Using an AI-based Voice Assistant to Manage Insulin in Diabetes: a Randomized-Control Trial

NCT05081011

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1. PURPOSE OF THE STUDY

a. Brief Summary

The purpose of this study is twofold:
(1) To evaluate the feasibility of a digital voice assistant to help patients manage insulin-dependent diabetes between routine clinic visits. Specifically, the custom app that we will develop will help patients log their blood sugars and medication use, as well as help them adjust their insulin dose based on a protocol that their physician prescribes.

(2) To evaluate the effects of such an intervention on specific medical outcomes, such as medication adherence, blood sugar control and time to optimal insulin dose, as well as patient self-efficacy measures.

The digital voice assistant used will be an Amazon Echo Dot and it will use a custom application (app) to help patients manage their diabetes at home.

b. Objectives

We hope to learn whether a digital voice assistant can be reliably used by patients at home between clinic visits to improve management of insulin-dependent diabetes. We hope that this improved management will translate into improved medical outcomes. In the future, the findings of this study could serve as a first step towards developing an integrated outpatient solution that leverages voice assistant technology in the patient's home to improve management of multiple chronic medical conditions.

c. Rationale for Research in Humans

The purpose of this study is to test the efficacy of a digital voice assistant in individuals with insulin-dependent diabetes.

2. STUDY PROCEDURES

a. Procedures

Screening:
Our team will recruit patients with uncontrolled type 2 diabetes who are being started on insulin or who are already on insulin and having active adjustments to their dose. To identify patients that may be eligible for recruitment, our team will use STARR's cohort discovery tool to create a report of patients at four Stanford Internal Medicine clinic sites with type 2 diabetes and a recent hemoglobin A1c greater than 8%. Our team will then contact the primary care providers of these patients to ask them if they think their patients would benefit from inclusion in our study. The four Stanford Internal Medicine clinic sites are Stanford Internal Medicine East, Stanford Internal Medicine Los Altos, Stanford Internal Medicine Portola Valley and Stanford Internal Medicine Santa Clara.
Recruitment process: When an eligible candidate is identified per the screening process above, the research team will contact the patient's primary care physician and inform them of this study. If the patient's primary care physician agrees that the patient would benefit from inclusion in this study, they will reach out to the patient and describe the trial to them. If the patient agrees to be contacted by the research team, their care team member will share their information with a member of the research team via secure message and a member of the team will reach out via the participant's preferred method of communication (phone, email, etc). Due to the COVID- 19 pandemic and the fact that diabetes is a risk factor for the virus, all participants will undergo the informed consent process remotely. The research team will make contact with the participant via the mechanism shared with them by the treating team, introduce the project and ask if the participant would like to undergo the informed consent process via an online REDCap survey (screenshots attached) or via a paper consent form sent in the mail. The research team member will then send the Informed Consent Form (ICF) to the participant via either a URL by email or a paper ICF by mail. The research team member will set up a time to discuss the ICF with the participant either by phone or video chat and will describe the study to the participant, review the risks and benefits outlined in the study consent form and address any questions from the participant before asking them for their consent to participate in the study. After consent is obtained, participants will complete an intake survey ("Participant Information Survey") and will be randomized to either the intervention or control group. All participant information obtained during enrollment will be stored securely in a HIPAA-compliant and PHIsafe Stanford Medicine Box folder.

Device setup:
After consent is obtained, the participant's treating physician will communicate their desired insulin protocol with the research team. The information communicated will include the following:
-Starting insulin prescription
-Goal fasting blood sugar
-Titration parameters (e.g. Increase starting dose by 2 units every 3 days if not at goal fasting blood sugar)
-Situations in which they would want their patient to contact their provider or seek immediate medical attention and call 911/report to an ER.

This information will be communicated with the research team via either a custom Epic order set currently in development or a secure online portal developed by the research team. The provider will only have to provide the patient's unique study ID in order to enter this information in the portal. This ID will be securely emailed to the provider upon enrollment of the patient. The provider will be asked to confirm their prescription inputs via the secure online portal to reduce the probability of erroneous data insertion. The provider will also have to confirm the ID of the patient to prevent the provider from erroneously placing a prescription for the wrong patient. No identifying information will be collected by the portal. For participants in the intervention group, this information will be programmed into the digital voice assistant application. For participants in the control group, this information will be recorded for future data analysis.

Intervention group:
Due to the COVID-19 pandemic and the fact that diabetes is a risk factor for the virus, we will mail devices to participants in the intervention group. We will also provide them with the option to set up a phone call or video chat with a member of the research team to help them with device set up.

Device setup will include the following steps:
-Open Alexa Echo Dot package and plug in to power
-Downloading the "Alexa" smartphone application
-Through the Alexa smartphone application, enabling our custom application (called an "Alexa Skill").
-Logging in to our custom application with a unique study ID that is linked to the participant's insulin protocol.

A detailed document called "Alexa Setup Instructions" will be provided to subjects that go into granular detail on how to set up the device as well as its functionalities (screenshots attached).

The entire set up process should take about 5-10 minutes.

Control groups:
For participants in the standard of care control group, we will email them a copy of a blood sugar and medication administration log for them to fill out electronically through REDCap or print and fill out ("Blood Sugar Log"). If a participant doesn't have access to a printer, we will mail them a copy of the log.

As an additional control, a subset of patients receiving the voice assistant device will also be given a blood sugar and medication administration log and will be asked to use both the voice assistant and the blood sugar and medication administration log for 2 of the 8 weeks they are participating in the trial ("Blood Sugar Log - 2 weeks only")

Data collection:

Data will be collected daily from participants in the intervention and control groups of the study. Participants in the intervention group will be able to interact with our custom app by speaking with their Echo Dot. Participants will be instructed to "check in" with the app once daily at which point the app will collect information about recently checked blood sugars and recent administration of insulin. Data collected by the device will be read back to the patient for confirmation. At the end of the check in, the app will remind patients about the details of their insulin regimen. Based on the patient's self-reported data, this reminder might include a prompt to change the dose of their insulin. All reminders and prompts will be strictly based on the physician-prescribed insulin protocol at the beginning of the study, and prompts will include a summarization of the rationale behind the recommendation (e.g. "Your fasting blood sugars are still above goal. Based on your prescribed treatment plan, you should increase your dose of Lantus to 17 units."). No automated decisions will be made by the voice assistant. The voice assistant will only be assisting the patient with instructions that patients are normally given in writing by their provider.

An instruction manual will be provided to the patient with details on how to interact with the device ("Alexa Setup Instructions"). The only data collected from the patient will be patient-reported blood sugar data and medication administration occurrences. The audio data collected by the device is encrypted and sent to the Amazon cloud for processing into relevant text. The text data is supplied to our application for analysis and storage. Our application will not receive or store any audio data. No protected health information will be collected by our app. All data will be de-identified and stored in the Amazon Web Services cloud. All data will be linked to a participant's unique study ID. A document linking a participant's unique ID to their name and medical record number will be stored on the secure PHI-safe Stanford Medicine Box server.

Patients in the control group will use their provided log, labeled with their unique study ID, to record their daily blood glucose checks and insulin adherence. This is part of the standard of care in patients with insulin-dependent diabetes. At the end of the trial period, we will collect this log from patients for data analysis. Participants can choose to securely email or upload this log to the research team through REDCap, or if they prefer, they will be provided with a pre-paid envelope to mail the log free of cost.

Finally, user satisfaction survey data will be collected at the beginning and end of the study from patients in the intervention and control groups. The first survey will include "Problem Areas in Diabetes" ("PAID") questions validated in the literature as a rapid screen for diabetes-related emotional distress (https://pubmed.ncbi.nlm.nih.gov/19841892/). This survey is labeled "Diabetes Attitudes (PAID) Survey" (screenshots attached). The second survey will include questions specifically tailored towards interrogating the patient's attitude toward and comfort with insulin dose adjustments ("Medication Adherence Survey"). The third and final survey will include questions on attitudes towards healthcare technology ("Health Technology Survey"). All surveys will be collected online via REDCap.

Data analysis:
Members of the research team will review the collected blood sugar and insulin administration data for analysis. Specifically, we will analyze the collected blood sugar data to determine how often blood sugars were checked and how well-controlled they were. We will also analyze insulin administration data to determine how adherent participants were to their prescribed regimen and how effectively participants were able to titrate their insulin to an effective dose. We will also analyze study survey data to assess participant's diabetes selfefficacy and attitudes towards healthcare technology.

In addition to reviewing data collected by our app and REDCap, the research team will also access the medical record of participants who have completed the trial to obtain certain lab results and medication data to help supplement any missing data from the trial. Specifically, the research team will obtain recent blood sugar and Hemoglobin A1c values, as well as the most recent insulin prescription. This will help the research team perform data analysis in cases where trial data are incomplete. Please note that this is only for participants who have been consented, enrolled and have completed the full 8 weeks of the trial.

If participants decide to withdraw from the study, they can do so at any time by contacting Ashwin Nayak at 650-308-8062 or aknayak@stanford.edu. After study completion, participants will be able to keep their Amazon Echo device for personal use. Their specific login ID will be disabled which will preclude them from using our custom application after study completion. If participants decide to withdraw from the study before completion, they will be asked to return their Amazon Echo device. They will be provided with pre-paid packaging to do so.

Infection control strategies implemented to ensure the safety of the research staff/faculty who will come to campus and to mitigate risks to them and their families:
1. Personnel are trained on the need to stay home and get tested if they have a new cough, fever, difficulty breathing, chills, muscle pain, headache, sore throat, recent loss of taste or smell.
2. All research staff/faculty will follow Stanford's social distancing protocol, which includes:
    a. Maintaining physical distancing.
    b. Use of face coverings and eye protection.
    c. Frequent handwashing and use of hand sanitizer.
3. Researchers and support staff returning to campus will be required to use the Health Check tool to report health status each day.
4. There will be no participant-facing research staff as the informed consent and patient enrollment process will be conducted virtually.
Infection control strategies implemented to ensure the safety of the research participants:
1. All devices will be cleaned prior to being mailed to the participant.
2. Participants will perform self-setup of their device to avoid the need for an in-person visit with research staff.

b. Procedure Risks

This study poses minimal risk to its participants. Patients in the control group will receive standard of care management of insulin-dependent diabetes. Patients in the intervention arm will not be subject to any risky treatments. They will be interacting with a digital tool that will collect information and remind them of their physician-prescribed treatment plan. The digital tool will not make any autonomous medical decisions or alter the physician's plan in any way. All data collected by the digital tool is anonymized. The voice assistant device will confirm the patient's self-reported data with readback to the subject and verbal confirmation by the subject, prior to storing the data. If a blood sugar reading is outside a standard safe range as determined by their physician, the voice assistant device will provide them the same instructions that would be provided on written instructions by their provider. For example, if a patient's reported blood sugar is less than 70, the voice assistant may notify the subject that their doctor has instructed at such blood sugars to consume something sweet and recheck their sugar. If a patient's reported blood sugar is greater than 350, the voice assistant may notify the patient that their doctor has instructed at such blood sugars to notify a medical professional immediately. If a patient's sugars are dangerously hypoglycemic or dangerously hyperglycemic as determined by their provider, the device will inform the patient to seek medical attention immediately and report to an ER/call 911 per their provider's instructions.

c. Use of Deception in the Study

No deception strategy will be used in this study.

d. Use of Audio and Video Recordings

Amazon Echo devices (and all similar voice assistant technologies) record audio during user interactions. This audio data is encrypted and sent to the Amazon cloud for processing into relevant text. The text data is supplied to our application for analysis and storage. Our application will not receive or store any audio data. All audio data collected by Amazon Echo devices are visible in the Alexa app for users to see and delete. Furthermore, Amazon explicitly states that its devices do not record audio data when users are not interacting with its devices. Whenever an Amazon Echo device is recording audio data, a special indicator light will turn on to alert the user. These details will be included in the informed consent process and patients will be instructed on how to delete audio recordings in their Amazon privacy settings if desired.

e. Alternative Procedures or Courses of Treatment

There are no other alternative procedures for collecting data from a digital voice assistant in a patient's home. No standard treatments will be withheld from participants. The alternative is not to participate in the study.

f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

Yes.

g. Study Endpoint(s)

We will be evaluating the end points every 2 weeks for 8 weeks. The clinical end points we will be monitoring are blood sugars obtained through standard of care treatment. The study will not be terminated early for any foreseeable reason. The study will end after two months of data collection per patient. During the two months of data collection, the treating physician will be able to make changes to the patient's insulin regimen at any time but logging into our secure research portal. These changes will be reflected instantly in our Alexa application.

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

There is a large amount of literature showing how digital health interventions can lead to improved clinical outcomes. In the area of voice assistant for use in diabetes care management, studies have shown that interactive voice responses through voice recognition software have the potential to improve medication and lifestyle modification adherence in diabetes and improve clinical outcomes. For example, in a randomized control trial of adults with diabetes, patients who received automated, interactive phone-delivered management interventions had greater decreases in hemoglobin A1c compared to standard of care (BMC Public Health 12 (2012), 602). Another randomized crossover study reported on a smartphone application that can synthesize verbal descriptions of meals and accurately return the corresponding insulin bolus dose (J Diabetes 10 (2018), 600-608). A similar voice-activated device was identified in calculating insulin dosages in the visually impaired with diabetic retinopathy (2011 24th Canadian Conference on Electrical and Computer Engineering (CCECE), 2011, pp. 000904- 000907.)

Ultimately, no study has yet embarked on what this study looks to investigate; however, a review of key leading opinions from clinical, engineering, and data security experts have identified smart devices, voice assistants and the Internet of medical things (IoMT) as a key untapped area of potential for optimizing the home health care ecosystem to reduce diabetic complications, including diabetic foot ulcers (Journal of diabetes science and technology 12 (2018), 577-586).

b. Findings from Past Animal Experiments

N/A

4. DEVICES USED IN THE STUDY

a. Investigational Devices (Including Commercial Devices Used Off-Label)

Investigational Device 1	
Name:	Echo Dot
Description:	Voice assistant
Significant Risk?	Non-significant risk
Rationale for Non-Significant Risk	This is a non-significant risk device because it doesn't pose a serious risk to health, safety or welfare of the subject. Its use is not of substantial importance in diagnosing, curing or treating disease.

Investigational Device 2	
Name:	**Insulin titration algorithm**
Description:	Insulin titration protocol algorithm
Significant Risk?	Non-significant risk
Rationale for Non-Significant Risk	PCPs routinely provide patients with instructions on how to titrate their insulin at home. This algorithm helps patients implement these instructions (which is something they would otherwise be doing with no assistance). We do not believe that the software is more dangerous than standard of care, and is hopefully safer for a few reasons: 1) The provider will be able to set a limit to how much and how often the algorithm will increase the insulin dose. 2) The provider will be able to set a maximum insulin dose. 3) The default insulin titration protocol that we provide mirrors the 2020 consensus statement from AACE (American Association of Clinical Endocrinologists) and ACE (American College of Endocrinology) guidelines (https://pro.aace.com/pdfs/diabetes/algorithm-exec-summary.pdf), but is more conservative to have less tolerance for hypoglycemic events 4) In partnership with Endocrinologists and as Internists ourselves, we have a well thought out, professional guideline-based, conservative hypoglycemia protocol that reduces insulin dose and automatically turns off the titration algorithm if needed to account for various clinical situations where hypoglycemia may be present. The protocol is also designed to account for when providers may have erroneously started too high an insulin dose. Please see our hypoglycemia protocol attached in section 16 for details. 5.) There are multiple steps for confirmation when reporting data to ensure correct data acquisition, including reminders with every single check in that a "fasting blood sugar" is one where one has not had anything to eat in the 8 hours prior

b. IDE-Exempt Devices

N/A

5. DRUGS, BIOLOGICS, REAGENTS, OR CHEMICALS USED IN THE STUDY

N/A

6. PARTICIPANT POPULATION

a. Planned Enrollment

(i) 50 participants
(ii) 50 participants
(iii) Patients at Stanford Internal Medicine Clinics with a diagnosis of Type 2 Diabetes who are clinically indicated to initiate or increase their long acting insulin.

b. Age, Gender, and Ethnic Background

The age range of this study is 18 years of age or older. There are no conditions on the gender or ethnicity of the participant. Male and female participants are going to be enrolled and we aspire to keep an appropriate demographic distribution.

c. Vulnerable Populations

No vulnerable populations will be targeted in this study.

d. Rationale for Exclusion of Certain Populations

Children will not be included in the study because the Internal Medicine team involved specialises in adult care.

e. Stanford Populations

N/A

f. Healthy Volunteers

None

g. Recruitment Details

Our team will recruit patients with type 2 diabetes who have been recently started on insulin (or who are having active adjustments to their insulin regimen). To identify patients that may be eligible for recruitment, our team will use Stanford's STARR cohort discovery tool and an Epic workbench report overseen by Dr. Anu Phadke, the Stanford Population Health Medical Director, and Jimmy Dang, the Stanford Population Health Quality manager. We will use these tools to create a report of patients at Stanford Internal Medicine and Endocrinology clinics with type 2 diabetes and a recent hemoglobin A1c greater than 8%. Specifically, this is done through a cohort discovery of patients who have seen providers who practice at the Stanford primary care and Endocrinology clinic sites. In addition, we will also be identifying patients through advertisements through the Stanford Diabetes Research Core (https://sdrc.stanford.edu/sdrc-research-cores/dctc/home). Specifically, the recruitment director with the core, Dr. Christopher Gardner, will be giving us access to a listserv of Stanford-affiliated patients who have requested to be contacted about diabetes-related clinical trial opportunities.

For potential participants identified through STARR or Epic workbench reports, our team will first contact the primary care providers and/or Endocrinologists of these patients (depending on which providers are managing or co-managing the patient's diabetes regimen). If the primary care providers and/or Endocrinologists agree that their patient might benefit from inclusion in our study, a member of the patient's care team will first contact the patient to notify them of the study and obtain approval for initiation of the research team's enrollment process. Upon approval, our research team will reach out to provide more information and conduct the informed consent process if the patient would like to participate.

For potential participants identified through Dr. Christopher Gardner's listserv, if these participants directly respond to our listserv advertisement, our research team will reply back to them directly. Our team will also contact their primary care providers and/or endocrinologists if the potential participant decides to enroll in the trial.

h. Eligibility Criteria

i. Inclusion Criteria

We will include patients who are 18 years of age or older with a diagnosis of Type 2 Diabetes with need for initiation or increase of a long-acting insulin regimen.

ii. Exclusion Criteria

We will exclude patients who:
- are 17 years of age or younger
- are on insulin pumps
- have impaired decision-making capacity
- do not speak English
- do not own a smartphone or have access to a WiFi network at home (due to the technological requirements of the device and application)

i. Screening Procedures

As stated above, our team will screen patients by creating a STARR report of patients at Stanford Internal Medicine clinics with type 2 diabetes and a recent hemoglobin A1c greater than 8%. Our team will then reach out to the primary care providers of these patients to identify patients who are candidates for starting long acting insulin, or who are already on long acting insulin but having active adjustments to their regimen.

j. Participation in Multiple Protocols

During the enrollment process, we will ask patients if they are involved in other studies. We don't anticipate there being conflicts but if there are co-enrollments we will look into complications.

k. Payments to Participants

Participants in the intervention arm will not be paid but they will be allowed to keep the Amazon Echo Dot after their involvement in the study concludes. At the conclusion of the study, participants in the control arm will also be given an Amazon Echo Dot for compensation.

l. Costs to Participants

None

m. Planned Duration of the Study

The probable duration of the entire study is 18 months.
(i) One month
(ii) Two months per participant
(iii) Up to 15 months

7. RISKS

a. Potential Risks

i. Investigational devices

As stated earlier, instructions to patients to change their insulin dose will always strictly adhere to the physician-prescribed insulin protocol. However, if the patient inaccurately self-reports blood glucose data, dose adjustments based on this data can cause medical complications. To minimize the risk of this, the application will ask the patient to confirm

self-reported data, and when the instructed intervention is read back, the device will again summarize the patient's self-reported data and be clear that the intervention is based on the data provided by the patient and is as instructed by the patient's provider (e.g. "Based on your reported fasting blood sugar of 182 this morning, your doctor has instructed you to increase your insulin glargine to 17 units tonight up from 15 units yesterday."). Furthermore, all dose adjustments will be small, making them very unlikely to cause major adverse events such as hypoglycemia.

ii. Investigational drugs

None

iii. Commercially available drugs, biologics, reagents or chemicals

None

iv. Procedures

No investigational procedures will be performed.

v. Radioisotopes/radiation-producing machines

None

vi. Physical well-being

vii. Risks of participating in this study include the possibility of inaccurate self-reporting by participants leadingto improper insulin dose adjustments. As stated above, our application will confirm all self-reported dataprior to logging it by reading back reported values to patients and requiring verbal confirmation from thepatient. Furthermore, all dose adjustments will be small (ranging from 2-4 units based on the participant'sprescription). Such small dose adjustments to long-acting insulin are very unlikely to cause major adverseevents such as hypoglycemia.Psychological well-being

No risk to psychological well-being. We hope that the intervention group psychologically benefits from increased engagement in their health. Furthermore, our application will provide patients with positive messages of encouragement.

viii. Economic well-being

No risk to economic well-being.

ix. Social well-being

No risk to social well-being.

x. Overall evaluation of risk

Low

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b. International Research Risk Procedures

N/A

c. Procedures to Minimize Risk

As stated earlier, all prompts delivered by the application will be strictly based on the patient's physician's care plan.

d. Study Conclusion

The experiment will terminate after two months of data collection per patient.

e. Data Safety Monitoring Plan (DSMC)

i. Data and/or events subject to review

N/A

ii. Person(s) responsible for Data and Safety Monitoring

N/A

iii. Frequency of DSMB meetings

N/A

iv. Specific triggers or stopping rules

N/A

v. DSMB Reporting

N/A

vi. Will the Protocol Director be the only monitoring entity? (Y/N)

Yes

8. BENEFITS

PHI will only be collected once during enrollment, which includes an entry survey on REDCap (screenshots attached). The least amount of information will be obtained to accomplish the purpose of the research. This data will be stored securely in a folder on the HIPAA-compliant Stanford Medicine Box. A unique study ID will be randomly generated for each patient (not derived from any identifiable information). This ID will be used with our application and will be linked with the self-reported patient data that we collect using the Amazon Echo Dot. No PHI will be collected or stored by our application on the Amazon Echo Dot.

9. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.