Statistical Analysis Plan (SAP)

NCT03936660

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

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Phase 4

Short Title:

COORDINATE -Diabetes

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Contents

1. Overview

The purpose of the statistical analysis plan is to describe the key components of the **COO**rdinating Ca**RDI**ology Cli**N**ics R**A**ndomized **T**rial of Interventions to Improve Outcom**E**s (COORDINATE) – Diabetes statistical analysis plan (SAP). This SAP is a supplement to the materials provided in the protocol version dated 4/2/2019 and will be revised (if needed) after implementation of protocol amendments (if any).

COORDINATE-Diabetes is a prospective cluster-randomized clinical trial to test the effectiveness of an innovative, clinic-level educational intervention to improve the management of patients with Type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). After IRB approval, sites will be randomized to a basic education arm or an intensive educational intervention arm, consisting of clinic-level multifaceted educational intervention aimed on improving evidenced-based care for patients with diabetes and cardiovascular disease. Site randomization will be stratified by Urban vs. non-urban. The aim is to enroll on average 30 patients at each site of 46 cardiology clinic centers (23 in each arm) in the United States.

1.1 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.

1.2 Site and Patient 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. Detailed patient inclusion and exclusion criteria are included in study protocol.

<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

1.3 Sample Size Justification

The primary outcome is the proportion of patients achieving 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").[1]

2. General Considerations for Data Analysis

We will follow the guidance and standards for reporting of key elements based on the CONSORT statement for cluster randomized studies[2]. Key elements will include the following items: descriptions of participants, interventions, objectives, outcomes, and sample size justification; and details about the randomization procedure, factors used to stratify randomization, (lack of) blinding, statistical methods, participant flow, dates of recruitment, baseline data by individuals and by cluster, numbers analyzed, outcomes and estimation, adverse events, and a discussion.

Trial population details, including the number of sites randomized, number of patients, median and range of number of patients across sites, the number of patients in intensive and basic arms,

and the number of patients lost to follow-up, withdrawn, or excluded from analyses will be presented in a flow diagram (Appendix 3. Figure 1).

All analyses will be conducted using SAS version 9.4 or higher software. All tests will be two-sided and a p-value of <0.05 will be considered statistically significant. As this is a cluster randomized trial, all p-values will account for site.

2.1 Analysis Datasets and Baseline Comparisons

Data from all enrolled patients will be included in the analysis. To be enrolled in the study, patients must meet trial inclusion and exclusion criteria as detailed in the protocol. Baseline comparisons of patient 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 patient characteristics between randomized arms will be assessed at the patient-level using absolute standardized differences and at the site-level using 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.

2.2 Missing Data

Operational efforts will be made to minimize missing data at baseline and during follow-up. Data quality checks will be built into the electric data capture system. Baseline and follow-up data will be reviewed on a regular basis and sites will be notified regarding any data quality concerns. DCRI study team will confirm with sites that missing data cannot be obtained. We anticipate negligible rates of missing data at baseline and follow-up as sites are conducting follow-up with their patients and electronic health system.

For the primary analysis, missing data for lab values and vital signs will be imputed to age and gender specific modes for categorical variables and medians for continuous variables. Missing data for medical history will be imputed to modes for categorical variables and medians for continuous variables. Missing medication data during follow-up will not be imputed, rather we will use a mixed-effects repeated measures model (MMRM) that effectively accounts for missing and correlated data within subject which is described in detail (Section 3.1)[3]. On indicated/guideline recommended therapy (yes/no) will be carried forward rather than the medication itself. Note, the intervention arm compared with usual care has additional follow-up at 3 and 9 months. This additional follow-up data will be used to help carry out the intervention through site audit and feedback reports, but will not be used as part of the primary outcome. Missing data may occur during follow-up due to a provider recommended temporary or permanent discontinuation of T2DM and CVD management in order to treat serious medical conditions, such

as leukemia. Rates of serious medical conditions should be similar by treatment arm. Missing data due to serious medical conditions will be treated the same as missing data for other known or unknown reasons. A sensitivity analysis will be conducted imputing missing last follow-up composite scores as failures. To better gauge the effect of truncating study follow-up time, we will conduct a sensitivity analysis that uses only 6-month outcome data.

3. Endpoints

3.1 Primary Endpoint

The primary study objective is to determine whether the proportion of patients prescribed guideline-recommended management for T2DM and CVD with a composite score of 3 at last follow-up will be higher in the intensive educational intervention arm than in the basic education arm.

Components of Composite Score:

1. Use of a regimen which includes an anti-hyperglycemic agent indicated and/or guideline recommended to reduce cardiovascular risk*
    - Acceptable alternative: metformin monotherapy at any time with baseline HbA1c<7% or metformin monotherapy at 12 months with 12 month HbA1c<7%. Note, HbA1c is only collected at baseline and 12 months for both arms. Metformin monotherapy with HbA1c<7% is collected as a reason for not prescribing SGLT1 or GLP2 among the intervention arm only and hence these reason variables will not be included as part of the composite score.
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 (6 or 12 months)**. This decision was approved by the Steering Committee. Medications started during the 12 month study period that receive FDA indication/guideline recommendation during that time will count towards the primary outcome. Medications use after the date of FDA indication/guideline recommendation will count towards the primary outcome even if the medication was started prior to FDA indication/guideline recommendation. For example, suppose patient started a new medication at 6 months and the new medication received approval at 10 months, if the patient was still prescribed the new medication at the 12 month visit, this will count towards the primary endpoint.

Medication data are collected from both patient report and clinic validated health record check. The primary outcome data source will be the clinic validated health record check that the medication was currently prescribed. For patients who die or discontinue from the study before their last planned follow-up, sites will be instructed to enter medication prescriptions at the last time the patient was stable.

The primary outcome will be analyzed using a mixed-effects model repeated measures (MMRM) multivariable logistic regression model with random intercept for the site to account for the clustering effect, an unstructured covariance for repeated-measures overtime, an interaction for treatment by time, as well as adjustment for potential baseline factors as covariates including the baseline composite score (see Appendix 1, Section 8.1 for list). Time is modeled as a categorical variable, which allows for an arbitrary trajectory. The interaction of treatment and time allows for different patterns of change by treatment overtime. All outcome data are used regardless of whether a patient has complete data. This model will provide the estimated adjusted odds ratio (that is odds of achieving a composite score of 3 at follow-up in the intervention arm to the similar odds in the usual care) and 95% confidence interval (CI). Intra-cluster correlation coefficients (ICCs) will be calculated from unadjusted and adjusted models overall and by treatment arms to quantify within-cluster heterogeneity.

Mixed model for the ith subject:

Logit $E[Y_i] = X_i\beta + Z_i\gamma_i + \varepsilon_i$

Where γ_i is independent of ε_i and both are normally distributed with mean zero and variance G and R_i; respectively. Y_i is the n_i x 1 response vector for the n_i observed responses for the i^{th} patient. β is the $p \times 1$ fixed-effects vector; X_i is the $n_i \times p$ fixed-effects design matrix; Z_i is the $n_i \times q$ matrix of random-effects design matrix; γ_i is the $q \times 1$ vector of random effects and ε_i is the $n_i \times 1$ vector of residuals. G is the $q \times q$ covariance matrix for the random effects, and R_i is the $n_i \times n_i$ covariance matrix for the residuals, which accounts for the repeated measurements. The only random effect is for cluster.

Example SAS code* with data in one record per patient per outcome time point:

```
proc glimmix data=indata;
   class futime intervention sitenum subnum &otherclass / ref=first;
   model defectfreescorefu (event='1') = futime intervention futime*intervention &othercovar
      / dist=binary link=logit s ddfm=betwithin;
   random intercept / subject=sitenum;
   random futime / subject=subnum(sitenum) type=un residual;
  nloptions tech=nrridg;
   run;
```

*Modifications to SAS code may be necessary pending model fit and/or convergence issues.

As a sensitivity analysis, we will assess a variation of the composite score where the acceptable alternative of metformin monotherapy with HbA1c<7 in component one is not considered part of the outcome.

3.2 Secondary Endpoints

All of the following secondary outcomes will be assessed at or through last follow-up.

3.2.1 Guideline Recommended Management Endpoints

Secondary study objectives include assessment of the effect of the intervention on cardiologist provider behavior as measured by the individual components of the primary outcome and a variation of the primary outcome. We will also assess the effect of the intervention on the individual components of the primary outcome and a variation of the primary outcome by any provider. For each outcome listed below, we will determine whether the proportion of patients will be higher in the intervention than in the usual care arm. The secondary outcomes will be analyzed using the same methods as the primary outcome; a mixed-effects repeated measures logistic regression model with random intercepts for site to account for the effect of clustering, an unstructured covariance for repeated-measures overtime, an interaction for treatment by time, as well as adjustment for potential baseline factors as covariates including the baseline composite score (see Appendix 1, Section 8.1 for list). Given relatively a large number of pre-specified secondary components below, the 95% CIs on the ORs will be used in the interpretation of these findings, rather than p-values.

Guideline Recommended Management as Prescribed by Cardiologist Endpoints

- Proportion of patients prescribed by Cardiologist achieving guideline-recommended therapy for T2DM
- Proportion of patients prescribed by Cardiologist an ACEi/ARB treatment
- Proportion of patient prescribed by Cardiologist a high-intensity statin treatment
- Proportion of patients achieving a composite score of ≥ 2 prescribed by Cardiologist

Guideline Recommended Management by any Provider Endpoints

- Proportion of patients achieving guideline-recommended therapy for T2DM
- Proportion of patients an ACEi/ARB treatment
- Proportion of patient a high-intensity statin treatment
- Proportion of patients achieving a composite score of ≥ 2

3.2.2 Intermediate Outcomes

A secondary objective of this trial is to assess whether the intervention will be associated with improvement from baseline on intermediate outcomes at last follow-up. Patients must have data at both time points to be included in the analysis.

For each of the continuous intermediate endpoints listed below, we will use a multivariable generalized mixed-effects linear model with random intercepts for site to assess the effect of the intervention after adjustment for potential baseline factors (see Appendix 1, Section 8.1 for list) including the baseline measure of each variable of interest. We will assess the relationship and the shape of association of each variable with the outcome and consider appropriate transformations for best fit. The unadjusted models will include intervention and the baseline measurement of variable of interest. Note, repeated measures model was not considered for the intermediate outcomes as labs were collected at only baseline and 12 months.

Continuous Intermediate Endpoints

- sBP at last follow-up
- dBP at last follow-up
- HbA1c at last follow-up
- LDL-C at last follow-up

For each of the binary intermediate endpoints listed below, we will use a multivariable mixed-effects logistic regression model with random intercepts for site to assess the effect of the intervention on reaching the target lab measure at last follow-up. We will adjust for potential baseline factors (see Appendix 1, Section 8.2 for list) including the interaction term in the model that is the interaction between the intervention and baseline achievement of target lab measure. The unadjusted models will include intervention and the baseline measurement of variable of interest.

Binary Intermediate Endpoints: Achieving targets at last follow-ups

- sBP<130 mmHg
- dBP<80 mmHg
- HbA1c<8%
- LDL-C<70 mg/dL
- Composite score of achieving all targets for sBP<130 mmHg, dBP<80 mmHg, HbA1c<8%, and LDL-C<70 mg/dL

3.2.3 Clinical time-to-event outcomes

A secondary important objective of this trial is to assess whether the intervention will be associated with decreased clinical outcomes with 12-months. The endpoint of interest would be the composite of all-cause death; hospitalization for: MI, stroke, decompensated heart failure, or urgent revascularization (coronary, peripheral, carotid). This endpoint will be measured in days from enrollment date to event date for those patients with an event; otherwise to time of last contact date for those patients without an event, ie censored. Each of the clinical time-to-first event outcomes will also be summarized individually with no formal statistical testing, ie will be

presented as hazard ratios (HRs) and 95% CIs. Estimates of the event rates by study arms will be displayed graphically using Kaplan-Meier cumulative risk[4]. Cox proportional hazards model with shared frailty[5] (ref) to account for clustering effect will be used to estimate unadjusted HR (95% CI). The primary analysis will be a multivariable Cox proportional hazards model with shared frailty to account for clustering effect, adjustment for pre-specified baseline factors (see Appendix 1, Section 8.1 for list).

4. Tertiary Endpoints

All-cause mortality, as assessed by vital status obtained through the National Death Index or other sources will be assessed at 2 and 5 years after the final visit. Patient death will be reported to Boehringer Ingelheim (BI) as an adverse event if the patient was known to be on BI medication for the treatment of T2DM.

5. Implementation Endpoints

At 12 months from site randomization, 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

Provider survey data will be summarized as the mean (SD), median (25th, 75th percentiles) for continuous variables, and as counts (percentages) for categorical variables by intervention arm. Depending on the primary results and site variation in implementation, we may explore the association between site implementation and the primary outcome.

6. Electronic Health Record Sub-study

A subset of sites with existing datamarts containing EHR data will be included in an observational analysis to describe the clinical characteristics, management, and outcomes of patients with T2DM and CVD in current practice across an array of health systems and to characterize trends in the quality of care for patients with T2DM and CVD over time. These data will be not be used to assess the effect of the intervention. A detailed description of the EHR sub-study endpoints and analysis will be contained in a separate statistical analysis plan.

7. Subgroup Analysis

The primary outcome will be assessed for the subgroups using the same methods as the primary analysis. Results of the subgroup analysis will be presented graphically with a forest plot. We will assess the following subgroups:

Subgroups:

- Age: Age ≥65 and age <65
- Sex: Males and females
- Race: White, Black, and Asian/Other
- LVEF≥40 and LVEF<40
- History of heart failure and no history of heart failure
- History of atrial fibrillation and no history of atrial fibrillation

8. References

1. Team RC. R: A language and environment for statistical computing. 2013
2. Campbell MK, Piaggio G, Elbourne DR, Altman DG. Consort 2010 statement: extension to cluster randomized trials. *BMJ.* 2012. 345:e5661
3. Mallinckrodt CH, Watkin JG, Molenberghs G, et al. Choice of the primary analysis in longitudinal clinical trials. Pharm Stat. 2004;3:161–9.
4. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Statist Assn 1958; 53: 457-481.
5. Austin PC. A Tutorial on Multilevel Survival Analysis: Methods, Models and Applications. *Int Stat Rev*. 2017 August ; 85(2): 185–203.

9. Appendix 1: Covariates of Interest

9.1 Potential Adjustment Variables for Primary Outcome Model

Variable	Variable Type
Intervention	yes/no
Site: Urban vs. non-urban	yes/no
Age	continuous
Male sex	yes/no
Race	categorical (Black, Asian/Other, vs. White)
Baseline composite score	ordinal (0-2)

Charlson Comorbidity Index (CCI)	categorical (severe defined as CCI scores ≥5, moderate defined as CCI scores of 3–4, vs. mild defined as CCI scores of 1–2)
Baseline systolic BP	continuous
Baseline diastolic BP	continuous

9.2 Potential Adjustment Variables for Binary Intermediate Outcome Models

Variable	Variable Type
Intervention	yes/no
Site: Urban vs. non-urban	yes/no
Age	continuous
Male sex	yes/no
Race	categorical (Black, Asian/Other, vs. White)
Baseline composite score	ordinal (0-2)
Charlson Comorbidity Index (CCI)	categorical (severe defined as CCI scores ≥5, moderate defined as CCI scores of 3–4, vs. mild defined as CCI scores of 1–2
**Achievement of Baseline HbA1c<8%	yes/no
Achievement of Baseline systolic BP<130 mmHg	yes/no
Achievement of Baseline diastolic BP<80 mmHG	yes/no
**Achievement of Baseline LDL-C<70 mg/dL	yes/no
Interaction* between intervention and achievement of baseline target	combination of intervention (yes/no) and achievement of baseline target (yes/no)

*For each outcome, we will test for interaction between intervention and achievement of that baseline target.
**Only the HbA1c and LDL-C outcomes will be adjusted for achievement of these Baseline metrics due to the rate of not drawn for these labs.

10. Appendix 2: Table Shells

Table 1. Patient-level Baseline characteristics by Intervention

PATIENT CHARACTERISTICS	Intervention	Usual Care
Age		
Sex		
Race: White Black Asian Other		
Ethnicity: Hispanic/Latino Not reported		
Insurance/payer: Medicare Part D Supplemental Plan Medicaid Private State-specific (non-Medicaid) Military health care Indian health services Other US insurance		
Medication prescription:		
Lipid lowering therapy: Statin: Low intensity Moderate intensity High intensity Ezetimibe Fibrate Niacin PCSK-9 Prescription-grade Omega 3 FA		
Glucose-lowering therapy: Metformin Insulin Sulphonylurea DPP4 Thiozolidinedione GLP-1RA SGLT-2		

Other Severity: Monotherapy > 1 glucose-lowering medication Average insulin dose		
Anti-hypertensive therapy ACE/ARB Beta-blocker Diuretic Calcium channel blocker MRA		
Anti-thrombotic therapy Aspirin P2Y12 receptor antagonist Warfarin DOAC		
Cardiovascular history		
Coronary artery disease Prior MI Prior CABG Prior PCI Obstructive (≥50%) CAD (CT/ICA)		
Cerebrovascular disease: Prior ischemic stroke Carotid artery stenosis (>50%)		
Peripheral arterial disease: Prior peripheral revascularization Prior amputation due to poor circulation History of Claudication with ABI <0.9		
Atrial fibrillation		
Heart failure		
Hypertension		
Dyslipidemia		
Cigarette smoking		
Non-Cardiovascular		
Charlson Index		
Diabetes history		
Time since diabetes diagnosis < 1 year		

> 1 to 5 years >5 to 10 years >10 years		
History of DKA		
Complications Retinopathy Neuropathy Diabetic foot Gastroparesis		
Physical characteristics		
Blood pressure SBP DBP		
Heart rate		
BMI		
Laboratory characteristics		
Lipids LDL HDL TG		
eGFR		
HbA1c		
Urine albumin-to-creatinine ratio <30 mg/g 30-300 mg/g >300 mg/g		

Table 2. Site-level baseline characteristics by Intervention

CLUSTER CHARACTERISTICS	Intervention	Usual Care
# of patients enrolled		
Location: Urban Non-urban		
Average baseline composite score (enrolled patients)		

Table 3. Effects of the Intervention on Guideline Recommended Medications

	No./Total (%) at last follow-up		Unadjusted		Adjusted	
Analysis	**Intervention**	**Usual Care**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Primary Outcome: Composite Score of 3						
Prescribed by Cardiologist: Achieving guideline-recommended therapy for T2DM ACEi/ARB treatment High-intensity statin treatment Achieving a composite score of ≥ 2						
Prescribed by Any Provider: Achieving guideline-recommended therapy for T2DM ACEi/ARB treatment High-intensity statin treatment Achieving a composite score of ≥ 2						

Table 4. Effects of the Intervention on Continuous Intermediate Endpoints at last follow-up

	Intervention			Usual Care			Unadjusted		Adjusted	
Analysis	**Baseline N, Mean (SE)**	**Follow-up Mean (SE)**	**Difference**	**Baseline N, Mean (SE)**	**Follow-up Mean (SE)**	**Difference**	**Coefficient (SE)**	**P-value**	**Coefficient (SE)**	**P-value**
sBP										
dBP										
HbA1c										
LDL-C										

SE- Standard Error
Population includes patients with data at both time points

Table 5. Effects of the Intervention on Achieving Targets at last follow-up

	Intervention		Usual Care		Unadjusted		Adjusted	
Analysis	**Baseline No./Total (%)**	**Follow-up No./Total (%)**	**Baseline No./Total (%)**	**Follow-up No./Total (%)**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
sBP<130 mmHg dBP<80 mmHg HbA1c<8% LDL-C<70 mg/dL Composite score of achieving all targets								

Population includes patients with data at both time points

Table 6. Effects of the Intervention on Clinical time-to-first event endpoints within 12 months

	Cumulative Incidence (95% CI)		Unadjusted		Adjusted	
Analysis	**Intervention**	**Usual Care**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Composite of all-cause death; hospitalization for: MI, stroke, decompensated heart failure, or urgent revascularization (coronary, peripheral, carotid)						
All-cause death						
Hospitalization for MI						
Hospitalization for Stroke						
Hospitalization for decompensated heart failure						
Hospitalization for urgent revascularization						

11. Appendix 3: Figure Shells

Figure 1: Trial Population Flow Diagram