired from JHS for this research under a waiver of authorization shall only be stored on the secured JHS SharePoint environment made available by JHS. I and the Study Team members shall not copy or store the JHS sourced personally identifiable

information (PII), including protected health information (PHI) data to any other system, including any systems maintained or provided by the University of Miami. I and the Study Team shall only copy or transfer JHS-sourced data that has been properly de-identified in accordance with all requirements contained in the HIPAA Rules by removing all of the identifiers listed in the instructions for Section 26 of this protocol.

## 23) **Provisions to Protect the Privacy Interests of Subjects**

Data will be confidentially collected from study participants and will only be used for research purposes. All paper records will be kept in locked file cabinets at *5555 Ponce de Leon Blvd, Suite 344B, Coral Gables, FL 33146.* All participant data stored in electronic form (UM approved cloud service) will be in folders that are password protected. Data confidentiality will be maintained and regulations regarding access to data by those other than the study staff will be followed. The code identification data will be kept in a locked file available only to the study doctors and staff unless requested by the appropriate regulatory authority

## 24) **Compensation for Research-Related Injury**

There will be no compensation for study related injuries.

## 25) **Economic Burden to Subjects**

The only research related intervention in this study is the change in the number of insulin injections. All other procedures, medications and testing supplies are part of

the standard care, and medically necessary for these patients. There will no research-related economic burden to the subjects in this study.

26) **Consent Process**

The Human Research Committee/Ethics Committee shall approve the consent form. It will include all elements required by FDA, state and local regulations, as well as any additional elements relevant to specific study situations.

The study will be completely explained to each prospective candidate and the subject must give consent by signing and dating the approved informed consent form. The Investigator will provide the subject with a copy of the consent form that is in a language that he or she understands.

Before study initiation, this protocol and the informed consent form will be submitted for review and approval to Health Sciences Institutional Review Board /Ethics Committee charged with this responsibility.

27) **Process to Document Consent in Writing**

One of the investigators will explain the study to the subject, answer any question and if the subject agrees to participate, an informed consent will be sought from the potential subject. We will follow the IRB guidelines for interaction with subjects and procedures for obtaining informed consent. The consent form will be reviewed in detail with each subject, and all questions will be answered. Subjects will be given as much time as they want to read, review, and complete the consent form. Subjects who prefer contemplating their decision for days or weeks or who wish to discuss their participation in the study with others (family members, friends, physician), will be encouraged to do so. We will stress that participation in our research study is voluntary, that subjects may withdraw from the study at any time, and that the

investigators reserve the right to discontinue the research protocol at any time. A copy of the signed informed consent form will be given to each subject. For the non-English speaking subjects, IRB policy on obtaining and documenting informed consent of subjects who do not speak English will be followed.

28) **Drugs or Devices**

The study does not involve drugs or devices that we plan to store, handle or administer to the subjects.