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A Randomized Study to Evaluate the Efficacy of Insulclock® in Patients with Uncontrolled Type 2 Diabetes

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Title:

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Research Objectives and Specific Aims:

Diabetes is arguably the most urgent healthcare challenge of the 21st century. An estimated that 1 in 11 adults have diabetes with an estimated 415 million individuals with diabetes worlwide.[1] In the United States, 21 million persons have been diagnosed with diabetes, with approximately 90–95% of cases due to type 2 diabetes (T2D).[2] Diabetes is a leading cause of cardiovascular disorders, blindness, end-stage renal failure, and non-traumatic amputations.[2] Extensive evidence from epidemiological and randomized control studies have shown that improved glycemic control decreases the risk of diabetic complications, and is likely to be of benefit in preventing long-term cardiovascular complications.[3] However, despite the availability of a large variety of antidiabetic drugs, insulin formulations, and clinical guidelines, only one-third of patients on basal insulin and one-fourth of those on basal insulin and oral antidiabetes drugs achieved target A1C <7.0%.[3-5]

Poor adherence to insulin regimens is common and reported in up to two-third of patients with diabetes.[6-8]The most common barriers with insulin injections are socio-economic factors, complexity of treatment and adherence to prescribed dosing time, which lead to frequent insulin omissions, as reported in more than half of patients with diabetes.[9] The frequency of insulin injection irregularities (omission, mistiming and dosing) are similar for patients using basal insulin alone versus those using basal with bolus insulin regimens.[7] Thus it is important to identify patients at risk and to develop strategies and tools to increase adherence to prescribed insulin regimens. Recent advances in this field include the availability of electronic reminders, mobile communication technology such as phone short message services, [10] smartphones and wrist-worn smartwatch, [11] and a variety of insulin pens with memory functions and electronic display.[12-14] However, current devices are designed for specific insulin brands, are not interchangeable among available insulin pens, and they lack alarm systems to notify patients and caretakers about insulin delays and missing doses.

Insulclock®[15] is a small electronic device easily plugged to any brand of insulin pen devices to help track date, time and dosage of the last injection, type of insulin used and temperature. Insulclock has an alarm system with visual and sound alerts to prevent insulin omissions and mistiming. Via Bluetooth and smart-phone technology, information is stored and readily available for data analysis by patients, caregivers and healthcare professionals. The Insulclock's real time memory and alert system are likely to improve treatment adherence, patient's satisfaction, and quality of life measures, which may improve glycemic control in insulin treated patients with T2D.

Study Aims:

Aim 1. To determine whether the Insulclock system results in improved treatment adherence and reductions in treatment irregularities (insulin omission, mistiming and dosing) compared to conventional insulin pen device. Patients with inadequately controlled T2D treated with oral antidiabetic agents and basal insulin (NPH, glargine or detemir) will be randomized to Group A: Insulclock device with feedback or to Group B: Insulclock without feedback. All patients will use the Insulclock device attached to glargine U100 insulin pens (SoloStar®) during the study period. Participants in Group A will receive daily information on their smartphone on insulin administration (time and dosing) as well as reminders in the event of missing doses. Participants in Group B, will use the Insulclock, but will not receive feedback on insulin administration. Differences in insulin injection irregularities (omission, mistiming and dosing) will be compared at each clinic visit during the study period.

Hypothesis: The Insulclock device will improve adherence reducing insulin omission, mistiming and dosing errors compared to standard pen device.

Aim 2. To determine whether the Insulclock system yields higher treatment satisfaction scores in poorly controlled patients with T2D compared to a conventional insulin pen device. Patients with inadequately controlled T2D (HbA1c ≥ 7.0%) treated with oral antidiabetic agents and basal insulin once daily (NPH, glargine or detemir) will be enrolled in a 24 week randomized, cross-over clinical trial comparing the

use of Insulclock device system vs standard insulin pen. Treatment satisfaction will be assessed with the Diabetes Treatment Satisfaction Questionnaire Status (DTSQs) [16,17] to be administered at baseline (week 0) and at weeks 12 and 24 to assess relative changes in the DTSQ between interventions. The amplitude of the score on the DTSQc gives the degree of change in satisfaction while the direction (positive or negative) will provide guidance on the preference of therapy.
Hypothesis: The Insulclock device will improve treatment satisfaction compared to standard insulin pen device.

Aim 3. To explore whether changes in adherence with the Insulclock improves glycemic control, as measure by change in HbA1c from baseline, when compared to conventional insulin pen device. HbA1c will be measured at week 0 and at weeks 12 and 24 to assess differences in glycemic control between groups.
Hypothesis: The Insulclock device by improving treatment adherence may improve glycemic control compared to standard pen device.

II. BACKGROUND AND STATUS OF WORK IN THE FIELD.

Basal Insulin therapy in Type 2 Diabetes

Insulin is the oldest and the most potent agent for the treatment of diabetes. Insulin therapy is the treatment of choice for patients with severely elevated HbA1c and symptoms of hyperglycemia, [18,19] and in patients with inadequate glycemic control despite treatment with OADs and non-insulin injectables.[18,19] Clinical guidelines recommend the use of basal insulin, given once (glargine, detemir, degludec) or twice daily (neutral protamine Hagedorn [NPH], detemir) as add-on to non-insulin agents. Basal insulin analogs are preferred over NPH insulin because a single basal dose provides a relatively flat serum insulin concentration for up to 24 hours. Newer basal insulin formulations – glargine U300 and degludec- have more prolonged and stable pharmacokinetic (PK) and pharmacodynamic (PD) characteristics than glargine U100 and detemir.[18,20] Despite of the multiple basal insulin formulations, a systematic review of 218 randomized clinical trials found that only 39% of patients with T2D treated with basal insulin achieve an HbA1c <7%.[5] Moreover, a recent study reported no overall improvements in glycemic control among patients with T2D during the past decade.[21]

Insulin Non-Adherence

Poor adherence to medical treatment is a significant contributor to negative outcomes and increased risk of morbidity in patients with diabetes.[22,23] Insulin non-adherence has been reported in up to two-thirds of patients,[6-8]with approximately one-third reporting an average of three episodes of insulin omission/non-adherence within the previous month.[7,24] Regimen complexity, in terms of the number of the treatments and frequency of administration, is known to have a negative impact on adherence.[25-27] Brod et al [7] reported that most missed or mistimed doses were unintentional (~80%). The most common barriers with insulin injections are socio-economic factors, complexity of treatment and adherence to prescribed dosing time, which lead to frequent insulin omission reported in more than half of patients with diabetes.[9] The insulin tracking and alert system will address the issue of nonadherence by reminding patients about insulin dosing and avoiding missing insulin injections. The alarm system can be programmed at any time(s) of the day alerting patients and caretakers on delayed injections, which may reduce missing doses.

Use of Insulin Pens and Patient Satisfaction

Multiple studies have reported that insulin pen devices are associated with greater treatment satisfaction and patient preference as well as improved dose accuracy compared to the traditional vial/syringe.[28-37] Standardized assessments of treatment satisfaction, including the Diabetes Treatment Satisfaction Questionnaires (DTSQs and DTSQc) and the Insulin Delivery System Rating Questionnaire (IDSRQ), have been validated and tested for reliability.[16,17,38,39] Some insulin pen studies have evaluated patient satisfaction with these tools.[28,30] Improving treatment satisfaction can lead to improvements in quality of life.[40] Improvements in quality of life are often cited as leading to greater adherence to treatment protocols and insulin administration.[41]

Advances in Insulin Treatment

Like most areas of medicine, treatment of diabetes has changed considerably over the past decade because of technological advances including glucose monitoring and insulin delivery options. Major advances to improve adherence in diabetes include the availability of mobile communication technology such as phone short message services, [10] electronic reminders, smartphones and wrist-worn smartwatches, [11] and a variety of insulin pens with memory functions and electronic display.[12-14]

Examples of smart pens commercially available or in development:

Easylog, a compact add-on module designed to fit pen injectors. Smart sensors collect injection data directly from disposable or reusable pen and connect to smartphones via Bluetooth.

Datapen, a Smart reusable injector pen connected to a mobile app. Each injection can be tracked and Bluetooth technology to allow access treatment data from mobile phone.

Smartplus Insulin Pen, an injection delivery compatible with insulin pen needle device that supports insulin cartridges from Eli Lilly and Sanofi-Aventis insulin formulations. The pen stores and displays 195 injection doses, including the date and time of the injection.

KiCoPen captures dose delivered and sends the information to an associated smartphone app.

Human Pen Memoir® (Eli Lilly & Co) and NovoPen5® (Novo Nordisk) durable insulin pens with the addition of a memory function that records the dose of and hours passed since the last injection.

Insulclock®[15] is a small electronic device which is plugged to all pen devices allowing tracking information on date, time, dose of the last injection, remaining insulin in the pen device, as well as type of insulin used and temperature. Insulclock has an alarm/reminder system with visual and acoustic alerts to reduce insulin omissions and mistiming. Via Bluetooth and smart-phone technology, information is store and readably available for data analysis by patients, caregivers and healthcare professionals.

Significance and Innovation: In the US, all patients with type 1 diabetes are treated with basal insulin alone and about 30% of patients with type 2 diabetes are treated with basal insulin alone or in combination with oral agents to achieve and maintain glycemic control.[3] About 30.3% of patients on basal insulin and 24.2% of those on basal insulin and oral antidiabetes drugs achieved target A1C <7.0%.[3] A systematic review of 218 randomized trials reported that 39% of patients with T2D treated with basal insulin achieve an HbA1c <7%.[5] Insulin non-adherence is reported in up to two-thirds of patients,[6-8]with one-third reporting an average of three episodes of insulin omission/non-adherence within the previous month.[7,24]

Recent devices have become available to improve adherence to insulin therapy in diabetes include the availability of mobile communication technology such as phone short message services,[10] electronic reminders, smartphones and wrist-worn smartwatch,[11] and a variety of insulin pens with memory functions and electronic display.[12-14] However, these devices are not interchangeable among different insulin pens and they do not have the alarm systems to notify patients and caretakers about insulin delays and missing doses. The insulin tracking and alert system may be of great help in reminding patients about insulin dosing and avoiding missing insulin injections. In addition, the Insulclock will also allow us to assess treatment nonadherence. Differences in treatment adherence before and after the crossed over will provide objective evidence of compliance and treatment adherence.

III. Research Design and Methods

Study Aims:

Aim 1. To determine whether the Insulclock system results in improved treatment adherence and reductions in treatment irregularities (insulin omission, mistiming and dosing) compared to conventional insulin pen device.

Aim 2. To determine whether the Insulclock system yields higher treatment satisfaction scores in poorly controlled patients with T2D compared to a conventional insulin pen device.

Aim 3. To explore whether changes in adherence with the Insulclock system results in improved glycemic control, as measure by change in HbA1c from baseline, when compared to conventional insulin pen device.

Study Rationale. Poor adherence to medical treatment is common and is associated with increased risk of morbidity in patients with diabetes.[22,23] Insulin non-adherence has been reported in up to two-thirds of patients,[6-8]with approximately one-third reporting an average of three episodes of insulin omission/non-adherence within the previous month.[7,24] Regimen complexity, in terms of the number of the treatments and frequency of administration, is known to have a negative impact on adherence.[25-27] Patients with irregular mealtime and active social-work schedule were more likely to have insulin irregularities, many of them intentional omissions. In patients with T1D, poor adherence is the main cause of hyperglycemic crises accounting for more than half of admissions with hyperglycemic crises.[42,43] Several devices have been designed to improve insulin adherence including new delivery options like smart pens with memory functions and electronic display;[12-14] however they have significant limitations and their efficacy in improving treatment adherence or in improving glycemic control have not been tested in rigorous randomized clinical trials. The Insulclock device allows to record date, time, dose of the last injection, as well as type of insulin used, and remaining insulin volume in the pen device. A major advance of Insulclock over available smart pens is its ability to send visual and acoustic alert message directly from the device or via text to patients and caretakers in the event of insulin omissions and mistiming. In addition, the large volume data storage will allow patients and healthcare providers to download information on insulin patterns and omissions over a long period, allowing for a better understanding of insulin adherence. The present study will test whether the Insulclock improves adherence, quality of life, treatment satisfaction, and glycemic control compared to the standard pen device.

Study Objectives:

Primary Objective.

To demonstrate the superiority of Insulclock in treatment adherence (insulin omission, mistiming and dosing) over conventional insulin injection pen devices.

Secondary Objectives:

To demonstrate non-inferiority of Insulclock compared with standard insulin pen device on:

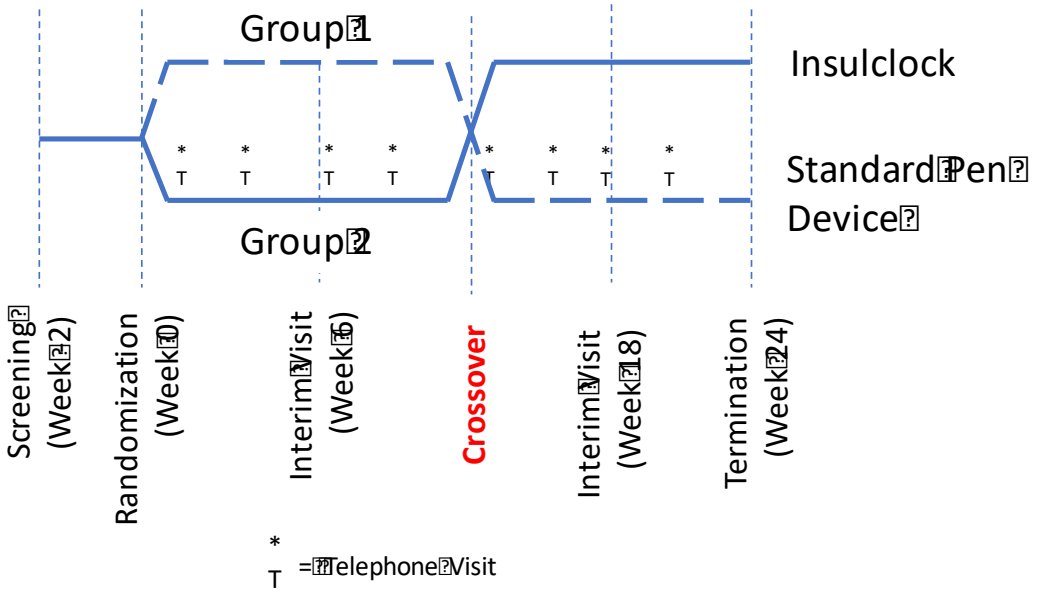
- Treatment satisfaction -Diabetes Treatment Satisfaction Questionnaire Status (DTSQs)[16,17]
- Diabetes Related Quality of Life (DRQoL)
- Adherence:
  - Frequency of insulin irregularities (omission, mistiming and dosing)
- Glycemic control:
  - Glycemic control, as measure by change in mean HbA1c from baseline
  - Frequency of hypoglycemia
  - 7-point SMBG profile
  - Daily fasting glucose profile

Methods:

This will be a randomized (1:1), controlled, 26-week cross-over clinical trial in patients with inadequately controlled T2D (HbA1c ≥ 7.0% to ≤ 12.0 %) while treated with oral antidiabetic agents and basal insulin (NPH, glargine or detemir). Participants will be randomized to use the Insulclock device (Group 1) and standard of care using an insulin pen device (Group 2). All patients will use the Insulclock device attached to glargine U100 insulin pens (SoloStar®) during the study period. During the study period. Participants in Group 1 will receive daily information on their smartphone on insulin administration (time and dosing) as well as reminders in the event of missing doses. Participants in Group 2, will use the Insulclock, but will not receive feedback on insulin treatment or alerts.

Randomization will be stratified by:

- HbA1c at Screening (≤8.0%, >8.0%)



Study Visits

Screening (Visit 1)

Approximately 1-2 weeks prior to the start of the study, all potential study patients will be screened to check their eligibility after signing the informed consent form (ICF) and assigned a patient identification number. Medical history, physical examination, height, weight, vital signs, pre-existing conditions, and concomitant medications will be recorded during this visit. Laboratory assessments performed at Visit 1 to determine eligibility for the study include pregnancy tests for females, and HbA1c, serum chemistry, assays. Patients who do not meet all the inclusion criteria at Visit 1 will be considered screen failures and will not be randomized to participate in the study.

Eligible patients will be trained on the use of the glucometer to monitor their BG levels. Patients will be given diabetes diaries and associated training to record all glucose levels, insulin doses, and episodes of hypoglycemia.

Insulin administration technique will be reviewed prior to randomization to ensure good technique. Reinforcement will be provided as needed during the follow-up visits.

Only eligible patients treated with a once daily insulin dose of NPH, detemir, glargine insulin will be switched to SoloSTAR pen (glargine U100) at a total dose (TDD).

Antidiabetic agents will be continued at the same dose, except insulin secretagogues which can be stopped if HbA1c is <8% or reduced by half if HbA1c is >8%.

Patients will be instructed in performing glucose testing at home before meals, with a minimum of 2 out of the 4 pre-meal and bedtime glucose measurements per day. In addition, patients must perform a 7-point SMBG (fasting, before meals, 2 hours after meals, and bedtime) done between 3 to 5 days prior to Visit 2.

One week after screening and before randomization, eligible participants will receive an Insulclock device. They will be properly trained on how to use it, charge and connect Insulclock to their mobile devices. Insulcloud will make smartphone available for subjects, who do not own a smartphone, during the course of the study. Technique skills such as the ability to navigate the app, press the button for 5 seconds while giving insulin injection[44], and how to connect the device to their phones will be explained. They will be asked to use the Insulclock with their insulin pen, to get familiarized with it. An assessment will be done after the week of using the device in order to review quality and understanding of the technology. Those subjects that fail to use the device properly will be deemed Screen Failures.

Instructions to be provided to Patients in Preparation for Visit 2 (Randomization visit)

- All patients will be instructed to provide daily glucose records. In addition, they will perform a 7-point SMBG done between 3 to 5 days prior to Visit 2.
- Insulclock usage, compliance, and technique will be reviewed.
- Patients who complied with the 7-point glucose testing (fasting, before meals, 2 hours after meals, and bedtime) and fulfill the eligibility criteria at Visit 2 will be randomized to participate in the study.
- Diabetes Treatment Satisfaction Questionnaire Status (DTSQs)

Randomization (Visit 2)

- Patients will receive detailed instruction on the use of Insulclock system according to randomization group.
- Study diaries will be collected and reviewed for BG levels, episodes of hypoglycemia, insulin self-administration
- Dose of glargine insulin will be adjusted as needed (page 8).

- Patients will be instructed in performing glucose testing at home before meals, with a minimum of 2 out of the 4 pre-meal and bedtime glucose measurements per day.

Telephone Visits (visit 3, 4, 6, 7, 9, 10, 12, 13)

- Between each office visit, patients will have a telephone visit with the investigator at 2 week intervals after randomization (Visit 2) and interim office visits (visits 5 and 11).

Interim Visits (visit 5 and 11)

The following activities occur during interim visits:

- Patients will receive detailed instruction on the use of the Insulclock system
- Study diaries will be collected and reviewed for BG levels, episodes of hypoglycemia, insulin self-administration
- Dose of glargine insulin will be adjusted as needed (page 8).
- Patients will be instructed in performing glucose testing at home before meals, with a minimum of 2 out of the 4 pre-meal and bedtime glucose measurements per day.

Crossover visit (Visit 8, week 14)

The following activities occur during crossover visit:

- At midpoint (week 12), patients will be converted to the alternate treatment Arm (cross-over design).
- Patients will receive detailed instruction on the use of the Insulclock system
- Diabetes Treatment Satisfaction Questionnaire Status (DTSQs)
- Blood sampling for HbA1c assessment to determine efficacy of treatment
- Study diaries collected and reviewed for BG levels, episodes of hypoglycemia, insulin self-administration
- Dose of glargine insulin will be adjusted as needed (page 8).

Visit 14 (End of Study)

- Diabetes Treatment Satisfaction Questionnaire Status (DTSQs)
- Blood sampling for HbA1c assessment to determine efficacy of treatment
- Study diaries collected and reviewed for BG levels, episodes of hypoglycemia, insulin self-administration

During each visit, participants will have their insulin dose titrated to achieve a fasting glucose <130 mg/dL as detailed in the glargine titration algorithm. Once the fasting glucose 3-day average is <130 mg/dL, insulin doses will be kept constant, unless the participant experiences recurrent hypoglycemia or severe hyperglycemia.

Insulin Glargine Titration Schedule. Make adjustment every 3 days after the subject has been on insulin U100 as follows:

Mean 3 day consecutive Fasting SMBG	Glargine U100 Dose Adjustment
>180 mg/dL	Increase glargine dose by 4 IU
130 – ≤ 180 mg/dL	Increase glargine dose by 2 IU
71 – ≤ 130 mg/dL	No change
≤ 70 mg/dL	Decrease insulin glargine dose by 10%
≤ 40 mg/dL	Decrease insulin glargine dose by 20-30%

Upward titration should be stopped for one week after a case of hypoglycemia confirmed by a SMBG reading < 70 mg/dL unless there is an adequate explanation (e.g. omission of a meal) for the event. The study staff should instruct the subject to contact the site for any questions on the insulin dose adjustments.

Treatment satisfaction will be assessed with the Diabetes Treatment Satisfaction Questionnaire Status (DTSQs) [16,17] to be administered at baseline (week 0) and at weeks 12 and 24 to assess relative changes in the DTSQ between interventions. The amplitude of the score on the DTSQc gives the degree of change in satisfaction while the direction (positive or negative) will provide guidance on the preference of one device over the other.

Concomitant Medications:
During the study treatment period, the following medications are prohibited:

- Initiation of any antidiabetic agents, including oral or injectable antihyperglycemic agents
- Systemic use of glucocorticoids for more than 10 consecutive days.
- Initiation of any weight loss drugs
- For patients in both groups, background metformin should be maintained throughout the study unless down-titration is required for safety reasons.

Assessment of Results:
The primary outcome of ***treatment adherence*** with the use of Insulclock with feedback or no feedback information (blinded) will be determined by the percentage of patients and number of insulin omission, mistiming and dosing. Number insulin irregularities will be registered on the Insulclock device and data will be retrieved during each clinic visit.

For treatment satisfaction, subjects' responses to questions 1, 7 and 8 of the DTSQc will be used. A comparison of the score on the DTSQs from week 12 to week 24 as well as using the score on the other questions of the DTSQc, which would overcome the ceiling limitation of using the DTSQs by itself, will also be used to assess treatment satisfaction [16,17]. The Diabetes Treatment Satisfaction Questionnaire Status (DTSQs) form will be administered at weeks 0, 12 and 24.

Questionnaires will be given at week 0 for standardization purposes. The amplitude of the score on the DTSQc gives the degree of change in satisfaction while the direction (positive or negative) will provide guidance on the preference of one device over the other (i.e., if we predict that patients greatly prefer alarm reminders over nothing and he/she started the group 1 with daily reminders then transitioned to group 2 without the daily reminders, his/her score would be '-3', whereas if he/she was initially not getting the daily reminders followed by the daily reminders then the score would be '+3').

Quality of life will be assessed at baseline and again at weeks 12 and 24 in order to determine the impact of the type of therapy on this outcome. Patients will be given the Diabetes Quality of Life Clinical Trial Questionnaire-Revised (DQLCTQ-R), the Problem Areas In Diabetes scale (PAID) and the Elderly Diabetes Burden Scale (EDBS) at baseline, weeks 12 and 24 to assess their quality of life and any potential impact of the treatment regimen [45-47].

Glycemic Control will be assessed via HbA1c at weeks -1, 12 and 24 and via fasting blood glucose averages at weeks 0, 12 and 24 from point of care testing during the preceding week.

Duration of study
The duration of this study will include a 26-week treatment phase and a safety clinic or telephone follow-up visit at week 28.

Interim analysis
There will be no planned interim analysis of the data.

Selection of Patients
Number of subjects planned. The total number of patients with T2D to be included in this pilot study is 150. We anticipate a dropout rate of 10% - 20% through week 24 so that each arm will have 32 subjects at week 32.

Inclusion criteria:
Subjects meeting all the following criteria will be considered for enrollment into the study:
1. Age: 18 to 80 years
2. Diagnosis of T2D
3. Screening HbA1c ≥ 7.0% to ≤ 12.0%
4. Continuous treatment with one or more oral antidiabetic agents, for at least 2 months and/or
5. Continuous treatment with daily basal insulin (NPH, glargine U100 or detemir), for at least 2 months, (insulin dose ≤0.5U/Kg/day).
6. If patients are on combination therapy of basal insulin and GLP1-RA, the dose of GLP-1 RA should be stable for the past three months.
7. Owns a smartphone compatible with the device
8. Signed, informed consent and HIPAA documentation
9. Subjects' ability to self-administer insulin, use the device and complete subject reported outcomes instruments
10. Subjects' ability & willingness to adhere to and be compliant with study protocol

Exclusion criteria
1. Refusal or inability to give informed consent to participate in the study
2. Subject is currently taking or was treated with glargine U300 insulin, degludec, insulin dose greater than 0.5 U/kg/day during the previous three months
3. Subject treated with prandial insulin during the previous three months
4. Impaired renal function as shown by, but not limited to, eGFR < 30 ml/min.
5. Muscle weakness or hemiparesis related to previous stroke or myelopathy resulting in incoordination, muscle weakness and inability to use pen device for insulin administration
6. History of diabetic ketoacidosis during the previous 6 months
7. Clinical evidence of active liver disease, or serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) 3 times the upper limit of the normal range
8. History of hypoglycemia unawareness
9. Pregnancy or lactation
10. Known hypersensitivity to insulin glargine or any of the components
11. Any malignancy within the last 5 years, except for adequately treated basal or squamous cell carcinoma of the skin or adequately treated cervical carcinoma in situ
12. Current drug addiction or current alcohol abuse, or history of substance or alcohol abuse within the last 2 years
13. Diagnosis of dementia
14. Severe gastrointestinal diseases including gastroparesis
15. Cardiac status NYHA III-IV
16. Acute infection
17. Patients on or planning to receive long term oral or injectable steroid treatment for greater than 10 days
18. Patient schedule to undergo general surgery during the next 6 months
19. Any disease or condition that in the opinion of the investigator and/or sponsor may interfere with the completion of the study

Potential Risks to the Subjects:
There are no major risks associated with the intervention.

Hypoglycemia. It is possible that following the proposed protocol, patients receiving basal glargine and metformin may develop hypoglycemia. For this analysis, **symptomatic hypoglycemia** is defined as an event with typical symptoms (i.e., sweating, palpitation, and feeling of hunger) with or without confirmation by plasma glucose <54 mg/dl (3.9 mmol/L).

Severe hypoglycemia is defined as episodes necessitating assistance and associated with measured plasma glucose < 40 mg/dl (2.2 mmol/L) or with prompt recovery after administration of carbohydrates, glucagon, or other resuscitative actions.

Protection against Risks:

We will follow safeguards to minimize the risk to our subjects: a) we will carefully monitor response to medical treatment every 2 weeks by telephone contact and during clinic visits, b) women of reproductive age who are sexually active will undergo a urine pregnancy tests prior to participation in the study, c) female subjects whom are pregnant, breast-feeding, or not willing to use appropriate contraception at time of enrollment will not be included in the study, d) patients with significant comorbidities such as chronic kidney disease > stage III, liver cirrhosis, gastroparesis, and pancreatic disorders will be excluded from the study.

Patients will receive diabetes education prior to discharge and will be instructed on hypoglycemia sign/symptoms and treatment. Patients will be asked to call the diabetes center and/or PCP in the event of hypoglycemia. If a patient develops hypoglycemia, the dose of insulin will be reduced (see treatment algorithm).

Statistical Analysis:

This pilot study will compare treatment irregularities (insulin omission, mistiming and dosing) between Insulclock versus conventional insulin injection pen device. We will also compare differences in glycemic control, as measured by change in mean HbA1c from baseline, number of hypoglycemic events, percentage of subjects maintaining therapy, 7-point SMBG profile, fasting plasma (FPG) profile, and HRQoL assessments (Patient reported outcomes) between groups.

Analysis of Primary Endpoint:

The primary outcome of ***treatment adherence*** with the use of Insulclock with feedback or no information (blinded) is whether a patient has a good adherent to the treatment regimen (assessed based on insulin omission, mistiming, and dosing). Given the 2 by 2 cross-over design, the superiority of the Insulclock system over the conventional insulin pen device will be determined by comparing the percent of patients showing a good treatment adherence with Insulclock but a poor treatment adherence with the conventional device to the percent of patients showing a poor treatment adherence with Insulclock but a good treatment adherence with the conventional device. We will perform this comparison based on McNemar's test assuming the period effect is negligible. We will further conduct logistic regression to accommodate potential period effect and adjust for other potential confounders. We will apply standard model selection and model checking procedures (such as the Hosmer-Lemeshow tests) to decide and evaluate the final model. A p value of <0.05 will be considered significant.

Analysis of Secondary Endpoints:

Secondary endpoints in this study include patient satisfaction (assessed by subjects' responses to questions 1, 7 and 8 of the DTSQc), quality of life score, insulin dose, rate of hypoglycemia, number of episodes of severe hyperglycemia and hypoglycemia. For a continuous secondary outcome (e.g. quality of life score), our analysis will be focused on determining whether the outcome difference between period after crossover (i.e. period 2) versus the period before crossover (i.e. period 1) in the Insulclock group is similar to that in the conventional device group. We will perform the analysis based on paired t-tests. Linear mixed models will be conducted to assess the study group difference while accounting for potential confounders. Appropriate transformations may be applied to make data better meet normality assumption. Standard model selection and checking procedures will be applied to determine the final linear models. For binary secondary outcomes, we will follow the analysis plan proposed for the primary endpoint.

Power Considerations

This is a pilot study and we plan to recruit 40 subjects for each study group. Our power calculation is mainly based on the binary primary outcome. We assume no more than 15% attrition rate, and assume no period

effect. In the following table, we give the power for detecting the superiority of Insulclock based on Exact Test for Binomial proportion with alpha=0.05, under different projections for the proportion of subjects showing treatment preference (i.e. adherent under one treatment but not under the other), denoted by P_{tp}, and projections for the probability of preference to Insulclock given showing treatment preference, denoted by p.

	P_{tp}					
Power		90%	80%	70%	60%	50%
p	0.6	31.2%	28.2%	21.5%	17.8%	13.9%
	0.7	87.9%	83.7%	74.9%	66.5%	55.4%
	0.8	>99%	>99%	>99%	97.6%	93.8%
	0.9	>99%	>99%	>99%	>99%	>99%

Regarding the secondary outcomes, the power calculations can be made conservatively based on superiority hypotheses without specifying the equivalent margins. For continuous secondary outcomes, we would have over 80% power to detect outcome difference of 0.41 times the standard deviation based on paired t tests, with alpha=0.05, assuming equal outcome standard deviations for Insulclock and the conventional device, and within subject correlation equal to 0.3.

Data Handing and Record Keeping:

Data collection records with personal identifiers will be stored in locked file cabinets. Presentation of the study results at regional or scientific meetings or in publications will not identify subjects. Access to research and confidential records will be limited to clinical investigators, research coordinators, and the IRB at Emory University.

Ethics:

Informed Consent.

After identification of eligible patients these individuals will be provided basic information regarding the study and, if interested, a member of the research staff using inclusion/exclusion criteria delineated elsewhere in the protocol will enroll patients. Informed consent will be obtained before any trial related procedures including screening procedures. The consent form, potential risks and benefits, and the rights of research participants will be explained to the participant by the investigators or research coordinator. Individuals will be asked if they have questions, and a member of the research staff will answer questions. The principal investigator will also be available always to answer questions that participants may have during the consent procedure or during the time a participant is enrolled in the study. The consent form will be completed in accordance with the IRB guidelines of Emory University. A signed copy of the consent form will be provided to the participant and a copy will be placed in the file that is maintained for each participant in the study office.

Informed consent will follow the procedure of Emory University Institutional Review Board. Every potential participant will be informed in writing and verbally with the important and key points of the study. One of the investigators or research coordinators will obtain a witnessed informed consent prior to inclusion of a patient into the study.

The study will be conducted in accordance with the Declaration of Helsinki and will be conducted in accordance with the ICH GCP guidelines. The sponsor-investigator will comply with all applicable regulatory and legal requirements, ICH GCP guidelines and the Declaration of Helsinki in obtaining and documenting the informed consent.

STUDY SCHEDULE:

FIRST PATIENT IN	**2017 NOVEMBER**
SCREENING	**~200**
RANDOMIZED	**80**
LAST PATIENT RECRUITED	**2018**
LAST PATIENT IN (COMPLETED)	**2018 DECEMBER**
DATA ANALYSIS	**JUNE 2019- FEBRUARY 2019**
SUBMISSION TO CONGRESS OR JOURNAL	**ADA 2020 MAJOR MEDICINE JOURNAL AND/OR DIABETES CARE**

Payment for Participation:

Participation in this study is voluntary. Patients will receive seventy- five dollars ($75, 00) after each clinic visit. Total compensation will be four hundred and fifty dollars ($450).

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