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PROTOCOL

Protocol Title:
COOrdinating Ca**RDI**ology Cli**N**ics R**A**ndomized **T**rial of Interventions to Improve Outcom**E**s (COORDINATE) - Diabetes

Protocol Number: Pro00101556

Study Phase:
Phase 4

Short Title:

COORDINATE-Diabetes

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Duke Clinical Research Institute

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1. Protocol Summary

1.1 Rationale

Type 2 diabetes mellitus (T2DM) is an established independent risk factor for atherosclerotic cardiovascular disease (CVD) and is responsible for nearly 2.2 million deaths each year from ischemic heart disease and stroke worldwide. Despite the enormous public health burden of T2DM, critical knowledge gaps exist with regard to contemporary patterns of diabetes management, quality of care, and long-term outcomes. Greater understanding is needed on how evidence-based therapies and CVD risk management strategies influence long-term risk trajectories in patients with T2DM.

The most important adverse outcomes for patients with T2DM are cardiovascular, including cardiovascular death. Now, there are a variety of evidence-based treatments to reduce cardiovascular risk for patients with T2DM. These include treatment of risk factors like hypertension and hyperlipidemia, avoiding smoking, diet and exercise, and use of anti-hyperglycemic therapies proven to prevent cardiovascular outcomes. Sodium-glucose cotransporter-2 (SGLT2) inhibitors and Glucagon-like peptide 1 (GLP-1) receptor agonists have recently been shown to be protective for patients with T2DM and cardiovascular disease or CVD risk.[1, 2]

Despite proven effective therapies, they are used in a minority of patients who would benefit. Possible barriers to uptake include lack of "ownership" over prescribing these medications (primary care provider vs endocrinologist/diabetes care specialist vs cardiologist), lack of familiarity and comfort with prescribing these medications, lack of a system to measure and provide feedback on performance, and lack of a comprehensive clinical pathway to provide multi-disciplinary evidence-based care to patients with T2DM and CVD.[3]

The most important opportunity to improve care is to more effectively implement proven risk factor management and tailored therapies. There is a critical need to show how effective treatments can be implemented at the clinic level. Few studies have been conducted in a rigorous way to test strategies to potentially improve implementation.

COORDINATE-Diabetes is a cluster-randomized clinical trial to test the effectiveness of an innovative, clinic-level educational intervention to improve the management of patients with T2DM and CVD. The trial will be performed and interpreted in the context of clinical diabetes care in the U.S. using data from select electronic health record (EHR) sites. A subset of sites with EHR data available for querying in existing datamarts will be recruited to participate in two EHR-focused objectives: 1) to perform a baseline characterization of patients with T2DM and CVD, including demographics, treatment patterns and healthcare utilization such as hospitalization; and 2) to assist with the identification of patients eligible for the educational intervention trial.

What follows is the protocol for the COORDINATE trial; the objectives and planned analyses of data from EHR sites is summarized in section 8 of this protocol.

Table 1. Trial Summary Table

Patient-level Inclusion and Exclusion Criteria **Site-Level Inclusion Criteria**	Sites will be recruited based on sufficient patient volume, cardiologist and endocrinologist or diabetes care specialist commitment, and site capacity to perform the trial as well as ability to effectively communicate with the study team and patients. Attempts will be made to achieve geographic, investigator, and patient diversity. Individual patients eligible to enroll in the trial will have a diagnosis of T2DM and cardiovascular disease as listed in the Inclusion Criteria. <u>Patient Inclusion Criteria</u>: 1. Age ≥ 18 years old 2. Diagnosis of Type 2 diabetes mellitus (T2DM) as reported in the patient's medical records. 3. History of at least one of the following conditions: a. Coronary artery disease (defined as prior MI, coronary revascularization (CABG or PCI), and/or obstructive CAD (≥50%) as documented by angiography or CTA) b. Stroke and/or carotid artery stenosis (≥50%) c. Peripheral Arterial disease (defined as claudication with ABI<0.9, prior peripheral revascularization, and/or amputation due to circulatory insufficiency) 4. Baseline composite score of guideline recommended therapy of <3 at baseline entry into the trial. Patients would receive a score of 1 for each of the following care elements: • ACEi/ARB therapy • High-intensity statin • Most recent HbA1c<7% on metformin monotherapy 5. Ability to communicate with site staff and understand and provide written informed consent and proof of Health Insurance Portability and Accountability Act (HIPAA) authorization <u>Patient Exclusion Criterion</u>: 1. Determined to be highly unlikely to survive and/or to continue follow-up in that clinic for at least 1 year, as identified by site investigator 2. GFR<30 mL/min/1.73m^2 3. Baseline composite score of 3 for guideline recommended therapy (as outlined in Patient Inclusion Criterion #4) 4. Absolute contraindication to any of the 3 guideline recommended therapies (as outlined in Patient Inclusion Criterion #4) 5. Already taking SGLT2i or GLP1RA therapy at baseline. <u>Site Inclusion Criteria:</u> 1. Cardiology clinic that is willing and able to perform the interventions in the trial to improve the quality of care of their patients with T2DM and CVD. 2. Have a cardiologist and endocrinologist or diabetes care specialist (for example, a PCP with experience in treating diabetes) who are willing to partner for the trial needs of creating and implementing care pathways with the support of the COORDINATE Diabetes Study Team; any site that has a highly organized partnership with cardiology-endocrinology with care pathways already established will not be included.

	3. Presence of an electronic health record (EHR) system that will enable identification and follow-up of patients.
Study Design	The design is a cluster-randomized clinical implementation trial of a minimum of 42 cardiology clinics in the United States. Sites will be randomized to a basic education arm or an intensive educational intervention arm, consisting of clinic-level multifaceted educational intervention with the aim to improve evidenced-based care for patients with diabetes and cardiovascular disease. The aim is to enroll approximately 25 patients at each site. The primary outcome is the proportion of patients achieving guideline-recommended management of diabetes and cardiovascular disease measured as a composite score of 3 at the last follow-up visit.
Treatment Regimen(s)	Participants will receive care at their physicians' discretion. • The patients receiving care in clinics that are randomized to the intensive educational intervention arm will be cared for by cardiologists and staff where a multifaceted implementation program will be conducted to improve the use of guideline-recommended therapies for patients with T2DM and CV disease. • The patients receiving care in clinics that are randomized to the basic education arm will be treated by clinicians who receive only basic information about guideline-based therapy.
Duration of Study Participation	Data collection will continue for all participants for 6 to 12 months after enrollment. For those who provide Social Security number information, we may collect vital status at up to 5 years following the last follow-up visit.
End of Study Definition	The trial will last for 6 to 12 months for all participants. Participants can withdraw from the trial at any time. Vital status will be obtained from all participants at the last follow-up visit. Vital status may be collected from the National Death Index at up to 5 years following the last follow-up visit.
Minimum Number of clusters (Sites) Required	42
Average cluster size	25 patients (yielding a total of 1050 patients)
Total Sample Size	Approximately 1050 patients* * Need to maintain an overall average of 25 pts per site from 42 sites

1.2 Trial Outcomes

A variety of clinical, process of care, and implementation outcomes will be assessed in the trial. Primarily, we will measure whether our intensive education intervention successfully changes provider behavior and improves secondary prevention management in patients with T2DM and CVD by collecting and analyzing patient level data. Therefore, our outcomes will assess differences at the last follow-up visit in guideline-recommended therapy between the basic education and intensive education intervention groups.

Table 2. Trial Outcomes Table

Trial Objectives	Trial Outcomes
Primary Objectives	
To test effectiveness of implementing a clinic-level multifaceted intervention that includes establishing cardiology and endocrinology partnerships and evidence-based care pathways to improve the medical management and care of patients with T2DM and cardiovascular disease.	The trial will examine the impact of the educational intervention on provider adherence to guideline-recommended therapy, which is the primary outcome, defined as the proportion of patients achieving guideline-recommended management for T2DM and CVD at the last follow-up visit, as initiated or confirmed by a cardiologist for all of the following (composite score of 3): 1. Use of a regimen which includes an anti-hyperglycemic agent indicated and/or guideline recommended to reduce cardiovascular risk* a. Acceptable alternative: metformin monotherapy with HbA1c<7% 2. Guideline-recommended medical therapy* with ACEi/ARB 3. Guideline-recommended medical therapy* with high-intensity statin: atorvastatin 40-80mg daily OR rosuvastatin 20-40mg daily *As new consensus or evidence emerges and guidelines are updated, the composite score and requisites will be evaluated by the Steering Committee for needed updates on an ongoing basis. For the first component of the primary outcome (related to anti-hyperglycemic agents), patients will be evaluated according to the list of "indicated and/or guideline recommended" agents in effect **at the time of their last follow-up visit**. This decision was approved by the Steering Committee. Medications started during the study follow-up period that receive FDA indication/guideline recommendation during that time will count towards the primary outcome. It is important to note that the FDA indications and guideline recommendations will only become more liberal with time, not more restrictive. Of note, patients who are on any GLP1-RA or SGLT2i therapy at baseline will not be eligible for enrollment.
Secondary Objectives	
	All of the following secondary outcomes will be assessed at the last follow-up visit.

	Assessment of cardiology provider behavior as measured by the following cardiologist-initiated medications for diabetes suggested by guidelines and FDA approved for CVD risk reduction:
	• Proportion of patients achieving guideline-recommended therapy for T2DM
	• Proportion of patients with an ACEi/ARB treatment
	• Proportion of patient with a high-intensity statin treatment
	• Variations on the Primary Outcome:
	  • Proportion of patients achieving a composite score of ≥ 2
	• Intermediate Outcomes:
	  • Changes from baseline to the last follow-up visit in the following: sBP, dBP, HbA1c, LDL-C
	  • Change from baseline to the last follow-up visit in proportion of patients achieving the following targets (individually and in combination): sBP<130 mmHg, dBP<80 mmHg, HbA1c<7%, LDL-C<70 mg/dL
	• Clinical time-to-event outcomes (While the primary outcome will be measured as of the last follow-up visit, data on clinical outcomes will be collected throughout the follow-up period for each patient):
	  • Composite of all-cause death; hospitalization for: MI, stroke, decompensated heart failure, or urgent revascularization (coronary, peripheral, carotid)
	  • Each of the clinical time-to-event outcomes will also be assessed individually

Exploratory Objectives	
	The following may be assessed at up to 5 years in patients who have provided social security number information: - all-cause mortality, as assessed by vital status obtained through the National Death Index
Implementation Objectives	
	Provider-level implementation outcomes: ▪ Acceptability ▪ Appropriateness

Since assessing differences in clinical outcomes is not the primary objective of this study, clinical events will not be independently adjudicated.

2. Overall Design

The design is a cluster-randomized clinical implementation trial of a minimum of 42 cardiology clinics in the United States. Clinics will be selected based on an interest in improving the quality of care of their patients with T2DM and CVD. Further, the clinics will need to demonstrate that they can identify and financially support the efforts of a clinical site leadership pair, consisting of an endocrinologist or diabetes care specialist and a cardiologist. Enrolled clinics will be randomized in a ratio of 1:1 either to a basic education arm or an intensive educational intervention arm. Each clinic will then enroll approximately 25 patients who have T2DM, CVD, and a baseline composite score < 3 at study entry. The study will be open-label, and randomization of clinics will be stratified according to clinic-level factors, including:

- Site location : Urban or non-urban

Randomization of clinics will occur after each clinic has been screened and deemed eligible—willing to participate in the trial and has IRB approval.

3. Disclosure Statement

This is a multifaceted implementation trial randomized at the clinic level to 2 arms, 1 intense educational intervention and 1 basic education or what is also referred to in these types of studies as usual care.

4. Study Arms, Data Collection, and Duration

4.1 Basic Education Arm

Clinics in the basic education arm will continue current standard of care (SOC). Sites will be compensated for their involvement including for patient recruitment and assessments. They will also receive basic education at study start to include the most updated ACC/AHA guidelines for cholesterol management and from the ADA about diabetes management as well as periodic educational updates.[2, 5, 6] They will also receive clinic-level education related to drug safety, including statin side effects and potential side effects of anti-diabetes medications with CV benefit (such as hypoglycemia, DKA, etc.). Beyond this basic information, sites (and physicians) in the basic education arm will not receive other instructions or intensive educational interventions. They will be left to care for their patients as they normally would. Patients in the basic education arm will be seen by their healthcare provider at baseline, either in clinic or via virtual visit, per local standard of care. Follow-up visits (i.e., standard of care in-person or virtual visit, or telephone call) will be conducted by enrolling sites in the basic arm at 6 months from baseline visit, and at up to 12 months from baseline visit, with a maximum of two visits. The overall length of follow-up will be 6 to 12 months, with all patients having a minimum of 6 months of follow-up. The date of the last follow-up visit determined by the patient's enrollment date. Data collected will be entered into an electronic data capture system. Clinic visits should be conducted as per standard of care.

4.2 Intensive Educational Intervention Arm

The cardiology clinics in the intensive educational intervention arm will receive guidance to develop an integrated, multi-disciplinary care pathway for patients with T2DM and CVD. The cardiologist and endocrinologist/diabetes care specialist co-PIs at each site will oversee this development. Prior to study start, a Manual of Operations will be developed by the trial team in conjunction with the trial Steering Committee. This manual will be available for dissemination after trial completion. It will build on professional society guidelines (such as ADA, ACC, as described in the primary endpoint) and will consist of evidence-based standards of care that should be included in the clinical pathway implemented at each site. Though these standards may be adapted to meet the needs of each individual site, the core components of the care pathway will be consistent across intensive educational intervention sites. Throughout the intervention, the care teams will be encouraged to communicate with the primary care physicians of individual patients to facilitate a team approach to patient care. Though the intensive educational intervention will not be specifically targeted towards primary care physicians, they are an integral part of optimal patient care and will be kept engaged throughout.

The intensive educational intervention will consist of the following:

- Each clinic is assigned a mentor pair of specialists from the COORDINATE-Diabetes National Academy Faculty (a cardiologist and endocrinologist/diabetes care specialist) and a DCRI quality improvement (QI) specialist (the "COORDINATE-Diabetes Trio")
- Each site's clinic leadership pair and research coordinators will attend an implementation training session virtually conducted by the COORDINATE-Diabetes Trio.
- This COORDINATE-Diabetes Trio will conduct a health system and clinic site visit prior to implementation training. This visit may be conducted on-site or virtually. During the visit, the Trio will:
    - Conduct a health system-wide grand rounds education program (if possible) on identification and care of the cardiovascular diabetic population, and
    - Meet with the clinic leadership pair (cardiologist and endocrinologist/diabetes care specialist) and the research coordinator. The clinical leadership pair, research coordinator, patient advocate, and study staff (for prior authorizations and patient education) will constitute the core study team at each clinic site, and
    - Respond to the clinic's current practice, care processes, and available outcomes data from the site survey, and help the clinic team develop a GAP analysis. This GAP analysis will be specific to each site. Each site will formally submit this GAP analysis within 2 weeks of site visit to the DCRI Project Lead.
- The COORDINATE-Diabetes Trio assigned to each clinic site will work with the clinic site study team to establish the final Clinic Action Plan. This Clinic Action Plan will be largely based on the Standard Manual of Operations developed by the COORDINATE-Diabetes study team, but may include some site-specific adaptations as deemed necessary by each site team. The implementation of any adaptations and their content will be recorded in the study database.
- Clinic healthcare providers will receive disease specific and study implementation training (Qualtrics Modules).

Specific Educational Intervention site activities conducted by the COORDINATE-Diabetes staff will include:

- Building a multidisciplinary clinic site team (cardiology and endocrinology/diabetes care specialist leadership pair, site research coordinator, patient advocate, staff for prior authorization and patient education)
- Conducting clinic-level education related to trial protocol, 2019 ADA guidelines[5, 6], 2013 ACC/AHA guidelines for management of blood cholesterol[9], data from recent cardiovascular outcomes trials in diabetes, safety education related to prescribed medications (example, hypoglycemia, DKA), and FDA label indications for relevant medications.
- Conducting clinic-level education related to drug safety, including statin side effects and potential side effects of anti-diabetes medications with CV benefit (such as hypoglycemia, DKA, etc).
- Helping site teams refine and implement a care pathway for managing diabetes and CV risk factors.
- Implementing audit and feedback system to improve the management of individual patients, and to improve systems of care in the clinics. We will establish a trial database that will provide regular reports to each clinical site team. The reports will track the progress of each enrolled patient against pre-defined metrics (as per the primary outcome) over time, and will also provide aggregate data across all patients in a given site. These reports will be sent to site teams monthly, with the expectation that the site teams will review them monthly. In addition, reports from each site will be reviewed quarterly by the COORDINATE-Diabetes National Academy Faculty, in conjunction with the clinical site teams. Feedback to providers at each site will occur in relation to specific enrolled patients who have yet to achieve optimal care (as per the primary outcome), and will largely be carried out through direct communication between the clinical site team and the providers. In addition, EHR-based communication may be employed at sites with this capability.

Specific intervention site activities targeted towards the study site staff will include:

- Educating in evidence-based management of patients with T2DM and CVD, as outlined above. This will occur at start of patient enrollment and will be standardized across sites, with at least one planned "booster" session during enrollment that will also be standardized across sites. Additional education sessions will be provided at the discretion of the clinic site teams who are monitoring the care being provided at each clinic, tailored to the needs of that specific clinic.
- Administering questionnaires at study end to assess provider perspectives on the intervention. Questionnaires have been developed for individual studies in the past, and we will draw from standard approaches used in prior similar successful studies (including IMPACT-AF).[4, 10]
- Assessing intervention acceptability and appropriateness via questionnaire at end of study, including assessing feedback from providers. We will develop these questionnaires to be specific to our intervention.

Specific educational intervention site activities that will directly involve patients will include:

- Consent of patients
- Clinic visits: Patients in the intense intervention arm will be seen by their healthcare provider at baseline, either in clinic or via virtual visit, per local standard of care. Follow-up visits (i.e., standard of care in-person or virtual visit, or telephone call) will be conducted every three months by enrolling sites in the intervention arm. All patients in the intervention arm will have two to four follow-up visits, with a minimum of 6 months of follow-up. The overall length of follow-up will be 6 to 12 months. The date of the last follow-up visit will

be determined by the patient's enrollment date. Patient reported prescription data for medications of interest will be validated by sites via medical record collection. All data collected will be entered into an electronic data capture system. Clinic visits should be conducted as per standard of care.

- Labs: The following laboratory assessments are collected from the patient's electronic health record and are recommended as part of standard of care in all patients at baseline and at the last follow-up visit: basic metabolic panel, HbA1c, lipid panel. As part of standard of care, providers will be encouraged to also order a basic metabolic panel 1-2 weeks after each dosage change in ACEi/ARB, HbA1c every 3 months until it is <8%, and lipid panel 8 weeks after each statin dose titration. In summary, sites will be educated to guidelines and will not be mandated to collect specific labs at specific times from patients enrolled for the purpose of the study. Rather, the study will be collecting data including labs that have been performed as part of standard of care and are not required as part of the study.

In both study arms, we will evaluate and compare various methods to communicate with and engage patients throughout the study. These engagement efforts may focus on encouraging the patients to enroll/comply with study requirements, and/or may focus on encouraging the patient to be engaged in their own health care, knowledgeable about their disease state(s), and adherent to their medications.

4.3 Study Duration

Follow-up for the overall study will end approximately 6 months after enrollment of the final participant. Participants will be followed for 12 months, except for those enrolled in the final 6 months of enrollment, who will have their follow-up complete at a minimum of 6 months. Thus, the last patient enrolled will have 6 months of follow-up, a patient enrolled 3 months before the end of enrollment will have 9 months of follow-up, and a patient enrolled 6 months before the end of enrollment will have 12 months of follow-up. Shortly following the completion of enrollment, study sites will be notified of a specific date on which follow-up will conclude.

4.4 Clinic-Level Data Collection

The following data will be collected in the clinic. All data will be entered by site personnel using an electronic data capture (EDC) system. Access to the EDC system, IBM Clinical Development, employed for collection of the patient data will be controlled centrally by the DCRI through distribution of EDC study specific access codes. DCRI data export services establishes regular exports of the data to be stored on the DCRI server.

Baseline

- Geographic classification: Urban vs non-urban will be collected by the DCRI study team prior to site activation.

12 Months or End of Study (intervention sites only)

A provider survey to be completed by the site investigator will be conducted to collect the following information:

- Acceptability of educational intervention
- Appropriateness of educational intervention

Table 3. Patient-Level Data Collection by the Site for Both Arms (gray shade denotes data that will be assessed in the intense education intervention arm only)

	Baseline	3 months	6 months	9 months	12 months
Required contact w/ patient	1) Informed Consent 2) SSN # (unless patient opts out) 3) Medications of interest, as reported by the patient	Telephone (or visit if done as SOC between 2-4 months after enrollment) 1) Vital Status 2) Medications of interest, as reported by the patient	Telephone (or visit if done as SOC between 5-7 months after enrollment) 1) Vital status 2) Medications of interest, as reported by the patient 3) Clinical events assessment as reported by the patient	Telephone (or visit if done as SOC between 8-10 months after enrollment) 1) Vital Status 2) Medications of interest, as reported by the patient	Telephone (or visit if done as SOC between 11-13 months after enrollment) 1) Vital Status 2) Medications of interest, as reported by the patient 3) Clinical events assessment as reported by the patient
Required health record check	1) Demographics (age, sex, race) 2) Baseline visit vital signs (sBP, dBP, BMI) 3) Most recent lab values (HbA1c, LDL-C, BMP) 4) Medications of interest prescribed, as collected from health record	1) Medications of interest prescribed, as collected from health record	1) Medications of interest prescribed, as collected from health record 2) Clinical events assessment, as collected from health record	1) Medications of interest prescribed, as collected from health record	1) Most recent vital signs (sBP, dBP, BMI), as collected from the health record 2) Most recent lab values (HbA1c, LDL-C, BMP), as collected from the health record 3) Medications prescribed, as collected from the health record 4) Clinical events assessment, as collected from health record

In addition to the above data collected by sites, the DCRI coordinating center may assess all-cause mortality by using patient social security numbers to access the National Death Index. Vital status may be assessed for all patients who have provided SSN at up to 5 years after last patient follow-up visit.

5. Independent External Review Committee

This committee will be an independent body that will provide critical, independent, and unbiased review of all components of the trial during the design, conduct, and dissemination phases. The committee will be responsible to assure the trial is being conducted in a way to assure patient

safety and thus will periodically review safety and clinical outcome data. This committee is analogous to a Data and Monitoring Committee to ensure protection of human participants. The committee may consist of 2 experts who meet several times over the course of the project and who will assess data. The data will be provided to the Independent External Review Committee via summary reports compiled by a statistician and programmer. After review of the data, they will make recommendations to the steering committee if trial modification is needed to assure patient safety or improve trial integrity. A charter for this committee will be developed prior to start of study.

6. Safety Management and Reporting of Adverse Events/Serious Adverse Events

6.1 Definition of Adverse Events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse drug reaction (ADR)

An adverse drug reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse drug reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event is defined as any AE which

- results in death
- is life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity or is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

6.2 Adverse Event and Serious Adverse Event Collection and Reporting

If an adverse drug event is reported by the patient participant during the COORDINATE-Diabetes study, the patient participant will be instructed to contact his or her study physician. The study physician is responsible for reporting via MedWatch, the FDA Safety Information and Adverse Event Reporting Program. The site Primary Investigator will be responsible for safety reporting AEs which occur during the conduct of the study to the competent regulatory authorities, accredited Institutional Review Boards and/or Independent Ethics Committee(s) (IRB/IEC(s)) in accordance with the applicable laws and regulations.

Adverse event reporting to Boehringer-Ingelheim (BI)

Each site shall report

(i) all ADRs (serious and non-serious)

(ii) all AEs with fatal outcome

(iii) pregnancies in female participants and partners of male participants

that are associated with the **BI Drugs administered for the disease in scope of the study** (**e.g., empagliflozin, linagliptin and its combinations** by fax to the BI Unique Entry Point using BI NIS SAE report form in following timelines.

BI Unique Entry Point:

Boehringer-Ingelheim Pharmaceuticals, Inc.
FAX: 1-203-837-4329

All serious ADRs and AEs with fatal outcome shall be forwarded immediately (within 24 hours or next business day whichever is shorter).

All non-serious ADRs and Pregnancy Monitoring Forms shall be forwarded within7 days.

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

DCRI is responsible for training the sites regarding the safety reporting to BI based on the agreement, protocol and BI training material.

Causal relationship of adverse event

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Causality should be assessed for each event as either “yes” or “no.” No other variation should be reported.

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated

Moderate: Enough discomfort to cause interference with usual activity

Severe: Incapacitating or causing inability to work or to perform usual activities

The intensity of adverse events should be classified and recorded according to the CTCAE Criteria in the NIS SAE form.

Pregnancy

In rare cases, pregnancy might occur in a study. Once a participant has been enrolled into the study, after having taken BI Drug administered for the disease in scope of the study, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to the Sponsor by means of BI Pregnancy Monitoring Form provided.

Reporting of related adverse events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than BI Drugs used for the disease in scope of the study according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

7. Statistical Hypotheses, Randomization, and Sample Size Determination

7.1 Hypothesis

The trial hypothesis is that the primary outcome (proportion of patients achieving guideline-recommended management for T2DM and CVD at 12 months, as initiated or confirmed by a cardiologist, with a composite score of 3) will be higher in the intensive educational intervention arm than in the basic education arm.

The null hypothesis is that the proportion of patients achieving guideline-recommended management for T2DM and CVD at the last follow-up visit, as initiated or confirmed by a cardiologist, with a composite score of 3 will be similar between the intensive intervention educational arm and basic education arm.

7.2 Randomization

Site randomization: Site will be randomized when eligibility to participate in the trial has been established. To minimize imbalance between population characteristics in the basic education and intensive educational intervention groups, a stratified randomization based on geographic classification (urban or non-urban) will be implemented to ensure that selected site characteristics are balanced within each stratum. Site randomization will be conducted through a database platform using the randomization scheme (block randomization based on stratification factors) generated by the study statistician and uploaded by data management. Site management has a "button" on their web portal that they can select when a site is ready to be randomized (must have IRB approval and contract executed). Randomized site will receive an official email with their randomization status/assignment.

Mitigation of potential sample bias after site randomization

The following processes will be implemented:

- Education before randomization, after randomization, and throughout the enrollment process that sites should AVOID enrolling only a certain type of patient (i.e., either high- or low-risk only)
- Assessment of patient enrollment characteristics once 25% and 50% of patients have been enrolled in the trial overall and by site to ensure that baseline characteristics are similar in the basic education arm and intensive educational intervention arm. If an imbalance is observed, measures will be taken to visit the involved sites and remedy the issue with the on-site clinical leads.
- Outcomes will be adjusted for differences in baseline characteristics, to be detailed in the statistical analysis plan.

7.3 Sample Size Determination

The primary outcome is the proportion of patients receiving guideline-recommended therapy, defined as a composite score of 3 at the last follow-up visit. The primary analysis is based on the comparison of primary outcome between the basic education and intensive educational intervention arms. The sample size provides adequate power to detect a clinically meaningful effect size of at least a 10% difference between treatment arms in the proportions of patients achieving a composite score of 3 by the last follow-up visit.

In this cluster-randomized trial, where the experimental unit is site, the effective sample size and power is impacted by intra-cluster correlation (ICC). For the primary outcome, the sample size calculation is based on the ability to detect at least a 10% difference between treatment arms in the proportion of patients achieving guideline-recommended management for T2DM and CVD with composite score of 3. The effect size of a 10% change has been chosen as a clinically meaningful difference between the intensive educational intervention and basic education arms.

A minimum of 42 sites ("clusters") with an average cluster size of 25 patients per site (a total of 1050 patients) will provide at least 85% power to detect a 10% difference in the primary outcome between educational intervention arms through the last follow-up visit (6 to 12 months). This estimate of a minimum of 21 sites per arm (average of 25 patients per site) is based on the assumption of 10% of patients in the basic education arm, and at least 20% in the intensive educational intervention arm, receiving guideline-recommended therapy at the last follow-up visit, with an intra-correlation coefficient (ICC) of 0.05, and two-sided type I error rate of 0.05. The sample size/power calculations were carried-out using R function "n4props" in (package "CRT Size").[11]

7.4 Planned Statistical Analysis

An initial SAP defining the analysis populations, known covariates of interest, and procedures for handling missing and spurious data will be established and archived prior to enrollment of the first patient. The full statistical analysis plan (SAP) will be finalized before database lock. This section is a summary of the planned statistical analyses of the primary and secondary outcome.

The primary outcome will be analyzed using a multivariable logistic regression model with a generalized estimating equations (GEE) using a compound symmetry working correlation matrix to account for the effect of clustering, as well as adjustment for potential baseline factors as

covariates (including the baseline composite score). This model will provide the estimated adjusted odds ratio and 95% CI.

For time-to-event outcomes, multivariable Cox proportional hazards models with shared frailties to account for clustering effects will be used. Adjusted hazard ratio and 95% CI will be estimated from the Cox model after adjustment for pre-specified baseline factors. The complete list of pre-specified adjustment variables will be described in the final study SAP.

Baseline comparisons of participant characteristics in each arm will be summarized as the mean (SD), median (25th, 75th percentiles) for continuous variables, and as counts (percentages) for categorical variables. Differences in baseline participant characteristics between randomized arms will be compared using a Wilcoxon rank-sum test for continuous variables and the Pearson's chi-square test or the Fisher's exact test for categorical variables. All trial objectives will be analyzed using the intention-to-treat principle.

The primary database lock is planned after the last patient enrolled has completed 6 months of follow-up. Patient death will be reported to BI as an adverse event if the patient was identified to be on a BI drug for the disease in focus of the study.

8. Electronic Health Record Study Plan

In addition to the educational interventional trial, an observational analysis will be conducted in tandem with a subset of sites with existing datamarts containing EHR data in a common data model (CDM) format. The objectives of this observational analysis are to describe the clinical characteristics, management, and outcomes of patients with T2DM and CVD in current practice across an array of health systems in the United States and to characterize trends in the quality of care for patients with T2DM and CVD over time.

8.1 EHR Study Cohort Creation and Longitudinal Assessment

Early in the project period, a query to describe the clinical characteristics, management, and longitudinal outcomes of patients with T2DM and CVD will be distributed to sites participating in the EHR study. Out of approximately 80 data partner (DataMart) sites, at least 15 are expected to return results for this first query. Sites that return query results are expected to be both those that do participate in the trial, as well as sites that have no further engagement. The results of this query will help establish a broad, national baseline to better understand this population and their management.

Additionally, for the EHR sites that participate in the trial, patient recruitment will be facilitated by use of a cohort identification query. This query will be programmed centrally and distributed to each site to run at desired intervals to identify patients with designated inclusion and exclusion criteria, as listed in the Patient Inclusion and Exclusion section of the Trial Summary table. Results of the cohort identification query will be utilized and remain at each site.

8.2 Query Creation, Distribution, and Return

The EHR query will be carefully created with input from the clinical and educational intervention team to include all relevant characteristics and possible management practices. While the final set of data elements will be selected by the study team based on feasibility and clinical relevance, elements of interest include (but are not limited to) the following and will be

selected from the PCORnet Common Data Model (CDM) v4.0 (see http://www.pcornet.org/pcornet-common-data-model/):

- Demographics (age, sex, race)
- Laboratory values (creatinine, hemoglobin A1C)
- Body mass index
- Blood pressure
- Comorbidities (hypertension, lipid disorders, cancer, pulmonary disease, heart failure, retinopathy, stroke/TIA, serious mental illness, atrial fibrillation)
- Medications (antithrombotics, antihypertensives, ACEI/ARB, beta blockers, calcium channel blockers, antiarrhythmics, lipid lowering medications, diuretics, oral glucocorticoids, metformin, sulfonylureas, meglitinides, thiazolidinediones, GLP-1 receptor agonists, SGLT2 inhibitors, DPP4 inhibitors).
- Inpatient and outpatient encounters within the health system, including cardiovascular and non-cardiovascular hospitalizations

Once all elements are defined, code lists comprising ICD9-10 codes and LOINC codes will be created so as to represent these elements according to the PCORnet CDM. From these code lists, the SAS-based queries will be programmed (i.e., query creation). As described below, queries are distributed to data partners via a secure file transfer system. Once received, data partners run the query locally against their standardized local data set, and then return the results of the query back for compilation (i.e., return). Data partners that are eligible to receive the baseline, descriptive query will be those that have populated the prescribing medication table according to the PCORnet CDM and have passed all relevant data quality checks during the most recent round of data curation (i.e., updating, which is conducted quarterly).

Participating EHR data partners will participate in a study cohort query in order to examine essential baseline, covariate, and outcome data to ensure they are correctly populated within the sites CDM and within acceptable boundaries of validity prior to responding to the descriptive queries. The study query package will be transmitted via a secure file transfer system which will be established for each participating site and which will be used for all queries and query results.

Each data partner will execute the study query package locally and return results to the coordinating center for review and approval. Upon notification that the data partner is approved, they will receive the descriptive query package and return results which will be compiled into a report for the sponsor and be used to inform the study education and implementation plan.

Analyses of these data will be detailed in a separate statistical analysis plan. All query results will be published in a manuscript.

8.3 Cohort Identification Query Impact

The estimated 10 EHR sites that participate in the educational intervention study will be supplied with a cohort identification query. This query captures inclusion and exclusion criteria available in the EHR and returns a list of potentially eligible participants for further consideration. The query can be run as frequently as the participating site decides once it has been initially programmed and distributed.

9. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

9.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines, where applicable
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) will be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC and the Funder, BI of SAEs or other significant safety findings as required by IRB/IEC procedures and in as described in section 1.2 of the protocol
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

9.2 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA (Health Insurance Portability and Accountability Act) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

9.3 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

9.4 Participant Engagement

The DCRI and BI/Lilly are committed to ensuring robust and diverse patient representation and engagement throughout the trial process – from trial design, to implementation, to dissemination of results. The DCRI's Research Together program provides access to DCRI thought leaders who understand the science of engagement and can advise on both patient and clinical engagement throughout the trial.

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