Racial Inequality in Inhaler Fills for COPD – A Trial of Reduced Cost-Sharing

Protocol and Analysis Plan

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A. Introduction

The prevalence of and morbidity from chronic obstructive pulmonary disease (COPD) is higher among Black populations than other racial groups in the United States. In this study, we will examine how elimination of cost-sharing for maintenance inhalers could potentially mitigate racial disparities in the care of patients with COPD. Maintenance inhalers for COPD are highly effective in reducing patient morbidity and mortality, but cost-sharing may reduce their utilization, particularly among vulnerable patient populations. Despite its ubiquity, there is little rigorous evidence on how cost-sharing might contribute to health disparities.

In partnership with a large Medicare Advantage (MA) insurer (Humana Inc.) and as part of a Center for Medicare and Medicaid Innovation demonstration program of Value-Based Insurance Design (VBID), we propose to study a randomized controlled quality improvement trial in which Humana randomized MA beneficiaries with COPD to receive proactive outreach for a VBID benefit that provided large reductions in cost-sharing for their maintenance inhalers and telephone-based COPD medication management services in 2020 and 2021. We will analyze changes in racial disparities for inhaler fills, clinical outcomes, health care spending, and acute care utilization. This proposal and analysis plan detail the intervention, randomization, and data source. Importantly, while this analysis plan is specified after the conduct of the trial, it does pre-specify the outcomes and statistical analysis prior to analysis of the trial data. Power analyses were conducted to inform the pre-specification of primary and secondary outcomes. No analyses of post-intervention outcomes were conducted prior to drafting and posting this proposal and analysis plan.

B. Treatment

The treatment is proactive outreach that sought to enroll individuals in a VBID program that was available to all eligible beneficiaries and provided: 1) large reductions in cost-sharing for maintenance inhalers, and 2) telephone-based COPD medication management services. Proactive outreach for those randomized to the treatment arm included, at a minimum, a phone call and letter in the mail from Humana. Proactive outreach could also have included an email, text message, and/or provider referral. Control group participants received no proactive outreach but could call to enroll themselves in the VBID program if they learned about it through traditional means, such as the benefits description manual. (As discussed in further detail below, the primary analysis will be on an intent-to-treat basis to account for incomplete take-up after outreach and crossover; in a separate analysis, we will also estimate a local average treatment effect using an instrumental variables approach.)

As noted above, the VBID program had two components. The first was a substantial reduction in beneficiary cost-sharing for maintenance inhalers. The specific maintenance inhalers eligible for cost-sharing reduction were those on tier 3 of the insurer's formulary (see Table 1 for full list). All other maintenance inhalers remained on a higher tier (i.e., tier 4) or were non-formulary, neither of which were eligible for cost-sharing reduction. Nebulized versions of these medications, regardless of tier, were similarly not eligible.

The cost-sharing reduction brought the out-of-pocket payment down to $0 if the participant elects to receive a 90-day supply at a preferred pharmacy (e.g., for delivery), or $10 if the participant elects to receive a 30-day supply at other in-network pharmacies. For beneficiaries in the deductible phase of their MA plan, the monthly payment for an inhaler therefore can go down from over $400 (maximum of $445 in 2021 and $435 in 2020) to either $0 or $10. For beneficiaries in the initial coverage phase of their MA plan, the monthly payment for an inhaler goes down from about $50 to either $0 or $10. For beneficiaries in the coverage gap phase or catastrophic phase of their MA plan, there is no additional cost-sharing reduction for participants who enrolled in the program. Individuals can be on more than one inhaler, and the cost-sharing reduction applies to all eligible tier 3 inhalers.

The second component of the program was up to three telephone calls for medication management services focused on addressing educational barriers to using the inhaler as prescribed. Participants enrolling in the VBID program were required to participate in the phone calls to receive the cost-sharing reduction. During the first phone call, a pharmacist ensured that the individual was on optimal therapy for COPD management, followed-up with the prescriber if the patient needed a new prescription, and connected the patient with a preferred pharmacy if desired. If the individual had their inhaler available at time of the first phone call, the pharmacist proceeded with additional education that included administering a COPD Assessment Test and adherence survey as well as coaching the individual on proper inhaler administration using the teach-to-goal methodology, an evidence-based technique that involves up to three iterative rounds of assessment and teaching. If the individual did not have their inhaler at the time of the first phone call, a subsequent phone call would be scheduled about 30 days later to complete the aforementioned activities. During the last phone call, which occurred about 60 days afterwards, a COPD Assessment Test was re-administered, and further coaching on proper inhaler administration was provided. If a beneficiary had entered, or would be likely to enter, the coverage gap phase of their prescription drug benefit (under which the cost-sharing reduction no longer applied), he or she would be counseled and referred for further assistance. Enrollees in 2021 who completed all three phone calls received a $75 gift card.

C. Randomization and Patient Eligibility

C.1. Randomization

Randomization occurred during the 2020 calendar year and again during the 2021 calendar year. In 2020, 51 MA plans with Medicare Part D prescription drug coverage (i.e., MAPD plans) across 16 states participated in the trial. In 2021, 138 MAPD plans across 25 states participated in the trial. MAPD plan participation was voluntary across Humana's local markets, and the VBID benefit was offered to all eligible beneficiaries enrolled in participating plans. Randomization into treatment (proactive outreach) versus control occurred at the patient level. After applying the inclusion and exclusion eligibility criteria detailed below, randomization was conducted by Humana in a one-to-one allocation between treatment and control. (As discussed in further detail below, the primary analysis will be pooled across both the 2020 and 2021 cohorts.)

After randomization and as discussed above, there was proactive outreach via phone and mail to those beneficiaries randomized to the treatment group to enroll them in the VBID program consisting of reduced cost-sharing for maintenance inhalers and telephone-based medication management services. Beneficiaries in the control group received usual care (no proactive outreach).

C.2. Patient Eligibility

- Inclusion Criteria
  - Has COPD diagnosis
  - Receives health services and prescription drug benefits through a Humana Medicare Advantage plan that includes Part D coverage
  - Has at least one prior fill of a COPD maintenance inhaler in the prior 12 months
  - Not fully adherent to maintenance inhaler (PDC < 80%) in year prior to randomization
- Exclusion Criteria
  - Enrolled in Part D Low-Income Subsidy program
  - On hospice
  - Has end-stage renal disease
  - Has mild COPD (i.e., COPD diagnosis but no maintenance inhaler fill, no pulmonary function tests in year prior year, and no acute care use for COPD)
  - Enrolled in Humana plan for less than 3 months
  - In the coverage gap phase of MA plan at time of assignment
  - Receives primary care at select locations of Humana subsidiaries (CenterWell or Conviva)

D. Data, Study Sample, Outcomes, and Other Variables

D.1. Data and Study Sample

We will use Humana Medicare Advantage claims data for all participants from January 2019 through December 2021. The study sample includes all MA beneficiaries in both the 2020 cohort and 2021 cohort who underwent randomization.

D.2. Planned Outcomes

All outcomes will be on a per-patient basis, annualized (for the utilization and spending outcomes), and measured using claims data for the year in which the participant was in the trial.

1. Primary Outcome
   a. Maintenance inhaler adherence

i. A maintenance inhaler is defined as any inhaler with an inhaled corticosteroid, long-acting beta-agonist, and/or long-acting antimuscarinic antagonist. This list includes but is not limited to the inhalers in Table 1.
ii. The proportion of days covered (PDC) is a common claims-based measure of adherence. It is calculated by dividing number of days covered by a prescription by the total number of days eligible for the medication. In constructing the measure, days covered (numerator) will be number of days on any maintenance inhaler (whether one of a single class, multiple of differing classes, or changes between inhalers), and the days eligible (denominator) will be number of days in the observation period. Early fills of the same medication will be moved to the end of the current fill period. In sensitivity analyses, we will ensure our results are robust to different versions of the PDC. The primary analysis will treat PDC as a continuous measure, but we will also dichotomize PDC to examine "full" adherence, which is defined as a PDC of 0.8 or greater.
iii. Because PDC is a rescaled and trimmed measure of number of inhalers filled, we will also assess number of inhalers filled, the underlying variable for our primary outcome.

2. <u>Secondary Outcomes</u>
    a. Frequency of acute moderate-to-severe exacerbations
        i. An exacerbation is defined as any acute worsening of symptoms that requires antibiotics or systemic steroids.
        ii. We will also assess exacerbations disaggregated by severity. Moderate exacerbations are those that do not result in hospitalization or death and therefore captures those exacerbations treated on an outpatient basis. Severe exacerbations are exacerbations that result in hospitalization.
    b. Number of short-acting inhaler filled
        i. A short-acting inhaler is defined as any inhaler with a short-acting beta agonist and/or short-acting antimuscarinic antagonist.
    c. Total spending
        i. Total spending includes both the insurer's payments and beneficiary's out-of-pocket payments.
        ii. We will also examine disaggregated spending according to payer (i.e., beneficiary out-of-pocket payment), type of service (i.e., drug spending) and setting (i.e., acute care spending, where "acute care" refers to emergency department visits, observation stays, and inpatient hospitalizations).

D.3. Covariates and Patient Characteristics

The data includes information on participants' age, sex, race, disability status, and geography. Using pre-randomization claims, we will also calculate or determine participants' COPD stage, presence of other chronic conditions, Hierarchical Condition Category (HCC) risk score, area-level sociodemographic characteristics, and utilization/spending prior to randomization. We

anticipate minimal missing data for these covariates. In the event that there are high levels of missingness for any key covariate (i.e., >2%), multiple imputation methods will be used.

Race is a key variable in our analysis. The race variable is derived from the Medicare enrollment database and comes from self-reported data on Social Security applications. Based on power calculations and the reliability of identifying racial/ethnic groups in the data, we focus specifically on Black versus White racial disparities.

E. Statistical Analysis

E.1. Evaluation of randomization, balance, and attrition

We will test for balance between treatment and control based upon observable baseline characteristics for the overall study population. These pre-randomization characteristics include those described in section D.3.

Because differential attrition correlated with treatment could introduce bias into our results, we will also evaluate the attrition rate and assess for balance between treatment and control based upon both baseline characteristics for the final analytic sample (and attritors) and potential causes of attrition (e.g., death, disenrollment).

E.4. Intent-to-treat analysis

Our primary analytic approach is an analysis based on the intent-to-treat principle that compares outcomes for those who were randomized into the treatment (proactive outreach) group to those who were randomized into the control group, regardless of actual enrollment to receive the supplemental cost-sharing reduction and care coordination benefits. We will estimate the following linear regression model:

$$y_i = \beta_0 + \beta_1 Treatment_i * Black_i + \beta_2 Treatment_i + \beta_3 Black_i + \beta_4 \boldsymbol{X_i} + \beta_5 \boldsymbol{V_i} + \beta_6 \theta_\tau + \varepsilon_i \quad (1)$$

In equation (1), y_i is the adherence, utilization, or spending outcome for participant i. See section D.2. for a list of our primary and secondary outcomes. "$Treatment_i$" is an indicator for whether individual i was randomized into the treatment group. "$Black_i$" is an indicator for whether individual i identified his/her/their race as Black. $\boldsymbol{X_i}$ is a vector of covariates, specifically patient characteristics (sex, age, geography), which are not explicitly necessary since they should be unrelated to treatment status, but they may increase the precision of our estimates to the extent that they explain some of the variance in the outcome. $\boldsymbol{V_i}$ represents the baseline value of the outcome y. The rationale for including baseline values in the model is to improve precision as well as account for potential imbalance after randomization or regression to the mean. Finally, θ_τ is a fixed effect for month of randomization because randomization occurred on monthly basis within each cohort.

As described in section C.1. above, randomization and treatment assignment were done at the level of the individual and occurred for one cohort of patients in the year 2020 and again for a new cohort of patients in the year 2021. We will examine cohort-specific outcomes, but our primary analysis will be pooled across both the 2020 and 2021 cohorts. To do so, we will include a cohort-specific fixed effect in equation (1) and saturate the model with corresponding interaction effects such that our parameter of interest is estimated within a single regression model.

β_1 is the coefficient on the interaction between the "$Treatment_i$" and "$Black_i$" indicator variables, and it is our main coefficient of interest. It represents the *additional* effect of being in the treatment group on Black patients beyond the effect of being in the treatment group on White patients. In addition to our primary specification (1), which we expect to be more efficient than individual regressions by subpopulation, we will also estimate the overall effect, regardless of race (i.e., pooled), and separately by race in a model similar to (1) but without the race indicator or interaction term. All observations will be weighted by number of months spent in the study after randomization. Standard errors will be adjusted for heteroskedasticity.

E.5. Local-average-treatment-effect analysis

In addition to our primary intent-to-treat analysis, we will also conduct a local-average-treatment-effect analysis, also known as the average causal effect on the compliers, pooled and separately by race. While the intent-to-treat analysis provides an estimate of the effect of being randomized into the treatment (proactive outreach) group on the outcomes, the local-average-treatment-effect analysis provides an estimate of the VBID program (i.e., reduced cost-sharing for maintenance inhalers and telephone-based medication management services) on the outcomes.

For this analysis, we use randomization into the treatment group as an instrument for receiving the supplemental benefits and estimate the following two-stage least squares (2SLS) model:

$$y_{it} = \pi_0 + \pi_1 CSR_{it} + \pi_2 \boldsymbol{X_{it}} + \pi_3 \boldsymbol{V_{it}} + \pi_4 \theta_t + v_{it} \quad (2)$$

where CSR_{it} in equation (2) is estimated via the following first-stage regression:

$$CSR_{it} = \delta_0 + \delta_1 Treatment_{it} + \delta_2 \boldsymbol{X_{it}} + \delta_3 \boldsymbol{V_{it}} + \delta_4 \theta_t + \mu_{it} \quad (3)$$

In equation (2) and (3), CSR_{it} is an indicator variable for whether after being randomized to the treatment group, the patient subsequently enrolled to receive cost-sharing reduction (CSR) for maintenance inhalers and care management calls. π_1 is the local average treatment effect (LATE) of receiving the cost-sharing reduction (CSR) for maintenance inhalers and care management calls.

E.4. Alternative specifications and sensitivity analyses

Our primary specification includes baseline values of the outcome in the model to improve power as well as account for regression to the mean and any chance imbalance between the study arms after randomization. As described in section E.1., we will compare covariates between the treatment and control groups, and as a sensitivity check, we will exclude baseline values of the outcome in the model.

To ensure our estimates are robust to method of estimation, we will also estimate generalized linear models assuming a negative binomial distribution for the count utilization outcomes, a generalized linear model with a Bournoulli distribution and logit link function for the binary PDC outcome, and generalized linear models with a gamma distribution and log link for the continuous adherence and spending outcomes. In a final robustness check, we will Winsorize the spending measure to ensure that our estimates are not sensitive to outliers.

E.5. Statistical significance and adjustments for multiple comparisons

Statistical significance was defined as two-sided $P<0.05$ for the primary outcome. Because we have one prespecified primary outcome and a single prespecified coefficient of interest from estimating equation (1), we will not make any adjustments for multiple inference. For our secondary outcomes, we will the Benjamini-Hochberg procedure to calculate adjusted p-values that account for testing of multiple outcomes.

F. Tables

Table 1. Maintenance Inhalers Included for Cost-Sharing Reduction
Advair Diskus 100 mcg-50 mcg/dose powder for inhalation
Advair Diskus 250 mcg-50 mcg/dose powder for inhalation
Advair Diskus 500 mcg-50 mcg/dose powder for inhalation
Advair HFA 115 mcg-21 mcg/actuation aerosol inhaler
Advair HFA 230 mcg-21 mcg/actuation aerosol inhaler
Advair HFA 45 mcg-21 mcg/actuation aerosol inhaler
Arnuity Ellipta 100 mcg/actuation powder for inhalation
Arnuity Ellipta 200 mcg/actuation powder for inhalation
Arnuity Ellipta 50 mcg/actuation powder for inhalation
Breo Ellipta 100 mcg-25 mcg/dose powder for inhalation
Breo Ellipta 200 mcg-25 mcg/dose powder for inhalation
Breztri Aerosphere 160 mcg-9mcg-4.8mcg/actuation HFA aerosol inhaler
Flovent Diskus 100 mcg/actuation powder for inhalation
Flovent Diskus 250 mcg/actuation powder for inhalation
Flovent Diskus 50 mcg/actuation powder for inhalation
Flovent HFA 110 mcg/actuation aerosol inhaler
Flovent HFA 220 mcg/actuation aerosol inhaler
Flovent HFA 44 mcg/actuation aerosol inhaler
Fluticasone-Salmeterol 100-50
Fluticasone-Salmeterol 113-14
Fluticasone-Salmeterol 232-14
Fluticasone-Salmeterol 250-50
Fluticasone-Salmeterol 500-50
Fluticasone-Salmeterol 55-14
Spiriva Respimat 1.25 mcg/actuation solution for inhalation
Spiriva Respimat 2.5 mcg/actuation solution for inhalation
Spiriva with HandiHaler 18 mcg and inhalation capsules
Stiolto Respimat 2.5 mcg-2.5 mcg/actuation solution for inhalation
Striverdi Respimat 2.5 mcg/actuation solution for inhalation
Symbicort 160 mcg-4.5 mcg/actuation HFA aerosol inhaler
Symbicort 80 mcg-4.5 mcg/actuation HFA aerosol inhaler
Trelegy Ellipta 100 mcg-62.5 mcg-25 mcg powder for inhalation
Trelegy Ellipta 200 mcg-62.5 mcg-25 mcg powder for inhalation
Wixela Inhub 100 mcg-50 mcg/dose powder for inhalation
Wixela Inhub 250 mcg-50 mcg/dose powder for inhalation
Wixela Inhub 500 mcg-50 mcg/dose powder for inhalation