PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR

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PROTOCOL TITLE

DRIVE Program: **D**iabetes **R**emote **I**ntervention to impro**V**e use of **E**vidence-based medications

FUNDING

Novo Nordisk, Inc.

VERSION DATE

November 9, 2021

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

The aim of this program to:

1.) Create a remote, or "virtual" diabetes management platform to improve adherence to new guidelines regarding use of glucose-lowering medications with cardiovascular and renal benefit for patients with type 2 diabetes and high cardiovascular and/or renal risk.

2.) Increase patient disease knowledge, activation, and engagement.

3.) Evaluate optimal timing of patient education within the program.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Patients with type 2 diabetes mellitus are at markedly increased risk of cardiovascular disease when compared to patients without diabetes. SGLT2 inhibitors (SGLT2i) and GLP1 receptor agonists (GLP1-RA) are glucose-lowering medications that have also demonstrated improved cardiovascular and renal outcomes in patients with cardiovascular disease, at high risk for cardiovascular disease, and with chronic kidney disease (CKD). However, to date, there has been slow clinical uptake of these medications, even in patients at high cardiovascular and renal risk. Utilizing a navigator-driven approach with a collaborative practice agreement-based clinical algorithm will allow for a cost-effective and scalable approach to medication optimization in patients with diabetes and cardiovascular disease, increased risk of cardiovascular disease, and/or CKD.

A navigator-driven, pharmacist led, remote disease management approach has been shown to be efficient and effective in patients who suffer from hypertension, hyperlipidemia, and heart failure (HF) with reduced ejection fraction within multiple MGB settings. To date, we have enrolled almost 10,000 MGB patients into our programs over the past 4 years. The goal of the proposed program is to expand to patients with diabetes who are at increased risk of poor clinical outcomes. The overarching goal of these programs is to partner with and support primary care physicians to help overcome the well-recognized therapeutic inertia that often delays adoption of new evidence-based therapy and prevents patients from achieving recommended care targets. Our programs utilize collaborative drug therapy management (CDTM) agreements, statutory legislation that allows pharmacists to start, titrate, and optimize therapy when using treatment algorithms designed by physicians. These CDTM agreements are approved by the BWH Pharmacy and Therapeutics Committee.

In this project, we will use a CDTM agreement to allow a pharmacist, in collaboration with a patient navigator, to initiate, discontinue, and titrate SGLT2i, GLP1-RA, and other diabetes medications based on an algorithm developed by physicians.

Importantly, medication selection in this program is guided by shared decision-making. In this project, the patient will decide whether to start a new medication and which medication to start if there is equipoise between medications. Patients are not “assigned” to take a medication in any of the navigator-CDTM interventions.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, “Enrollment at Partners will be limited to adults although the sponsor’s protocol is open to both children and adults.”

Eligible patients will be identified prospectively utilizing a search paradigm previously described in Phase 1 of this project (Reference Protocol 2020E000255). Eligible patients will be selected from several sources, including the EHR and the Digital Care Transformation (DCT) cohorts, which are groups of patients who previously participated or are currently participating in medication titration for management of hypertension, hyperlipidemia, and HF with reduced ejection fraction. These patients will be screened for eligibility for inclusion in this program.

Inclusion Criteria: Patient is eligible if they meet ALL the following criteria.

- Type 2 diabetes currently on, or intolerant to, metformin (treated with diet, DPP4 inhibitor, sulfonylurea, pioglitazone, glinides, and/or basal insulin);
- Age 27-79 years;
- Hemoglobin A1c (HbA1c) 6.5-8.9% at the time of screening;
    - Participants whose baseline HbA1c after enrollment is 5.7-6.4% or 9.0-9.9% will remain in the program.
- At elevated cardiovascular and/or renal risk defined as any atherosclerotic cardiovascular disease (ASCVD)[1], estimated ASCVD risk ≥10%, HF, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2, urine albumin-to-creatinine ratio greater than 300 mg/g, or non-alcoholic fatty liver disease, and those aged 60 years or older with at least two of: tobacco use, dyslipidemia, hypertension, or abdominal obesity.

Exclusion Criteria: Patient is ineligible if they meet any ONE of the following criteria.

- Type 1 diabetes, type 3c diabetes (pancreatogenous), maturity onset diabetes of the young (MODY)
- Currently prescribed an SGLT2i or GLP1-RA;
- Currently prescribed basal and bolus insulin;
- History of diabetic ketoacidosis (DKA)
- History of hypoglycemia[2];
- Frequent hypoglycemia (as defined as >2 episodes in 1 week)[2], OR
- Prior liquid or solid organ transplant
- Limited life expectancy, difficulty managing one's medications, or any competing medical condition that, in the opinion of the investigator would diminish their ability to participate in the trial (i.e., active malignancy)
- Pregnancy, breastfeeding, or without adequate birth control utilization
- eGFR below 15 ml/min/m^2
- eGFR below 30 ml/min/m^2 with a history of pancreatitis

[1] ASCVD for this project is defined as history of myocardial infarction, angina, unstable angina, coronary revascularization, percutaneous coronary intervention, transient ischemic attack (TIA) stroke, peripheral artery disease, carotid artery disease (>50% luminal obstruction)
[2] Hypoglycemia for this project is defined as a blood sugar < 70 mg/dL

Patients recruited into the program will enter either 1) a gradual education period for 2 months followed by pharmacist and navigator-based medication titration, or 2) rapid education in conjunction with pharmacist and navigator-based medication titration via a Collaborative Drug Therapy Management (CDTM) algorithm designed to improve medical therapy for the treatment of type 2 diabetes with cardiorenal comorbidities. The CDTM will be approved by the BWH Pharmacy and Therapeutics committee. We will use A/B testing to optimize the timing of the educational program. Outcomes will include percentage of patients prescribed SGLT2i or GLP1-RA, percentage of prescriptions filled, HbA1c, change in the diabetes treatment satisfaction questionnaire short (DTSQs) score, and Patient Activation Measure (PAM) at enrollment and completion of the program.

Participants whose HbA1c rises to 9.0-9.9% following enrollment as part of their program baseline labs will automatically be assigned to immediate pharmacist and navigator-based medical titration and rapid education. As a result, participants with baseline HbA1c between 9.0-9.9% will remain in the program but will not be part of the A/B testing.

We will generate prototype software to guide DM medication changes based on patient-specific information and to longitudinally monitor each participant's progress through the algorithm and document

clinical and laboratory information. Basic patient demographic, laboratory, medication, and medical history data will be housed in a secure platform database for clinical management and communication.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

Potential participants will be screened for eligibility through CardioCompass – an application housing medical data currently in use at DCT – as well as the EHR as described in protocol 2020E000255. If eligible, the patients will be contacted by navigators trained to describe the study procedures, who will ask them whether they would be willing to participate.

Participants who agree to participate will enter either early pharmacist and navigator-led medical titration and concurrent education, or a gradual titration, through which patients will undergo 2 months of diabetes self-management education followed by pharmacist and navigator-led program of medication optimization. Navigators will contact the patient at regular intervals and monitor symptoms and laboratory tests will be obtained per protocol to ensure safety of the prescribed medications. Any symptoms will be evaluated by the program nurse practitioner or physician and managed per standard of care.

The education program for all patients will follow standard diabetes self-management education curricula, focusing on medication adherence, the role and benefit of medical therapy for the treatment of type 2 diabetes, and other self-management behaviors. We will offer written materials of current guideline recommendations and an online web portal with short educational videos about diabetes, cardiovascular risk, and lifestyle and medical interventions. Educational videos produced by study staff will be made available to participants through the Mytonomy (www.mytonomy.com) web-based portal. In addition, materials from https://knowdiabetesbyheart.org/ – a collaboration between the American Heart Association and the American Diabetes Association – will be shared with patients virtually. We will also offer live webinar, question/answer sessions for patients and providers to gain education and ask questions regarding the medications and program.

Once each participant has been followed for six months, the intervention will conclude with formal written handoff to the patient's primary care provider (PCP), and the ongoing monitoring of labs, disease management, health care utilization, health outcomes, and medications will continue beyond the program period as per the patient's PCP.

If an enrolled participant decides that they no longer want to take the medication prescribed within the program, they will be asked whether they can be contacted one final time to answer a few questions about their current health and the program. This contact would take place at the same time they would have completed the program had they remained on the prescribed medication.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

Current standard of care at Mass General Brigham (MGB) includes an individual's PCP, endocrinologist, nephrologist, or cardiologist being aware of the available treatment options, the benefits of the medications as demonstrated by medical research, recognizing the patient's eligibility for the medication, the risks and benefits of utilizing and not utilizing the medication, prescribing the medication, and following up laboratory and symptoms to assess for efficacy and further medication titration.

Our innovation creates an organized, protocolized manner in which to screen patients, determine eligibility for medication initiation, and educate, prescribe, and monitor the effects of these medications over the initiation period, when education, monitoring, and titration are required.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

Risks are minimized with pharmacist and physician oversight, a rigorous medication prescription and monitoring protocol, and frequent patient engagement, contact, and laboratory monitoring. Moreover, all medications in this program are FDA-approved and being used according to the prescribing instructions and guidelines.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

The program requires that particular prescriptions and titrations be accompanied by an appropriately timed laboratory test. In parallel with the laboratory draws, navigators will routinely ask participants to report potential adverse events. Program pharmacists carry out all prescribing decisions per standardized protocol, and physicians oversee the process and are available for consultation on any patient as needed. All dosing information as well as reported medication side effects and/or intolerances will be entered into the EHR. Moreover, all medications in this program are FDA-approved and being used according the prescribing instructions and guidelines.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

All digital health technologies containing participant data will be secure according to MGB standards. Patient-identifying data will be accessible only to those assigned to the protocol who require this data to ensure patient safety. All health information is stored on MGB encrypted computers.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

Clinical trials have demonstrated that SGLT2i and GLP1-RA can improve cardiovascular and renal outcomes. The EMPA-REG OUTCOME, DECLARE-TIMI 58, CANVAS, and VERTIS-CV trials demonstrated, in aggregate, a reduction in mortality, major adverse cardiovascular events, HF events, and renal adverse events for patients with type 2 diabetes and ASCVD and CKD (1, 2, 3, 4). The LEADER,

EXSCEL, Harmony Outcomes, and REWIND trials, in aggregate, similarly demonstrated a reduction in mortality and major adverse cardiovascular events for patients with type 2 diabetes and ASCVD (5, 6, 7, 8). With these benefits, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD), American College of Cardiology (ACC), and Kidney Disease: Improving Global Outcomes (KDIGO) guidelines have recommended these two classes of medication for patients with ASCVD, HF, or CKD (9, 10, 11, 12, 13). Registries, however, have found low utilization of these classes of medications, including in the MGB health system (14, 15).

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

The study population will be drawn from the EHR and/or the BWH Innovation database of patients, and eligible patients will be consecutively contacted for potential participation with no bias. We will focus on enrolling patients at high cardiovascular and renal risk (based on the presence of ASCVD, high ASCVD risk score, and/or a known diagnosis of HF or CKD) in whom these medications have FDA indication and the support of society guidelines for their use.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

Our navigators are fluent in English. For patients who do not speak English, MGB's interpreter services will be used for both the initial enrollment call and all future verbal communications. A written consent form will not be used, as detailed in the Consent Procedures section.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Non-English-Speaking-Subjects.pdf

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

- The study population will be recruited through both A) an algorithm designed specifically for this protocol that identifies eligible patients within the MGB EHR and B) the existing BWH Innovation cohort defined earlier.

- Through email or the Epic in-basket, the navigator will notify each potential participant's PCP of their patient's eligibility and the program details. The PCP can choose to tell the study team not to contact their patient.
- The navigator will then send a Patient Gateway or email message to the patient informing them of the program details, requesting they take a brief Intake Survey, and notifying them that they will contact them by phone if they do not opt out.
    - Prior to sending program information via an email message, the navigator will first send the IRB-approved Email Consent email message.
- Lastly, the navigator will call the patient.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

Participants will not be paid or receive any type of remuneration / compensation for their time and expenses. Participants will pay for laboratory draws in accordance with their personal health insurance plans.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Recruitment-Of-Research-Subjects.pdf

Guidelines for Advertisements for Recruiting Subjects
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Guidelines-for-Advertisements.pdf

Remuneration for Research Subjects
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Remuneration-for-Research-Subjects.pdf

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Potential participants will be notified by letter or Patient Gateway message that they will soon receive a call from a navigator about possible enrollment into the program.

The navigator will review the program details with the participant over the phone. The participant can agree to participate during this initial phone call but will also be given the opportunity to ask questions, review written materials, and/or separately speak to their PCP prior to enrollment. There is no time

constraint within which the patient must agree to participate. However, enrollment will be capped at the first 200 patients who agree to participate. The patient's decision to participate or not to participate in this program will be documented in the EHR. The patient will be informed that the decision to participate or not will not affect the care they receive from other providers.

As this project is using FDA-approved medications prescribed according to guideline recommendations and therefore the primary risk to subjects is no more than minimal and no different from standard of care, the study will be conducted with a waiver of consent/authorization.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects:
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Informed-Consent-of-Research-Subjects.pdf

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

The study team will review laboratory results and potential adverse event data, as needed, within 3 weeks of initiation or titration, and for the period the program is responsible for the medication and until diabetes care is handed back to his/her PCP. Participants will also be encouraged and asked to report any side effects that they experience while in the program. The principal investigator will determine whether the research should be altered or stopped.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

Clinical outcomes will be monitored periodically as per standard of care with regular and appropriate laboratory and clinically reported events. For those taking SGLT2i, we expect DKA ~0.2%, hypoglycemia ~3%, UTI, and/or mycotic infections at a rate of ~6% and will prospectively collect and monitor clinical data related to this program. We will also review the EHR for hospitalizations. GLP1-RA are known to cause gastrointestinal side effects in ~20% of users; these are mitigated by slow titration. More serious AEs such as gallbladder events are rarer and occur at a frequency lower than may be observed in a sample of this size. The details of the management protocol, including monitoring for safety, will be based on existing guidelines. This will be submitted separately to the P&T committee. HbA1c will be checked at 3 and 6 months after the initiation of therapy per ADA guidelines for usual care after diabetes medication change.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

The study data will be monitored regularly by the principal investigator and clinical leads, supported by data analysts for quality assurance.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/DSMP-in-Human-Subjects-Research.pdf

Reporting Unanticipated Problems (including Adverse Events)
https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Reporting-Unanticipated-Problems-including-Adverse-Events.pdf

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data;

use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

All digital health technologies containing participant data will be secure according to MGB standards. Patient-identifying data will be accessible only to those assigned to the protocol who require these data to ensure patient safety. All health information is stored on MGB encrypted computers.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

Identifiable information will not be shared with persons or entities outside of MGB. Research collaborators will be provided with high-level tables that do not include any patient identifiable information.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

No specimens or data will be stored at collaborating sites outside of MGB for future use.

Participants can withdraw their participation from the study. However, since the study is done in collaboration with patients' PCPs and all data is entered within the EHR, their data will not be removed.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

Specimens will not be obtained from outside MGB.