Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

Principal Investigator:	Nancy Haff, MD, MPH
Project Title:	Addressing diffusion of responsibility and prescribing burden to improve use of diabetes medications
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1. Background and Significance

Type 2 diabetes control in the US is suboptimal, and poor control is tightly linked to morbidity and mortality. For example, one year with a hemoglobin A1c (HbA1c) >7.5% is estimated to equate to a loss of approximately 100 life days.[2] Thus, disease control is imperative for healthy aging among patients with diabetes. Two newer classes of antidiabetic agents, SLGT2is and GLP-1Ras, improve glycemic control, induce weight loss, reduce the risk of cardiovascular events and renal disease, and decrease all-cause mortality.[3-5] The American Diabetes Association recommends the use of these medication classes for patients with type 2 diabetes and kidney disease, cardiovascular disease, heart failure, or obesity.[6] Despite this, adoption has been slow.[7-10] While over 50% of patients with diabetes are eligible, only 1-5% of eligible patients receive one of these drugs.[1,8,9]

While diabetes is commonly managed by primary care providers, SGLT-2i and GLP-1Ras are indicated for individuals with type 2 diabetes who also have other comorbidities, and so multiple specialists are often involved in this care. This results in significant "diffusion of responsibility," a behavioral concept that refers to the tendency of people (in this context, prescribers) to feel less responsible for individual actions in a setting or system when there are multiple actors and responsibility is unclear.[11,12,13-15] This behavioral barrier is increasingly recognized in the medical context.[16-21] In the case of SGLT-2i and GLP-1RA prescribing, diffusion of responsibility across multiple providers may explain the suboptimal prescribing of these medications by primary care providers.

Interventions to address diffusion of responsibility have been evaluated in a few medical and several non- medical contexts and suggest promising approaches. Modeling the desired behavior, assigning responsibility to individuals or smaller groups, highlighting individuals' competence to act, and highlighting the perceived harm of the situation to be addressed all have been shown to be effective.[17,22-24] Each of these factors can be translated to an intervention designed to address diffusion of responsibility in diabetes prescribing.

Because SGLT-2is and GLP-1Ras are relatively new, prescribing can be complicated. For example, the initial medication choice may not be covered by insurance, which results in the patient or pharmacy communicating with the prescriber's office who then communicates with the insurance company to

resolve the issue. Sometimes the provider will need to prescribe a different medication; other times a prior authorization or "peer to peer" conversation with the insurer is needed. At best, this series of denials and changes to the plan delays the start of the medication, but often it prevents initiation completely. The complexity and work required for this process is burdensome for providers and can deter future prescribing.[25] This will be partly addressed through electronic prior authorization, which is beginning to be used in routine practice, but further simplification of the process with administrative support could also promote prescribing.

As with non-health behaviors,[13] the impact of diffusion of responsibility on prescribing, and the success of interventions to address it, may vary based on the patient, provider, and clinical scenario. If it were possible to predict, using routinely collected data from the EHR, when addressing diffusion of responsibility is sufficient or when additional prescribing support is needed, this would allow for more precise intervention tailoring and allocation of resources.

2. Specific Aims and Objectives

Sodium-glucose cotransporter-2 inhibitors (SLGT-2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) are evidence-based medications that reduce morbidity and mortality for individuals with diabetes but remain significantly underused.[1] Diffusion of responsibility in prescribing across multiple providers and a burdensome prescribing process are barriers to their optimal use. To address these issues, we propose the following Aims:

Aim 1: Test the impact of an intervention to target diffusion of responsibility with and without additional reduction in prescribing burden on SGLT-2i and GLP-1RAs prescribing compared to usual care. We will conduct a randomized trial among primary care providers. The primary outcome will be SGLT-2i and GLP-1RA prescribing for patients with poorly controlled type 2 diabetes and a clear indication for one of these medications.

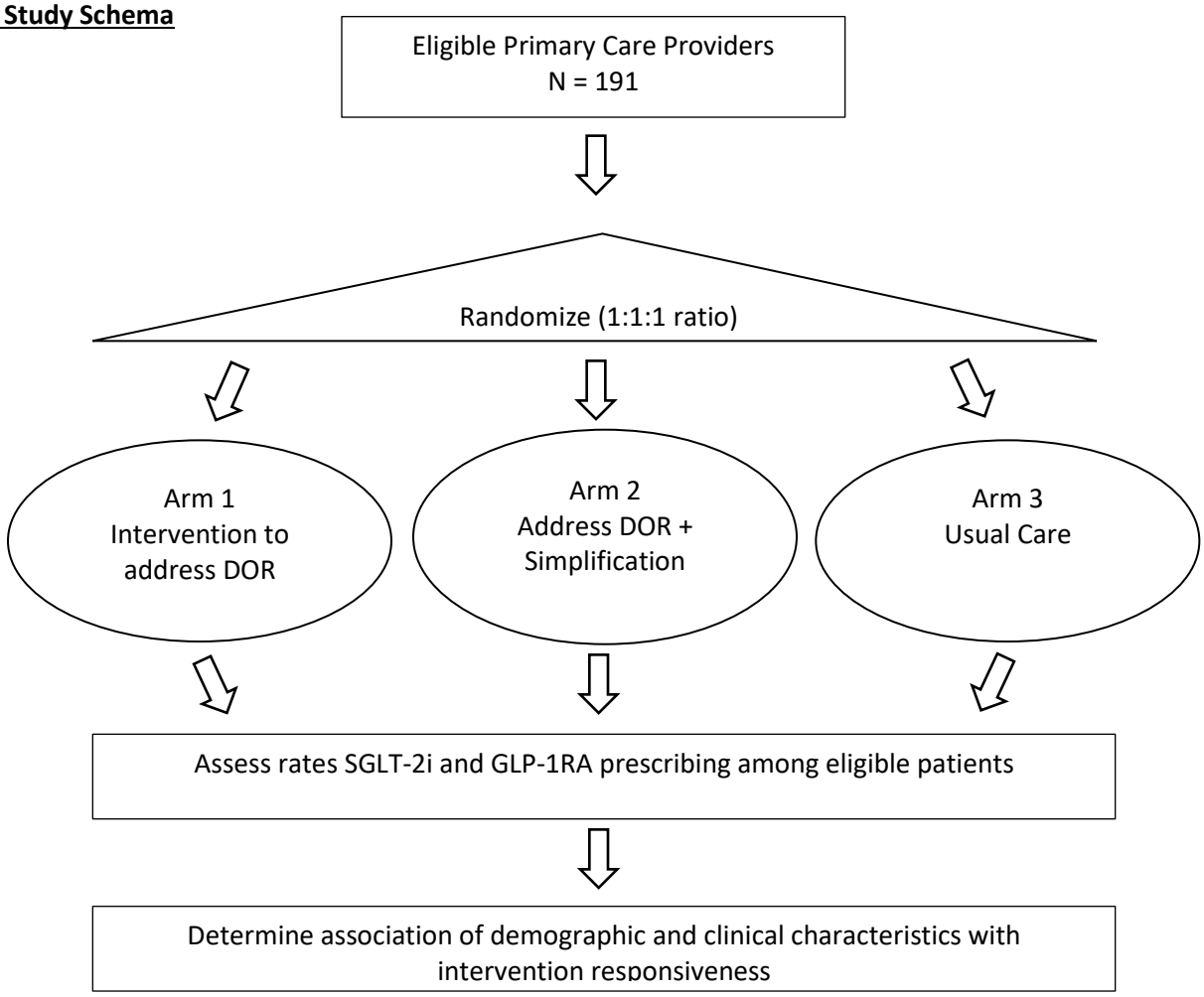
Aim 2: Identify characteristics of the patient, provider, and their clinical interaction that are associated with responsiveness to each intervention using routinely collected EHR data. The effectiveness of these interventions may vary based on characteristics of patients, providers, or the clinical scenario. Identification of predictors of responsiveness will help target interventions to those most likely to benefit.

3. General Description of Study Design

This study will be conducted within MGH primary care. As with prior work, we will use the hospital's EHR database, the Epic Enterprise Data Warehouse, to identify patients. Patients will be eligible if they are: adults 18-84 years of age with poorly controlled type 2 diabetes (defined as HbA1c >7.0%) and a compelling indication for an SGLT-2i or GLP-1RA (including cardiovascular disease, kidney disease, heart failure, or obesity), who are not already prescribed one of these therapies. We will exclude individuals with end stage renal disease, dementia, type I diabetes, or an EHR indicator of hospice care. We will also exclude patients who are not on the MGH diabetes registry, because patients who are excluded from the registry typically have a clinical reason for alternative diabetes goals or care plans. All attending MGH PCPs (excluding those involved in the design or delivery of the intervention) will be included in the trial. Eligible PCPs will be randomized to one of three arms: (1) intervention to address diffusion of responsibility, (2) intervention to address diffusion of responsibility plus additional simplification of the prescribing process, and (3) usual care. Providers randomized to arm 1, the intervention to address diffusion of responsibility will receive an email from a peer offering encouragement and support in

prescribing SGLT-2is and GLP-1RAs that includes specific components designed to reduce diffusion of responsibility. The email will also offer for direct support from the peer. Providers randomized to arm 2, the intervention addressing diffusion of responsibility and simplifying the prescribing process will receive the same contact addressing diffusion of responsibility as in arm 1, but they will additionally have access to an experienced administrative team for diabetes medication insurance authorization support. The primary outcome will be the rate of prescriptions for SGLT-2is and GLP-1RAs among eligible patients.

3.1 Study Schema



4. Subject Selection

This study will be conducted within MGH primary care, which consists of over 190 attending PCPs caring for more than 13,300 patients with diabetes, approximately 25% of whom have an HbA1c above goal. There will be two participant populations included in the study. First, we expect to enroll 191 providers to receive the intervention. Second, although they will not be receiving the intervention, we expect to accrue 1468 patients whose information will be used to determine study outcomes. Details for waiver of informed consent and waiver of HIPAA authorization are detailed below.

4.1 Inclusion/Exclusion Criteria

We will include attending primary care physicians meeting the following criteria:

- Practicing in primary care at Massachusetts General Hospital

Providers will be excluded if they are involved in the design or conduct of this study (e.g. Drs. Haff and Horn, and the peer PCPs delivering the study intervention).

We will accrue patients as part of study intervention delivery and outcome collection. Patient inclusion criteria are:

- 18-84 years of age
- HbA1c >7.0% and a compelling indication for an SGLT-2i or GLP-1RA (including cardiovascular disease, kidney disease, heart failure, or obesity)
- Not already prescribed an SGLT-2i or GLP-1RA at the time of the intervention

We will exclude individuals with end stage renal disease, dementia, type I diabetes, or an EHR indicator of hospice care. We will also exclude patients who are not on the MGH diabetes registry, because patients who are excluded from the registry typically have a clinical reason for alternative diabetes goals or care plans.

4.2 Patient Identification

Patients will not directly receive intervention, but their clinical parameters will be used to identify upcoming visits with potential opportunities for prescription of an SGLT-2i or GLP-1RA medication. As with prior work, we will use the hospital's EHR database, the Epic Enterprise Data Warehouse, to identify eligible patients.

4.3 Recruitment Procedures

We will use the hospital's EHR database, the Epic Enterprise Data Warehouse, to identify eligible patients.

As with similar minimal-risk quality-improvement studies that we have performed that involve the use of routine clinical tools such as patient portals or physician reminders, informed consent will not be sought in this study, and we request a waiver of informed consent. The nature of this intervention involves the use of messages delivered via email and in-basket (using information already available to providers and delivered via a similar infrastructure they use during regular clinical care). Obtaining written informed consent would also not produce generalizable knowledge about the effectiveness of the intervention, a foundational aspect of pragmatic clinical trial principles. With an approved waiver of informed consent for provider participation, all attending MGH primary care providers will be directly included in the study.

While providers and patients will not be consented into the study, an organization-wide announcement will be circulated across MGH Primary Care Practices to inform providers of the launch of this support for improved prescribing for adults with sub-optimally controlled diabetes.

Providers will be able to request unenrollment from the study at any time by replying to the intervention email. However, because the intervention includes only emails and in-basket messages that support prescribing, we anticipate that retention rates in the study will be very high. Study staff and data analysts will track any physician turnover in the study as they have done in prior work, and though minimal physician turnover is expected, we expect any turnover to bias the trial results towards the null.

5. Subject Enrollment

We will use the hospital's EHR database, the Epic Enterprise Data Warehouse, to identify eligible patients.

5.1 Informed Consent

As with other minimal-risk studies we have performed where informed consent is impracticable, we are requesting a waiver of informed consent and HIPAA authorization for patients and providers. There are several reasons for this. First, we plan to use routinely collected EHR data to identify eligible providers, administer interventions, and assess study outcomes. Because this is of minimal risk to patients, the study team will have no interaction with patients, all medical decisions will be made by the patients' PCP as in usual care, and it would be impracticable to obtain patient consent, we feel that a waiver of consent and HIPAA authorization for patients is needed for this study. Similarly, for providers, the interventions are minimal risk, designed to provide decision support for diabetes care, are consistent with professional guidelines and MGH-specific quality metrics, and are similar to supports that are put in place in routine quality improvement interventions. The interventions will be delivered using email and Epic in-basket which are routinely used in primary care. Providers will be given the opportunity to unenroll from the study at any time by replying to a study email or by contacting the study team; if they request to be unenrolled they will receive no further study-related contact.

5.2 Treatment assignment and randomization

All eligible providers will be randomized in a 1:1:1 ratio to one of three arms: (1) intervention to address diffusion of responsibility, (2) intervention to address diffusion of responsibility plus additional simplification of the prescribing process, and (3) usual care. Randomization will be stratified by primary care clinic.

6. STUDY PROCEDURES

6.1 Study Site

Study participants will be selected from Mass General Brigham (MGB), a large integrated delivery network in Boston, MA, specifically from Mass General Hospital primary care clinics, where Dr. Haff (PI) practices.

6.2 Overall Design

This study will be conducted within MGH primary care, which consists of over 250 PCPs caring for more than 13,300 patients with diabetes, approximately 25% of whom have an HbA1c above goal. As with prior work, we will use the hospital's EHR database, the Epic Enterprise Data Warehouse, to identify eligible patients and providers. All eligible PCPs will be randomized to one of three arms: (1) intervention to address diffusion of responsibility, (2) intervention to address diffusion of responsibility plus additional simplification of the prescribing process, and (3) usual care.

The primary outcome will be the rate of prescriptions for SGLT-2is and GLP- 1RAs among eligible patients. Secondary outcomes will include the rate of SGLT-2i and GLP-1RA prescribing among all patients with diabetes, change in A1c among eligible patients between baseline and last HbA1c within 6 months after intervention start, and implementation outcomes including frequency and nature of interactions with the emails, links, administrative support team, and prescribing model PCP peer. We will extract routinely collected data on prescribing and HbA1c from the EDW, as we have done with prior

projects. Implementation outcomes will be tracked by research assistants utilizing a secure RedCap database.

6.2.1 Aim 1 Design

In Aim 1 of the study, we will conduct a 3-arm randomized controlled trial to compare the effectiveness of two interventions compared to usual care on SGLT-2i and GLP-1RA prescribing. We will include Massachusetts General Hospital Attending Primary Care Providers. Interventions will be linked to upcoming visits with patient aged 18-84 years with poorly controlled type 2 diabetes (HbA1c >7.0%) and a compelling indication for an SGLT-2i or GLP-1RA (including cardiovascular disease, kidney disease, heart failure, or obesity), who are not already prescribed one of these therapies. We will exclude patients with a documented allergy to both medication classes, end stage renal disease, dementia, type I diabetes, an EHR indicator of hospice care and those who are excluded from the MGH diabetes registry.

Providers will be randomized equally to one of three arms: (1) intervention to address diffusion of responsibility, (2) intervention to address diffusion of responsibility plus additional simplification of the prescribing process, and (3) usual care. The intervention period will continue for 6 months.

Providers randomized to arm 1, an intervention to address diffusion of responsibility, will receive an email from a peer offering encouragement and support in prescribing SGLT-2is and GLP-1RAs that includes specific components designed to reduce diffusion of responsibility. Specifically, these elements are adapted from interventions that mitigate diffusion of responsibility in other contexts, including (1) assigning a responsibility to individuals or smaller groups, (2) increased perceived harm of the situation to be addressed (3) highlighting competence to act, and (4) modeling the desired behavior. The email will also contain an offer for direct support from the peer. Four MGH primary care physicians will administer the intervention. The email will be sent by the study team on their behalf and will contain a personalized subject line and/or text to increase the likelihood of opening and reading (see Study Interventions Document]).

The email will be accompanied by an additional personal outreach like walking through the practice and initiating brief, informal conversation or a short, hand-written note left on the PCP's desk 3-4 and 6 months after the start of the intervention. After the initial email, PCPs will receive up to 3 additional follow-up Epic in-basket messages, per provider, per week, notifying them of patients with upcoming visits who are eligible for one of these therapies and offering support in prescribing. The PCPs delivering the intervention will be trained in the clinical and administrative nuances of prescribing SGLT-2is and GLP-1RAs and remunerated for time spent assisting their peers. They will also have access to a diabetologist to consult for challenging clinical questions. Any additional interactions between study PCPs and the peer delivering the intervention will be offered and tracked but not required. If providers assigned to this arm reach out with questions about prescribing, the peer will respond and may provide clinically existing resources that are currently available in routine care.

Providers randomized to arm 2, an intervention to address diffusion of responsibility plus additional simplification of the prescribing process, will receive the same contact addressing diffusion of responsibility as in arm 1, but they will additionally have access to an experienced administrative team for diabetes medication insurance authorization support. In this arm, the list of each PCP's patients who are potentially eligible for an SLGT-2i or GLP-1RA will be reviewed by MGH's Central Authorization Unit (CAU). The CAU is an administrative team that currently supports prescribing for MGH diabetes specialists and other divisions by completing insurance authorization requests and helping providers

navigate variable insurance coverage for medications. For eligible study patients, the CAU will review the patient's chart and insurance coverage and provide information on which medication options are likely to be most affordable for each patient. This information will then be sent to PCPs via Epic in-basket message 3 business days before the patient's visit. In-basket messages will come from the shared in-basket pool, be signed by both the PCP peer and the CAU team, and will contain information about which SGLT-2is and GLP-1RAs are covered for that patient. In-basket messages will be capped at no more than 3 per provider per week, providers will be messaged about a single patient no more than 3 times over the course of the study. PCPs will also be informed in the initial outreach how to access the administrative team through Epic in-basket or email with any administrative questions or for any follow-up.

As in Arm 1, the initial email will be accompanied the additional personal outreach 3-4 and 6 months after the start of the intervention, and up to 3 follow-up Epic in-basket messages per provider, per week, but in Arm 2 the follow-up messages will also include information on the covered medication choice(s) for each patient how to access additional CAU support. Providers will be invited to reply directly that in-basket message to request assistance with prior authorization if needed. This team will then follow up with the pharmacy to determine coverage, communicate with clinic medical assistants, complete prior authorizations, determine alternative covered options, and track the process, as needed in each case. From the primary care doctor's perspective, this will be a markedly smoother process than current prescribing. If providers assigned to this arm reach out with questions regarding insurance coverage or prior authorization for an eligible patient that does not have an upcoming visit, the CAU staff will deliver the intervention with covered medication choice(s) to the provider at that time. If the patient later has an upcoming visit and has still not been prescribed the medication, the CAU staff will deliver the intervention again in the typical time frame (3 business days prior to the visit). Interventions regarding a single patient will be capped at no more than 3, including any interventions not associated with visits but delivered after PCP request. If providers assigned to this arm reach out with questions regarding ineligible patients, PCP peers will provide them with the same generic resources given in arm 1 that are currently available in routine care.

Prior to enrollment of providers into this trial, the CAU will pilot test Epic in-basket versus email workflow to determine the most efficient workflow. This pilot testing will be done with panels of those PCPs who are not included in the study due involvement in the study (i.e., PI and peer providers).

All providers will receive the second personal outreach 6 months after the start of the intervention. The outreach will consist of an email notifying them that the study is ending and inviting them to participate in a brief survey. The fact sheet for survey participation will be attached to the email. The survey will be accessed through a unique link to a secure REDCap survey embedded into the email. REDCap is a secure, HIPAA-compliant web-based platform hosted on Mass General Brigham servers. Providers who click on the link to the survey will be met with a landing page that displays the fact sheet describing the study. They will then be able to click a button to indicate that they agree to participate. Providers who select that they agree will then proceed to the rest of the survey. All providers will be allows to respond. Participants will be offered remuneration in the form of a $25.00 Amazon gift card for completing the survey. An email will be sent to the physician upon completion of the survey containing the claim code they will use to access their gift card. In addition, an electronic copy of the prescribing chart given to intervention providers in the first personalized outreach will be attached for all providers. In both intervention arms, providers will also receive a list of the patients who remain eligible for one of these medications but who have not had a visit during the study intervention period. Providers will then have

the option to ask their administrative staff to schedule visits with these patients, consider prescribing asynchronously, or otherwise generate a plan of care. The survey to intervention providers will capture opinions on the interventions, mechanisms behind diffusion of responsibility in prescribing these medications, and thoughts about potential helpful interventions moving forward. Providers in the control arm will only be asked the questions about mechanisms behind diffusion of responsibility in prescribing these medications and thoughts about potential helpful interventions moving forward. All providers who have not completed the survey within 2-3 weeks of receiving the email invitation will receive a follow-up email asking them again to participate in the survey.

Providers randomized to arm 3, usual care, will not receive any outreach outside of the end of study notification and survey.

After study completion, we will conduct an exploratory chart review of the visit notes from a random sample of patients in all three arms. Within each study arm, we will randomly sample visit notes from charts of 20 patients who were prescribed an SGLT-2i or a GLP1RA during the target visit (primary outcome occurred) and 20 patients who did not receive a prescription (primary outcome did not occur) to qualitatively explore the nature of the conversations that were documented at the visit. This will also include reviewing other encounter types in patients charts like telephone notes, patient gateway messaging, and other visits. This data collection will come from Epic chart review only. We will review the chart and summarize the nature of that conversation that was had around initiating SGLT-2is or GLP-1s, if one was documented. We will review the notes from the visit that was targeted by the intervention as well as subsequent notes in the chart as needed (such as telephone encounters, patient gateway encounters, and specialists visits notes) in order to understand if a medication was prescribed, and if not, then what the barriers were to starting. We will collect information on whether the patient filled the new prescription at the pharmacy, if available. This will include a total of 120 sampled charts, and the qualitative analyses will help us identify potential characteristics to extract from routine EHR data for Aim 2 and help understand remaining barriers to prescribing as well as potential mechanisms behind intervention effectiveness. Finally, we will also review the charts of all patients who received a prescription for a new medication to see what proportion of these prescriptions were actually filled by patients.

We will use the MGB standardized deployments of AI/ML services in MGB's secure cloud infrastructure, specifically the Azure OpenAI models as a tool to analyze qualitative data from the study and compare results from the LLM to those obtained by investigator analyses. Use of the LLM will permit faster analysis of large amounts of qualitative free-text data.

6.2.2 Aim 2 Design

In Aim 2, we will identify characteristics of providers, patients, and their interactions, that are measurable in routinely collected EHR data, that are associated with intervention responsiveness. We will extract provider demographic and practice data, patient demographic and clinical information, and data on the patient-provider interaction. We will also pre-specify which of these characteristics may be related to diffusion of responsibility.

6.3 Participant Remuneration

Subjects will be remunerated for participation in the end-of-study survey. Providers who complete the survey will receive a $25 Amazon gift card; an access code for their payment will be delivered by email.

7. Risks and Discomforts

We believe there is no more than minimal risk involved to the physician subjects, as the physicians will receive interventions designed to help with the provision of guideline-concordant diabetes care. The study recommendations are consistent with professional guidelines and MGH-specific quality metrics and are similar to supports that are put in place in routine quality improvement interventions. The interventions will be delivered using email and epic in-basket which are routinely used in primary care. The main potential discomfort for providers is burden from receiving additional messages. To mitigate this, messages will be kept to the minimum necessary to deliver the intervention, and providers will be given the opportunity to unenroll from the study at any time by replying to a study email or in-basket message. If they request to be unenrolled, they will receive no further study-related contact.

For patient-subjects, we also believe that the risks, to participation is no more than minimal for several reasons. First, the interventions aim to emphasize guideline-recommended treatments for patients with diabetes and a compelling indication for these treatments. Second, all treatment decisions will ultimately be made by licensed primary care physicians. Finally, the intervention is specifically physician-focused and uses information already available to physicians. There is a small risk associated with altering diabetes medication prescribing, including hypoglycemia, allergic reactions, and others. However, the diabetes control and cardiovascular benefits of these medications are typically considered to outweigh the infrequent risks, and PCPs can weigh these risks and benefits with each individual patient and decide whether or not to prescribe, as they always do in usual care. For this reason, we believe the potential risks of treatment initiation as part of this trial are the same as what is encountered during routine, guideline-concordant diabetes care. The study team will not be providing any direct care to patients and all medical decisions are ultimately made by the physician. This trial will otherwise not interfere with the usual workings of primary care practices. Thus, the main potential risk to subjects in this study is related to privacy of data, and we will take several measures to ensure that this risk is minimal, and that patient information is safeguarded.

Patient data for study outcome evaluation will be drawn from EHR information in the Epic Enterprise Data Warehouse (EDW). The investigators are aware of the sensitive nature of the data and are committed to protecting patient privacy. Only the minimum necessary identifiable health care data needed to achieve the intended purpose will be used. All the data in the registry is contained within the Mass General Brigham firewall, and its usage is logged and audited. It is only accessible to IRB-approved researchers. In addition, supplementary qualitative data for implementation evaluation will be drawn through traditional chart review by the research assistants. Research assistants will review conversations documented through multiple encounter types, like telephone notes, patient gateway messaging, and other visits and summarize what happened. Information will only be summarized from encounters that are viewable from the patient's chart; we do not need access to provider-to-provider inbasket messaging that is not saved into the chart. Summarized qualitative information will be stored using a secure REDCap database and all efforts will be taken to ensure that this information is safeguarded and only accessible to study investigators who are actively involved in the research.

For all study data, we will safeguard any identifiable information in accordance with IRB practices, limit access to the information to study investigators actively involved in the research who have all undergone human subjects research training and store any data in accordance with IRB practices. Finally, as is our routine practice, great care will be taken to ensure the confidentiality of all data and to protect the privacy of participants through translation of all potentially traceable identifiers into untraceable coded subject numbers whenever possible.

To ensure the confidentiality and security of all data, the research team operates a secure, state-of-the-art computing facility housed at MGB's data center. The MGB data center is a secure facility that houses both computing environments as well as clinical systems and electronic medical records for several large hospitals in Eastern Massachusetts. Entry into the computer room requires staffed computer room security. The Division's computers are connected to the MGB networking backbone with 10 gigabit-per-second fiber links. Network security is overseen by electronic medical records systems to the research team's data. All data are transmitted to programmers' workstations in an encrypted state. Backups are created using 256-bit AES encryption, the current Department of Defense standard for data security, and are stored in a locked facility. The redundancy, extensive data power, and security of our computer facility confirm our capacity to collect and manage data and ensure confidentiality for all project participants.

For the use of the Azure Open AI models, we will utilize the secure MGB environment on the Azure cloud to access the Open AI tools. The cloud setup has been previously established by MGB for research team use and complies with the legal, cybersecurity, and data security requirements at MGB. Our team has completed a Cloud Architecture Consult with the IT team and we will abide by MGB's published AI/LLM Guidance. Within the Azure environment, only team members included on the IRB who are participating in the data analysis will be given access to the LLM and data, following the same principles for our data management in other systems.

8. Benefits

Interventions to address diffusion of responsibility and simplify the prescribing process could help increase utilization of SGLT-2is and GLP-1RAs in diabetes care. Thus, the research could have both immediate benefits for physicians by increasing diabetes treatment knowledge, as well as for their patients who might benefit from improved glycemic control.

9. Statistical Analysis

9.1 Data Analysis Plan

9.1.1 Aim 1 Analysis Plan

For analyses we will use generalized estimating equations to compare outcomes between each intervention versus usual care and each other.

Qualitative analyses will be conducted on the random sampling of charts from patients who did and did not have the primary outcome in each study arm. Data will be coded and themes extracted and used to inform interpretation of the primary and secondary outcome results.

We will use the Azure Open AI LLM to assist with data analysis of free text qualitative data including that from chart review and free-text responses from physicians to the survey. Specifically, we will engineer prompts to guide the LLM in coding of data, extraction of themes, and summary of content. This will be used to compliment direct qualitative analysis by study investigators and will permit faster analysis of qualitative data. Results from this will be reported as part of trial results and will also help inform which predictors may be impactful for Aim 2.

9.1.2 Aim 2 Analysis Plan

For analyses, we will fit separate logistic and boosted regression models using sets of these predictors to evaluate the ability to predict responsiveness to each intervention, and we will incorporate classification

and regression trees where appropriate. Boosted regression is a machine learning method robust to multi-collinearity and overfitting. For each regression, we will use 10-fold cross-validation to compare C-statistics for the ability to predict intervention response and calculate a continuous net reclassification index to assess changes in predicted response with additional predictors.[26,27]

9.2 Power Analysis

We estimate that 191 providers caring for 1468 eligible patients will provide 80% power to observe an 11 percentage-point difference in prescribing rates between each intervention arm and control, assuming a control arm prescribing rate of 30%, an ICC of 0.07, an average of 7 patients per provider, and a type I error rate of 5%.

10. Monitoring and Quality Assurance

10.1 Adverse Events and Reporting

Oversight of the pilot will be the responsibility of the pilot PI: Nancy Haff, MD, MPH. Dr. Haff and study investigators will meet on a regular basis throughout the study period and will be in direct contact with the peer PCPs to obtain ongoing feedback. In addition, the protocol will undergo Institutional Review Board (IRB) evaluation.

De-identified study data will be accessible at all times for the BWH pilot PI and coinvestigators to review, if applicable. The study team will also ensure that all protocol deviations for the pilot study are reported to the NIH and the IRB according to the applicable regulatory requirements. Compliance of regulatory documents and study data accuracy and completeness will be maintained through an internal study team quality assurance process.

Definition:

Adverse Event (AE): Any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

Adverse Events will be classified using the following rating scales:

- Severity: Mild, Moderate or Severe
    - Mild: Awareness of signs or symptoms but are easily tolerated
    - Moderate: Events introduce a low level of inconvenience or concern but may interfere with daily activities but are usually improved by simple therapeutic measures.
    - Severe: Events interrupt the participants' normal daily activities and generally require systemic drug therapy
- Expectedness: Unexpected or Expected
    - Unexpected: nature or severity of the event is not consistent with the condition under study.
    - Expected: event is known to be associated with the intervention or condition under study

Serious Adverse Event (SAE): Any adverse event that:

- Results in death
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization

- Causes persistent or significant disability or incapacity
- Results in congenital anomalies or birth defects
- Is another condition which investigators judge to represent significant hazards

Given the minimal risk nature of the study, in which the intervention involves enhanced education and guideline concordant care for patients with at MGB, the PI does not expect any SAEs or AEs related to the information delivered in this trial. Patients' own primary care physicians will have ultimate decision-making authority for prescribing choices, as they would in routine clinical practice, and we expect any adverse events related to diabetes medication prescribing, such as hypoglycemia, to be the same as those experienced in routine clinical care.

Reporting:
As previously described, no additional SAEs or AEs are expected as part of this study. Any adverse event from medication prescribing will be handled in the course of regular clinical care, as is done currently, and through established safety reporting and review systems within MGH. In his role as the Director or Population Health and Quality in the Division of General Internal Medicine at MGH, Dr. Horn routinely reviews the safety reporting within MGH primary care and can be alerted to any reports that may relate to the study intervention.

Any reports of deaths will be submitted to the NIA Program Officer and to the NIA-appointed Standing Roybal DSMB Chair within 24 hours of the study team's knowledge. Any unexpected SAEs will be reported to the NIA PO and DSMB Chair within 48 hours of the study's knowledge of the SAE. All other reported SAEs received by the study team will be reported to the NIA Program Officer and to the DSMB quarterly, unless otherwise requested by the DSMB. AEs will be reported per IRB policies. They will also be reported to the NIA and DSMB at a frequency requested by NIA and/or by the DSMB (annually, at a minimum).

10.2 Planned Safety Monitoring

General oversight of this project by the Brigham and Women's Hospital (BWH) pilot PI (Dr. Haff) will occur throughout the study period, including regular contact with MGB clinical leadership involved in the project to obtain ongoing feedback. In addition, this protocol will undergo Institutional Review Board (IRB) evaluation.

We will have oversight from both the NIA Director-approved Roybal Centers Program Data Safety Monitoring Board (DSMB) for all aspects of this research (see **Appendix A**). The DSMB will act in an advisory capacity to the NIA to monitor participant safety, evaluate the progress of the study, and review procedures and management of the study. Our plan for data and safety monitoring also includes oversight by the project principal investigators (Dr. Haff) throughout the study period.

Meetings of the DSMB will be held regularly (e.g., every six to nine months) at the call of NIA or the DSMB Chair and review data related to study protocols and ensure protection of patient confidentiality and safety. At each meeting, the DSMB will make recommendations as to whether the studies should continue or if changes to the protocol are necessary for continuation. This trial will also be registered with clinicaltrials.gov.

10.3 Data Management

To protect against the risk of inappropriate disclosure of personal health information, the investigators at MGH will only access study data with encrypted identifiers. As described, all members of the research team have completed or will complete appropriate human subjects research training and patient privacy training related to the Health Insurance Portability and Accountability Act (HIPAA). We have a history of collaborative evaluations with delivery organizations that involves transfer of the minimum data necessary to complete rigorous evaluations, involving the use of encrypted identifiers to ensure patient confidentiality.

To ensure the confidentiality and security of all data, the research team operates a secure, state-of-the-art computing facility housed at MGB's data center. The MGB data center is a secure facility that houses both computing environments as well as clinical systems and electronic medical records for several large hospitals in Eastern Massachusetts. Entry into the computer room requires staffed computer room security. The Division's computers are connected to the MGB networking backbone with 10 gigabit-per-second fiber links. Network security is overseen by electronic medical records systems to the research team's data. All data are transmitted to programmers' workstations in an encrypted state. Backups are created using 256-bit AES encryption, the current Department of Defense standard for data security, and are stored in a locked facility. The redundancy, extensive data power, and security of our computer facility confirm our capacity to collect and manage data and ensure confidentiality for all project participants.

We will also safeguard any identifiable information from the physicians in accordance with IRB practices, limit access to any information in accordance with IRB practices, and limit access to the information to study investigators actively involved in the research who have all undergone human subjects research training.

For the use of the Azure Open AI models, we will utilize the secure MGB environment on the Azure cloud to access the Open AI tools. The cloud setup has been previously established by MGB for research team use and complies with the legal, cybersecurity, and data security requirements at MGB. Our team has completed a Cloud Architecture Consult with the MGB IT team and we will abide by MGB's published AI/LLM guidelines. Within the Azure environment, only team members included on the IRB who are participating in the data analysis will be given access to the LLM and data, following the same principles for our data management in other systems.

10.4 Outcomes monitoring

Given the minimal risks involved in participation in the study and its short duration, we will not perform any interim analysis for study outcomes.

10.5 Internal monitoring of source data, protocol adherence, and recordkeeping

The PI and study team will meet at least monthly to review study activity including recruitment, status of enrolled subjects, safety issues, internal quality assurance and peer review information. Meeting minutes will be maintained documenting the date of the meeting, names of those in attendance, and summary of information discussed and reviewed.

The Program Manager will complete an internal quality review of regulatory files prior to study enrollment begins and at least annually. The quality assurance review of regulatory files will be completed using the MGB Human Research Affairs Compliance and Education Office Regulatory Binder

Checklist. Any missing documents will be noted on the Regulatory Binder Checklist and then will be retrieved and filed as appropriate.

The Research Assistant(s) and Research Scientist will perform quality assurance reviews of the data entered into electronic case report forms for accuracy and completeness. Source data verification will be completed. Discrepancies will be documented for the study team to resolve. Once data entered on the eCRF have been verified and determined to be accurate and complete, the form will be locked the indicate that review is complete.

11 Privacy and Confidentiality

- ☒ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☐ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☒ Additional privacy and/or confidentiality protections

Data for the study will be safeguarded by state-of-the-art security protocols. The facilities have 24-hour security and are protected by locked entrances. MGB has computer networks in place that employ up to date virus protection software and enable password protected access only to study investigators. The setup for analysis of these data will be the same as all the other IRB applications that the MGB research division submits for secondary use of data. All the datasets, including limited protected health information (PHI), will be stored only on secure servers at MGB's data center and will only be accessed by a limited number of individuals in the study team from this division who are all trained in data security and patient privacy.

To ensure the confidentiality and security of all data, the research team operates a secure, state-of-the-art computing facility housed at MGB's data center. The MGB data center is a secure facility that houses both computing environments as well as clinical systems and electronic medical records for several large hospitals in Eastern Massachusetts. Entry into the computer room requires staffed computer room

security. The Division of Pharmacoepidemiology's computers are connected to the MGB networking backbone with 10 gigabit-per-second fiber links. Network security is overseen by electronic medical records systems to the research team's data. All data are transmitted to programmers' workstations in an encrypted state. Backups are created using 256-bit AES encryption, the current Department of Defense standard for data security, and are stored in a locked facility. The redundancy, extensive data power, and security of the computer facility confirm the capacity to collect and manage data and ensure confidentiality for all project participants.

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For the use of the Azure Open AI models, we will utilize the secure MGB environment on the Azure cloud to access the Open AI tools. The cloud setup has been previously established by MGB for research team use and complies with the legal, cybersecurity, and data security requirements at MGB. Our team has completed a Cloud Architecture Consult with the MGB IT team and we will abide by MGB's published AI/LLM guidelines. Within the Azure environment, only team members included on the IRB who are participating in the data analysis will be given access to the LLM and data, following the same principles for our data management in other systems.

All members of the research team have completed or will complete appropriate human subjects research training and patient privacy training related to the Health Insurance Portability and Accountability Act (HIPAA).

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APPENDIX A

Data Monitoring Committee / Data and Safety Monitoring Board Appendix

- *To be completed for studies monitored by Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) if a full DMC/DSMB charter is not available at the time of initial IRB review.*
- *DMC/DSMB Charter and/or Roster can be submitted to the IRB later via Amendment, though these are not required.*

A Data and Safety Monitoring Board (DSMB) will be convened for safety monitoring of this research study. The following characteristics describe the DSMB convened for this study (Check all that apply):

☒ The DSMB is independent from the study team and study sponsor.

☒ A process has been implemented to ensure absence of conflicts of interest by DSMB members.

☒ The DSMB has the authority to intervene on study progress in the event of safety concerns, e.g., to suspend or terminate a study if new safety concerns have been identified or need to be investigated.

☒ Describe number and types of (i.e., qualifications of) members:
This study will be monitored by the NIA-appointed standing Roybal DSMB, which acts in an advisory capacity to the National Institute of Aging (NIA) Director to monitor participant safety, data quality and progress of the Roybal Centers. DSMB members, which have been approved by the NIA Director include:

- Andrea B. Troxel, ScD (Chair), Professor, NYU School of Medicine
- Abby King, PhD, Professor, Stanford University School of Medicine
- Jerry Gurwitz, MD, Professor, University of Massachusetts Medical School and University of Massachusetts Graduate School of Biomedical Sciences
- Hae-Ra Han, PhD, RN, FAAN, Professor, Johns Hopkins University School of Nursing
- Hang Lee, PhD, Associate Professor, Harvard Medical School
- Ezra Golberstein, PhD, Associate Professor, University of Minnesota School of Public health
- David Kim, MD, PhD, Chief Resident, Stanford University
- Christopher Celano, MD, Assistant Professor, Massachusetts General Hospital

☒ Describe planned frequency of meetings:
Per the NIA Notice of Award, recruitment is restricted until the DSMB has reviewed and recommended approval to NIA, with NIA's concurrence, the DSMP, IRB-approved study protocol, consent documents, and Manual of Operating Procedures.

Per the Data Safety Monitoring Plan, the DSMB will meet twice annually, either in-person or by teleconference call to review study progress, data quality, and participants safety.

☒ DSMB reports with no findings (i.e., "continue without modifications") will be submitted to the IRB at the time of Continuing Review.

☒ DSMB reports with findings/modifications required will be submitted promptly (within 5 business days/7 calendar days of becoming aware) to the IRB as an Other Event.