Title: Glycemia in Diabetic Elders Trial

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Type 2 diabetes is a common disease in elderly individuals. The population of Medicare enrollees with diabetes is projected to rise from 8.2 million in 2009 to 14.6 million in 2034 and associated spending is estimated to rise from $45 billion to $171 billion[1]. Any systematic treatment recommendations for these patients could have profound clinical and financial implications. However, the optimal choice of drugs for diabetic elders is uncertain: older drugs have been tested extensively, but the results of those trials have been mixed and limited to middle-aged populations[2]; several newer drugs have better short-term safety (less hypoglycemia) and side-effect (less weight gain) profiles, but have not been well studied in the elderly. The optimal strategy for glycemic control in elderly adults with diabetes is also uncertain because of competing risks from non-diabetic conditions and higher risk of adverse drug effects and polypharmacy. Therefore, developing effective strategies for diabetic elders that will achieve and maintain HbA1c control while minimizing adverse effects and overall drug exposure is a clinical priority.

This study is a randomized controlled trial of 30 elderly type 2 diabetes patients conducted at the MODEL Clinical Research (MODEL), Research Division of Bay West Endocrinology Associates in Baltimore, Maryland and a member of Johns Hopkins Clinical Research Network (JHCRN). We hypothesized that compared to a regimen base solely on traditional drugs, a regimen including incretin-based drugs will achieve glycemic target faster and induce less hypoglycemia, weight gain, and other side effects, over the short run.

2. Objectives (include all primary and secondary objectives)

The objective is to conduct a pilot comparative effectiveness trial with MODEL Clinical Research (MODEL), Research Division of Bay West Endocrinology Associates (BAY), an affiliate of GBMC and a member of the Johns Hopkins Clinical Research Network, to compare two treatment strategies (regimen using traditional drugs only vs. regimen including incretin-based classes of medication) in the elderly patients with type 2 diabetes on time to achieving glycemic target, overall hypoglycemia, weight gain, adverse events, and quality of life. This study will provide preliminary data on a 'preferred' anti-diabetic regimen for elders by comparing and quantify short-term effects from treatment regimens in diabetic elders.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

The optimal approach to glucose control for patients with type 2 diabetes is uncertain, particularly in older patients. For over a decade, glucose lowering recommendations have been primarily based on the results of the United Kingdom Prospective Diabetes Study (UKPDS) in middle-aged patients with new onset diabetes[4]. This trial showed that patients with an average HbA1c of 7.0% had a lower rate of microvascular complications than patients with HbA1c of 7.9% More recently completed trials suggest possible harm associated with tighter targets (e.g. HbA1c 6.5%) [5, 6]. Nonetheless, geriatric diabetes care guidelines also have endorsed pursuing an A1c<7.0% for healthy older patients with life expectancies greater than 5 years[7], admittedly without a firm evidence base. However, even traditional targets for glycemic control may include treatments that increase the chances of polypharmacy, hypoglycemia, weight gain, geriatric syndromes, and worsened quality of life. Severe hypoglycemic episodes have been associated with the development of dementia[8]; polypharmacy has also been shown to increase risk of injurious falls [9,10]. To develop optimal treatment strategies for diabetic elders, clinical trials specifically conducted in older patients with diabetes are needed.

As type 2 diabetes progresses in older persons, intensification is often required to achieve adequate glycemic control but with increased risk of adverse effects as a result of age related changes in drug metabolism. Incretin-based classes of medication, for example incretins, improve glycemic control in older persons. Some clinical evidence suggested that certain DPP-4 inhibitors (e.g. vildagliptin and sitagliptin) are particularly suitable for frail and elderly patients because less gastrointestinal effects than metformin and α- glucosidase inhibitors, and have a low risk of the hypoglycaemic events[11]. The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) Consensus Statement[12] recently included incretin-based classes of drugs in the Diabetes Algorithm for Glycemic Control. However, the recommendation is largely based on expert opinions, not head-to-head comparisons. A recent federally-sponsored literature synthesis by our group[2] pointed out the deficiencies of evidence in evaluating newest agents and two-drug combinations. Most important, evidence supporting one regimen over the other for elders is lacking. In this pilot trial, we will test real-world, practice-based strategies comparing traditional treatment to treatment including incretin-based drug classes in reducing glycemia safely in diabetic elders in the short run (3-6 months).

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Design Overview: This study will be a single center, randomized controlled trial (RCT) with 2 parallel arms. The participants will be 30 adults age 65 or older with type 2 diabetes mellitus. After informed consent and screening, these elderly adults will be randomly assigned to one of two anti-diabetic regimens (both regimens use only FDA-approved medications):

1) a regimen with traditional drugs only (e.g. insulin, metformin, sulfonylureas, TZDs); or
2) a regimen including incretin-baseder drugs (e.g. GLP-1 analogues and receptor agonists, DPP-4 inhibitors, amylin analogues).

The primary outcome variable is time to achieve glycemic target (HbA1c <7.5%). Secondary outcomes are overall hypoglycemia, weight, diabetes quality of life, and adverse events.

Setting: The setting for this trial will be MODEL Clinical Research (MODEL) affiliated with Bay West Endocrinology Associates and now part of the Johns Hopkins Clinical Research Network (JHCRN). This practice sees private patients and also covers the Greater Baltimore Medical Center (GBMC) .

Recruitment: We will have a rolling recruitment and anticipate we will recruit, randomize, and follow 30 participants in 8 months. We aim to recruit 30% or more African American or Hispanic. As part of the recruitment process, we will first search the existing Bay West Endocrinology database to identify potential patients. Then, with approvals from their providers, we will contact potential patients when they come in the office to see their providers. IRB-approved recruitment flyers will also be placed in the Bay West Endocrinology office, including lobby, check in/out and exam rooms. We do not plan to initiate recruitment by phone. However, if patients call or leave message, the study coordinator will call back based on the IRB approved telephone script.

Informed Consent: To participate in GLiDE Trial, participants must provide written, informed consent using procedures reviewed and approved by the Johns Hopkins Institutional Review Board.

Data Collection Visits: Screening, baseline, and follow-up data will be collected at in-person visits at MODEL or phone calls. Table 1 presents the data collection schedule by visit.

	SV	RV	**FV1**	Call	**FV2**	Call	**FV3**
Months	— 1	0	1	1.5	3	4.5	6
Informed consent	■						
Contact information	■						
Intervention		■	■		■		
Randomization		■					
Blood Pressure		■	■		■		■
Weight		■	■		■		■
Waist		■					■
Height	■						
Fasting blood work†		■			■		■
Fructosamine		■	■				■
HbA1c		■			■		■
Questionnaires							
Demographic/ Medical history	■						
Medication Use	■		■	■	■	■	■
EQ-5D Health Status Patient questionnaire	■				■		■
Diabetes Quality of Life questionnaire	■				■		■
Diabetes Distress Screening Scale – 2 items	■				■		■
Self care	■				■		■
Incontinence – 1 item	■				■		■
†Including lipids and glucose Phone calls at 1.5 and 4.5 month to check in.							

Screening Visit (SV): After being identified as part of the recruitment process, there will be a SV to determine eligibility and commitment to the study. Interested persons will attend one visit at which the trial is described in detail, all patient questions are answered, written informed consent obtained, and physical measurements performed. Demographic and contact information,

medication use, and medical history will be obtained. To maximize the generalizibility of the trial results, there will be no run-in period in this study.

Randomization Visit (RV): Upon confirmation of eligibility and informed consent process, weight, height, waist circumference, and blood pressure will be measured according to standard research protocols. Screening Visit and Randomization Visit can be combined. Patients will complete the study questionnaires. Fasting blood work will be completed during the same visit or the participants can come back in a few days. Participants will then be randomized into one of the two groups.

Follow-Up Visits (FVs): Participants will be asked to attend in-person follow-up visits at 1 month (FV1), 3 month (FV2), and 6 (FV3) months after randomization and will receive a phone call at 1.5 month and 4.5 month. The total intervention period is 6 months.

Interventions: Under the leadership of Dr. Levin, the primary investigator at MODEL, a panel of 7 experts in endocrinology (Drs. James Mersey at MODEL & BAY and Tom Donner at JHSOM Endocrinology), primary care (Drs. Frederick Brancati of Hopkins GIM Division and Gary Noronha at JHCP), and geriatrics (Drs. Elbert Huang at U of Chicago and Cynthia Boyd at JHSOM Geriatrics) has convened and developed the clinical algorithms for each treatment group. Table 2 outlines the proposed regimens for the two treatment groups. Please refer to Appendix 1 for detailed interventions and Appendix 2 for a list of potential medications. Traditional drugs listed in the Standard Treatment Group are widely used in current clinical practice. The Incretin-based Drug Treatment Group is adapted from the 2010 AACE Consensus Statement. The patient's primary endocrinologist will follow the randomly assigned algorithm to provide treatment as part of patient's routine diabetes care. Participants in both groups will receive the same dietary and lifestyle advice based on the American Diabetes Association Standard of Care 2012 guideline. Baseline medications will not be discontinued unless due to adverse event or contraindication developing. Incretin- based arm will not discontinue baseline medications, either, unless addition of intensification drug triggers clinical indication to discontinue DPP-4 or SU. There will be medication overlap between groups as all patients start with oral agents or basal insulin +/- orals regardless of study arm. However, the standard group will not use injectable incretins and will use a DPP4 Inhibitor only as a last resort oral agent if other oral agent additions are not clinically indicated in a given patient. At the end of each study visit, the study coordinator will review current treatment plan to ensure protocol adherence by physician and patient. Investigators at MODEL will review status of each study patient with coordinator at weekly research meeting.

Table 2. Proposed regimens for two treatment groups (Refer to Appendix for detailed interventions)

Standard Treatment Group		**Incretin-based Treatment Group**	
Baseline; HbA1c 8% - 12%			
On one of more oral meds	**On basal insulin +/- orals**	**On one of more oral meds**	**On basal insulin +/- orals**
Add one more oral: Metform, Sulfonylureas, or TZD (i.e.Actos)	Intensify basal, or add bolus	If not on DPP-4, add DPP-4 or start GLP-1 and decrease SU. If already on DPP-4, then discontinue DPP-4, add GLP-1 and decrease SU	Add GLP-1, decrease SU If already on DPP-4, then discontinue DPP-4, add GLP-1, and decrease SU. Self-directed basal insulin titration (3-0-3 scheme) until visit 2
↓ ↓	↓ ↓	↓ ↓	↓ ↓
FV 2 (3 month visit)			
HbA1c >7.5%	**HbA1c <=7.5**	**HbA1c >7.5**	**HbA1c <=7.5**	**HbA1c >7.5%**	**HbA1c <=7.5**	**HbA1c >7.5**	**HbA1c <=7.5**
Add basal or oral(s) if not at max	Continue regimen	Intensify Basal/Bolus	Continue regimen	Add basal	Continue regimen	Basal/Bolus Continue GLP-1	Continue regimen
↓							
FV3 (6 month visit)							
Obtain final HbA1c and other outcomes							

b. Study duration and number of study visits required of research participants.

The study duration is 6 months.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Upon confirmation of study eligibility, signed informed consent form, and the baseline data collection, 30 participants will be randomized in a 1:1 ratio to one of the two groups. Randomization will be in variable blocks (2 and 4) after stratification by age (65 to 74; vs 75 and older), using the Moses-Oakford algorithm, adapted for SAS statistical software. The randomization scheme will be generated by the Statistician and the Study Coordinator will convey actual randomization assignment to participants. Trial participants will know their intervention assignments, as will intervention physicians. However, study staff involved in follow-up data collection will be kept masked to participants' randomization assignments.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

N/A. Patients will receive routine diabetes care

e. Justification for inclusion of a placebo or non-treatment group.

Not applicable.

f. Definition of treatment failure or participant removal criteria.

Participants can be removed from study by Dr. Philip Levin, the leader of clinical intervention at any time without patient consent for any of the following reasons: (1) if the participant fails to follow directions for participation in the study; (2) if a specific FDA-approved diabetes regimen appears harmful to participant; or (3) if the study is cancelled.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Participants will remain under the care of their personal physician both during the study and after the study ends.

5. Inclusion/Exclusion Criteria

Patient inclusion criteria**:**

- Type 2 diabetics diagnosed for at least 6 months
- Patients ages ≥ 65 years and older
- Active patients in the Bay West Endocrinology practice
- Inadequately controlled on oral agents and/or basal insulin with HbA1c between 8.0% and 12%
- Eligible for randomization to either treatment group
- Patients willing to follow either treatment arm including regimen using one or more injectables
- Patients to have an English Reading Level of Grade 6 or above
- Patients residing at home

Patient exclusion criteria:

- Unwilling to use a regimen that may contain using one or more injections
- Using short acting insulin prior to the study
- Using GLP-1 in past 10 weeks
- History of hypoglycemia unawareness or episodes needing emergency intervention
- End-stage renal disease
- Dementia
- Blindness
- Terminal illness

- Judged by investigators as unlikely to follow protocol because of known non-compliance, psychiatric disease, alcohol or drug abuse.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

The study objective is to compare the effectiveness of two diabetes treatment strategies (regimen using FDA approved traditional diabetes drugs only vs. regimen including incretin-based classes of FDA approved diabetes medication) in elderly patients with type 2 diabetes. All of these diabetes drugs are FDA approved for standard use.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

This study will use FDA approved drugs for diabetes treatment.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

Not applicable.

7. Study Statistics

a. Primary outcome variable.

Time to achieve glycemic target (HbA1c <7.5%). This goal will be defined as HbA1c measures at follow-up visits.

b. Secondary outcome variables.

Secondary Outcomes: a) Percent achieving glycemic target at 6 month; b) Overall hypoglycemia measured by glucose meter; c) Total cholesterol, HDL cholesterol, and triglyceride; d) Fasting glucose insulin, and fructosamine; e) blood pressure (BP) and heart rate determined by the OMRON 907-XL; f) Weight, height, and waist circumference; g) EQ-5D Questionnaire; h) Diabetes Quality of Life Questionnaire[14]; i) Diabetes distress[15] (2 screener questions); j) self-care; k) incontinence[16] (1 question).

Other Data: a) Demographics: tobacco use, health insurance status, education level, and live alone status; b) Medication history including monitoring adherence, which will be self-reported for each of the prescribed medications for glycemic control.

Adverse Events: Hypoglycemic episodes requiring assistance by medical/paramedical personnel, overnight hospitalization, diabetes-related deaths, and other outcomes that the Medical Monitor deems important.

c. Statistical plan including sample size justification and interim data analysis.

One of the purposes of this pilot trial is to collect needed parameters for future planning of a larger scale confirmatory RCT. To this end, the frequency distribution of parameters of interested will be collected and described at baseline and over follow-up. Repeated measures over follow-up will provide estimate for intra-individual correlations that will be needed in sample size/power determination for the future trial. Repeated measures of HbA1c will also allow examination of HbA1c trajectory over time to inform the feasibility of interpolate the time to reaching HbA1c target threshold based on fixed interval assessments.

Using width of 95% CI as a measure of precision in parameter estimation, a sample size of 30 will provide estimation precision of ± 0.31xSD for a continuous variable, ± 15.5% for a binary proportion of 50%, and ± 9.3% for a binary proportion of 10%. For subgroup estimation with N = 15 per group, the above precision will be inflated by 1.4.

d. Early stopping rules.

Formal stopping rules are not planned for this pilot trial.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

This study uses FDA-approved drugs and regimens in routine clinical settings. Being a part of this study does not in itself increase any medical risks to participants as the risks are the same risks that participants have while being treated with any diabetes drugs by their own physicians. These standard FDA-approved diabetes regimens used here will also not increase risk of hypoglycemia beyond those risks found in standard clinical practices. Closer monitoring by study staff could minimize hypoglycemic risk during this trial. Potential participants will be provided with more detailed information about all of the possible risks and discomforts of the specific diabetes drugs that are given to them.

b. Steps taken to minimize the risks.

This study will follow participants more closely than they would typically be followed by their own physicians in routine clinical practice. Hypoglycemic risk and adverse effect in particular should be mitigated by closer than typical observation by medical/study staff. See Section x related to protection of data confidentiality.

c. Plan for reporting unanticipated problems or study deviations to the JHM IRB.

Adverse Events required to be reported to the JHM IRB are defined as those events that are serious, unexpected and associated with the FDA-approved ‘study’ medications (Medications used as part of this study, also known as study medications, are all FDA-approved diabetes medications.) Serious will be defined using the FDA’s description of “serious”.

Participants in the GLIDE Study are expected to have medical events due to disease, which typically can occur in this elderly study population and are not associated with the FDA-approved medications that patients will receive in this study. Events exempted from IRB reporting, i.e. events

due to progression of an existing disease, development of a new disease, treatments, procedures or hospitalization for these diseases, or known side effects or concomitant therapies, other than the FDA medications, received by these patients. These events are exempted from the usual JHM IRB SAE reporting requirements, i.e. will not be reported individually to JHCRN and/or JHM IRB during the conduct of the study unless they are reported as drug related SAEs by the investigator.

All serious adverse events will be documented in patient's study chart, collected as part of study procedures and also reported to Medical Monitor; however, only those that meet the criteria that are serious, unexpected, and associated with the FDA-approved study medications will be reported to both JHU/GBMC IRBs within 10 working days. If in doubt about whether or not the event meets the criteria of serious, unexpected and associated with the FDA-approved diabetes medications, it will be up to the JHU Principal Investigator to make the final determination after consulting with at least 1 of the study's sub-investigators.

Safety Monitoring Plan
There will be no formal Data and Safety Monitoring Board (DSMB) for this pilot trial using FDA-approved medications in the manner that they were approved for the patient population that FDA approved. Patients will remain under their own physicians' care. Dr. Tom Donner at Johns Hopkins, will serve as Medical Monitor for the study and for serious and unexpected adverse events. As stated in section 8c. of this protocol, all serious adverse events will be documented in patient's study chart, collected as part of study procedures, and also be reported to Medical Monitor Principal Investigator. All other AEs will be logged and submitted to the IRB at Continuing Review.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

The investigative team and MODEL are keenly aware of the need to protect participant confidentiality, as well as corresponding legal requirements, including those mandated by HIPAA (Health Insurance Portability and Accountability Act). All data collected and stored electronically will be password protected and saved in a secured fashion. All study related computers will be under firewall protection and will maintain automated virus update mechanisms. Timely notification regarding relevant patches will be provide. Hard copy of the data collection forms will be store in locked cabinets or areas. Only authorized personnel will have access to these locked areas. In addition, all study staff annually sign a confidentiality statement attesting to their understanding of, and willingness to abide by, the staff written policies on research ethics and confidentiality. Access to the data entry system is password protected and restricted to personnel trained to use the system.

e. Financial risks to the participants.
There will be no financial risks to the participants. The clinical care will be a part of the routine medical care and the cost of medication will be covered through patient's own insurance plan and/or by patient's own funds.

9. Benefits

a. Description of the probable benefits for the participant and for society.

Participants will receive additional medical monitors from study visits and phone call. From a societal perspective, if this pilot study is successful, it will set the stage for a large-scale trial that should provide a solid evidence base for decision-making about diabetes treatment in elders.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

A participants will receive a total of $80 if he/she complete the study, which includes $20 for baseline visit, the interim visits (4 weeks and 12 weeks) and final visit (including questionnaires. Parking will be reimbursed. There will be no penalties for not completing protocol.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

The cost of medications will be covered through patient's own insurance plan and/or by patient's own funds. All the medications used in this trial are eligible for reimbursement by Medicare and major insurance companies. If insurer denies use of a given drug category or patient is without insurance, then medication will be supplied by this study at no cost for the duration of study. There will be no charge for blood tests, interviews, or physical measurements that are for research purposes only.

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