Using Double Negative Control Method to Adjust for Unmeasured Confounding When Evaluating Vaccine Effectiveness Among Medicare Older Adults (PDUFA VII Methodology Development Project)

Study Protocol

Date: 11/20/2025

Prepared by:

FDA: Yun Lu*, Rich Forshee*, Stephen Chang, Weidong Gu, Yin Huang, Hector Izurieta, Aneesha Sahu, Katherine Szarama, Barbee Whitaker, Jessica Zhou

Acumen, LLC: Ellie Smith, Arnstein Lindaas, Michael Wernecke, Kamran Kazemi, Ivy Zhang, Yogi Chillarige

University of Michigan: Xu Shi

**Denotes FDA study lead; remaining FDA authors listed in alphabetical order*

VERSION CONTROL

Version	Description	Date
1.0	Final 508-remediated protocol	11/20/2025

Table of Contents

1. BACKGROUND

Real-world evidence (RWE) has been increasingly used to inform regulatory decision making at the US Food and Drug Administration (FDA). FDA is building Sentinel/BEST (Biologics Effectiveness and Safety) methodology to improve understanding of robustness evaluations used to address the consistency of RWE with respect to study design, analysis, or variable measurement. FDA Center for Biologics Evaluation and Research (CBER) will develop new methods to support causal inference in BEST that could address product safety questions and advance our understanding of how RWE may be used for studying effectiveness.

Many potential sources of bias such as variable misclassification, unmeasured confounding, or selection bias could potentially impact the results of studies using real-world data (RWD). As stated in the Prescription Drug User Fee Act (PDUFA) VII commitment letter, FDA CBER will initiate a method development project to develop a method to use a double negative control adjustment to reduce unmeasured confounding in studying effectiveness of vaccines.

This method development project focuses on using a double negative control approach to adjust for the impact of unmeasured confounding in studying vaccine effectiveness. A double negative control approach uses a pair of negative control exposure and negative control outcome to control for unmeasured confounding.[1] The negative control exposures need to be associated with the unmeasured confounder but do not directly affect the outcomes. The negative control outcomes need to be associated with the unmeasured confounder but will not be directly affected by the exposures. The type of unmeasured confounding could vary by data source, study population, study design, exposure, and outcome. The selection of negative control exposure and outcome pairs in real-world studies is critical and needs to be evaluated case by case.

In non-interventional vaccine effectiveness studies, vaccinated individuals tend to seek health care more than unvaccinated individuals, so unmeasured health-seeking behavior could potentially bias the results. To minimize the impact of sources of bias other than health-seeking behavior, this study will develop methodology using zoster vaccine as an example due to minimal exposure misclassification and outcome misclassification, and limited impact of time-varying confounders.

This protocol describes the specifications for a planned case study on zoster vaccine effectiveness based on prior work conducted by the team.[2]

2. OBJECTIVES

The objective of this project is to develop a method to use a double negative control adjustment to reduce unmeasured confounding due to health seeking behavior in studying effectiveness of zoster vaccines.

3. METHODS

3.1 Study Design

This study will evaluate effectiveness of the Shingrix vaccine in preventing herpes zoster (HZ) using a retrospective cohort study. This protocol will focus on community-dwelling Medicare beneficiaires aged 65+. The primary analysis will compare individuals fully vaccinated with Shingrix to unvaccinated invididuals, and follow up analyses will use a vaccinated comparator.

3.2 Data Sources

The primary data sources for this study are Medicare enrollment records and claims data from Centers for Medicare and Medicaid Services (CMS). Details on the data sources are below:

- Demographic information and information on death is derived from the enrollment databases.
- Information on vaccinations, health covariates, preventive services and outcomes are derived from Medicare Part A (inpatient), Part B (outpatient and community settings), and Part D (prescription drug) claims.
- The American Community Survey (ACS) will provide information on beneficiaries' local population density, and the Area Deprivation Index (ADI) data is used to assess ADI at the block group or at the zip-code level based on the last known address of the beneficiary in the enrollment databases.[3]
- Medicare beneficiaries' skilled nursing facility and hospice residence status will be identified from claims, and Medicare beneficiaries' nursing home residence status will be ascertained from the Minimum Data Set (MDS). MDS is a monthly-updated dataset with routine assessments during a beneficiary's stay at a Medicare- or Medicaid-certified nursing homes.

3.3 Study Period

The study period will start on November 1, 2017 and extend through January 14, 2020.

3.4 Exposure and Index Date Definition

Vaccination status is identified with the use of National Drug Codes (NDCs) for the Shingrix vaccine in Medicare Part D claims. Beneficiaries with a Part D claim for the Shingrix vaccine are classified as vaccinated according to claims received. Beneficiaries are considered fully vaccinated after completion of their eligible second dose, with follow up beginning 30 days after date of second vaccination (Section 3.6). Second doses must occur between 30 and 180 days after the first dose. For the vaccinated cohort, index date will be assigned as the date a beneficiary is fully vaccinated.

The primary analysis will use an unvaccinated comparator group selected from the general population. Unvaccinated individuals will be matched to vaccinated individuals on birth date ±30 days and sex, then the matched unvaccinated individual will be assigned the same index date as the matched vaccinated individual. To avoid immortal time bias, unvaccinated individuals must only be unvaccinated at their index date and remain unvaccinated through follow up start. They may be vaccinated in the future, at which point they will be censored from the unvaccinated cohort, and may be included in the vaccinated cohort with a different index date. Matching with replacement will be conducted, meaning an unvaccinated individual may be matched to multiple times to multiple different vaccinated individuals.

A sensitivity analysis will restrict to flu-vaccinated population and utilize a flu-vaccinated and shingrix-unvaccinated comparator (3.10.4).

Beneficiaries with only one Shingrix dose will not be eligible for the vaccinated cohort. Beneficiaries can be included in the unvaccinated cohort and then censored at the time of vaccination (Section 3.6).

3.5 Study Population

The primary study population will include Medicare older adults enrolled in Parts A/B Fee-for-Service (FFS) as well as Part D:

- The beneficiary must be age 65 years or older on the index date.
- The beneficiary must have been continuously enrolled in Medicare Parts A/B FFS and Part D for 730 days prior to index date and through the date follow-up begins, with no Part C (Medicare Advantage) enrollment at any time during this period.
- The beneficiary must have aged into Medicare without ESRD or disability.
- The beneficiary must not have evidence of chronic/regular dialysis (defined through dialysis facility claims indicating chronic dialysis) in the 90 days prior to index date and through the date follow-up begins.
- The beneficiary must not be enrolled in hospice on index date through the date follow-up begins.
- The beneficiary must not be residing in a nursing home on index date through the date follow-up begins.
- The beneficiary must be alive on the date follow-up begins.
- The beneficiary must have *not* had a HZ claim in the IP/OP/PB setting in the 365 days prior to the index date through the date follow-up begins.
- The beneficiary must not meet any of the censoring criteria (Section 3.6) between index date and follow-up start date.

3.6 Follow-up Time and Censoring

Beneficiaries are followed starting 30 days following index date. Follow-up will continue until the occurrence of any of the following:

- Disenrollment from Medicare Parts A/B and/or D or enrollment into Part C
- Admission into a hospice care facility
- Admission into a nursing home facility
- Treatment of ESRD in a dialysis facility
- Occurrence of the outcome of interest
- Death
- End of the study period
- A subsequent HZ vaccine

3.7 Outcome Definitions

3.7.1 *Primary Outcomes*

This study uses one primary outcome, evaluating vaccine effectiveness against community HZ, using International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes and NDCs for antivirals to treat HZ:

(1) Community HZ is defined by a claim in the inpatient (IP), institutional outpatient (OP) or community (PB) setting with an ICD-10 diagnosis code for HZ in any position, combined with a claim for a prescription fill for HZ-specific antivirals within seven days of the diagnosis.

3.7.2 *Secondary Outcomes*

The secondary outcomes of HZ disease are defined as community ophthalmic zoster (OZ), and post-herpetic neuralgia (PHN), using ICD-10 diagnosis codes and NDCs for antivirals to treat HZ:

(1) Community OZ is defined by a claim in the IP, OP or PB setting with an ICD-10 diagnosis code for OZ in any position, combined with a claim for a prescription fill for HZ-specific antivirals within seven days of the diagnosis.
(2) PHN is defined in the 90-180 days after HZ onset using a modified version of the PHN algorithm from N Klein, et al.[a] and from Klompas, et al.[b]
    a. A beneficiary must have at least one subsequent ICD-10 B02.xx diagnosis in 90-180 days after initial HZ event

[a] Klein NP, Bartlett J, Fireman B, et al. Long-term effectiveness of zoster vaccine live for postherpetic neuralgia prevention. Vaccine. 2019;37(36):5422-5427. doi:10.1016/j.vaccine.2019.07.004
[b] Klompas M, Kulldorff M, Vilk Y, Bialek SR, Harpaz R. Herpes zoster and postherpetic neuralgia surveillance using structured electronic data. Mayo Clin Proc. 2011;86(12):1146-1153. doi:10.4065/mcp.2011.0305

b. AND at least one of the following:
    i. At least one incident Rx for anti-PHN drugs (anticonvulsant or analgesic drugs) in 0-60 days and without anti-PHN drugs in the 365 days prior to initial HZ event. Each drug class is handled separately.
    ii. A diagnosis for ICD-10 B02.2x (HZ with other nervous system involvement) in 90-180 days of HZ onset
    iii. A new diagnosis for ICD-10 M79.2 (neuralgia and neuritis, unspecified) or M54.10 (radiculopathy, site unspecified) in 0-180 days of HZ onset and without neuralgia or radiculopathy in the 365 days prior to HZ onset

3.8 Covariate Summary

Demographic factors including age, sex, and race/ethnicity are well-studied risk factors of HZ. Other factors, including socioeconomic conditions, functional immunocompromising chronic conditions, frailty characteristics, and health utilization characteristics, believed to be plausibly associated with both risk of HZ and propensity to seek care once HZ is contracted, are also included. Preventive service utilization variables are included. Also, analyses covariates for all studies include prior Zostavax vaccination and frailty characteristics.

Data on these factors are collected for the eligible study population. Demographic factors and socioeconomic conditions will be determined on date of cohort entry. Medical history and vaccination covariates will be measured in the 365 days prior to and including index, while preventative care covariates will be measured in the 730 days to 366 days prior to index.

3.8.1 *List of Covariates*

The list of covariates and full suite of definitions are separately documented and include the following covariates:

- Age (Continuous; modeled with spline to account for non-linear effects)
- Sex (Male; Female)
- Race (White; Black; Other)
- Census Region (West; Midwest; South; Northeast; Other)
- Low income susbsidy status
- Area Deprivation Index (ADI)
- Hospitalization stay in 1 year prior
- Outpatient-ER visit in 1 year prior
- General medical visit
- Zostavax vaccine in the 5 years prior to index date
- Health conditions, including: respiratory conditions, diabetes, cardiovascular conditions, renal diseases, liver disorders, neurological conditions

- Frailty conditions
- Preventative services (measured in -2 to -1 years prior to index):
    - General preventative services: Annual wellness visit (AWV); Counseling & Health risk assessment
    - Specific preventative services (defined as ordinal variable; 0, 1, 2, and 3+)
    - Vaccines: flu vaccines, pneumococcal vaccine, hepatitis B, tetanus
- Immunocompromised status

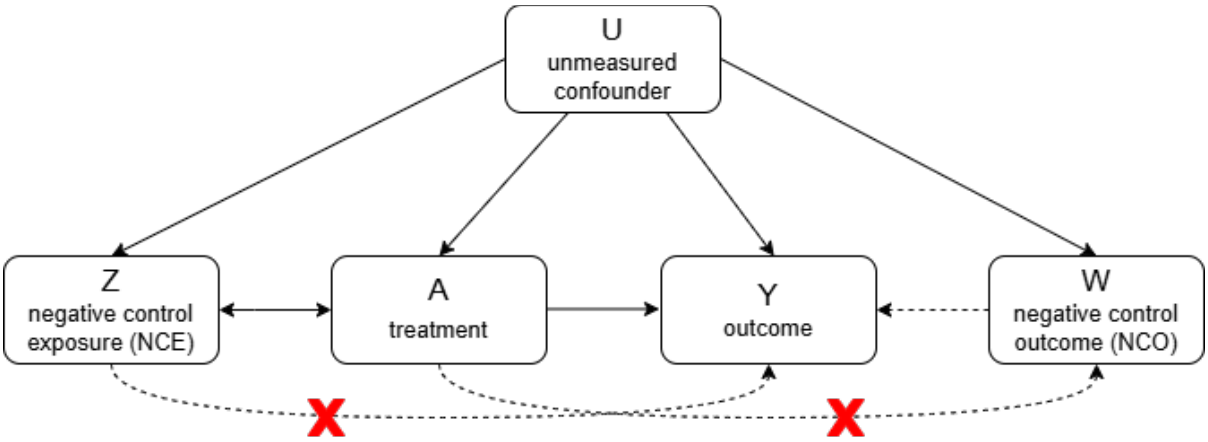
3.9 Negative Control Selection

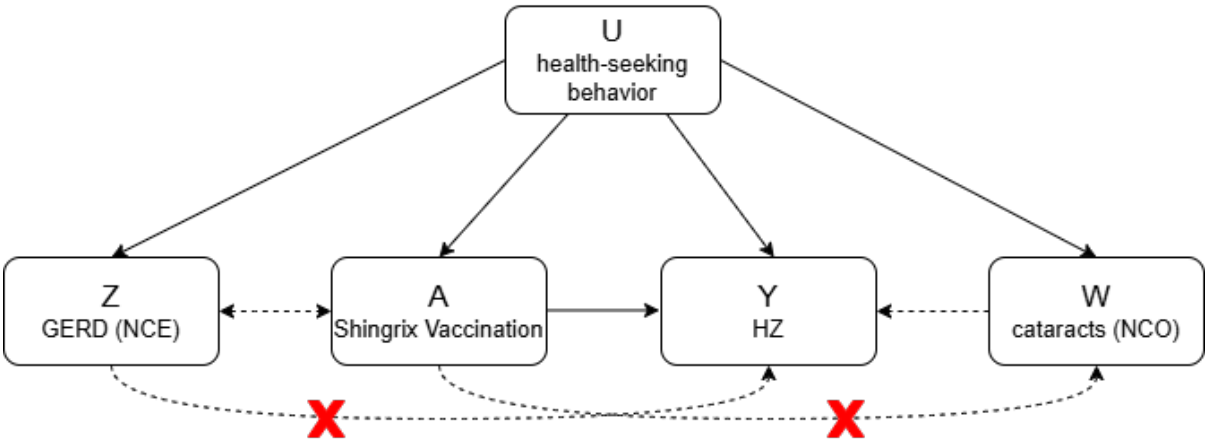
Potential negative control pairs are described below. The primary negative control pair will be GERD and cataracts. All negative controls will be identified in the 365 days prior to index date.

Table 1. Negative Control Exposure and Outcome

Z (NCE)	W (NCO)	Violation of Assumptions?
GERD	Cataracts	N/A
Cataracts	GERD	Potential violation for OZ outcome due to Z → Y
GERD	Earwax impaction	N/A
GERD	Eye Visit	N/A
Flu Vax	Cataracts	N/A
Wellness	Cataracts	Potential violation due to W → Z
Wellness	GERD	Potential violation due to W → Z
GERD	Wellness	Potential violation due to Z → W
Eye Visit	Cataracts	Potential violation due to W → Z

Directed acyclic graphs (DAGs) showing generalized and study-specific causal relationships are below.





Z is considered an NCE if Y (a,z) = Y(a) and Z ⫫ Y(a) | U , meaning Z cannot causally affect Y and must be associated with Y(a) only though U.

W is an NCO is W(a,z) = W and W ⫫ (A, Z)| U, meaning W cannot be causally affected by A and is associated with A, Z only through U.

3.10 Statistical Analysis

3.10.1 *Overview*

For all analyses, both a propensity-score weighted Poisson regression model and the double negative control method will be used to estimate the RR and 95% confidence interval for risks of the outcome among Shingrix-vaccinatated population compared to unvaccinated. The β_1 estimate from the Poisson regression will be compared to the marginal RR obtained from the double-negative control method.

3.10.1.1 Propensity-Score Weighted Poisson Regression

Inverse probability weighting (IPW) will be used to adjust for imbalances between cohorts across all measured covariates to obtain average treatment effect (ATE) weights.

A doubly robust Poisson model will be estimated as follows:

$$\log\big(\mathbb{E}(Y|E,X)\big) = \log(t) + \alpha_1 + \beta_1 * E + \sum \theta_j * X_j$$

$$Y = Herpes\ zoster\ outcome\ variable$$
$$E = Vaccinated\ cohort\ term$$
$$X_j = jth\ column\ of\ covariate\ matrix\ X$$

3.10.1.2 Double Negative Control Method

The double negative control analysis will adapt methods decribed in Shi (2020)[1] and related papers.[4-9] Details of the implementation are described in a technical appendix.

3.10.2 *Primary Analysis*

For the primary analysis, we will assess both primary and secondary outcomes (Section 3.7). Preventative care covariates will not be included the double negative control model (3.10.1.2) nor in the propensity score or propensity-score weighted poisson regression outcome model (3.10.1.1). All specified NCE/NCO pairs will be implemented for the primary outcome (Section 3.9).

3.10.3 *Secondary Analysis: Inclusion of Preventative Care Covariates*

The secondary analysis will include the specified preventative care covariates in the double negative control method and in the propensity-score weighted Poisson regression propensity score and outcome model. All outcomes and all negative control pairs will be implemented.

3.10.4 *Sensitivity Analysis: Flu-Vaccinated Population*

This analysis will restrict to a flu vaccinated population to reduce imbalances in health seeking behavior in the underlying population. All beneficiaries will be required to be flu vaccinated in the year prior to index date.

Both the primary analysis and secondary analysis (3.10.3) will be conducted for this specification. The primary HZ outcome and secondary PHN outcome will be evaluated. The

secondary OZ outcome will only be evaluated if substantial differences were noted in the primary analysis. Similarly, the primary NCO/NCE pair will be evaluated, with other pairs being included on a case-by-case basis according to the results seen in the primary analysis.

3.10.5 *Sensitivity Analysis: 365 Day Lookback*

This analysis will use a 365 day lookback for all covariates to assess if the method is robust to potential violations of causal assumptions.

Both the primary analysis and secondary analysis (3.10.3) will be conducted for this specification. The primary HZ outcome and secondary PHN outcome will be evaluated. The secondary OZ outcome will only be evaluated if substantial differences were noted in the primary analysis. Similarly, the primary NCO/NCE pair will be evaluated, with other pairs being included on a case-by-case basis according to the results seen in the primary analysis.

3.10.6 *Subgroup Analyses*

Subgroup analyses will be performed by age, sex, or health conditions (e.g., immunocompromised status).

3.10.7 *Medicare Current Beneficiary Survey (MCBS) Analysis*

We will link Medicare claims data with MCBS data and assess the balance of MCBS covariates unavailable in the claims-based databases for the subset of cohorts linked to MCBS. For the propensity-score weighted Poisson regression approach, we will assess pre- and post-weighting balance for the subset of cohorts linked to MCBS. The approach is detailed in the technical appendix.

4. FURTHER ANALYSES

In the course of protocol development, the team identified several development areas that were deemed out of scope of the current work. Areas for potential future work are noted below:

4.1 Health-Seeking Behavior Population Restriction Analysis

An alternative analysis restricting the population to beneficiaries with an indication of healthcare use will be conducted. This analysis may (a) exclude patients with no claim activitiy in the lookback and/or (b) restrict to patients with any preventative care use.

4.2 Average Treatment Effect of the Treated (ATT) Analysis

An analysis obtaining the average treatment effect of the treated (ATT) will be conducted.

4.3 Two-Dose Vaccine Exposures

This extension will adapt the methodology to allow for two-dose vaccine cohorts.

4.4 Alternate Negative Control Specifications

We will explore creating a categorical negative control and/or combing more than one condition into a binary negative control. This categorical negative control may capture:

- combinations of different types of health-seeking behavior (e.g., preventative care, and/or vaccinations and/or treatment for mild health conditions)
- different levels of health-seekingness
- frequency of health-seekingness

4.5 Alternate Case Study

To address the concern that the chosen case study is not subject to substantial bias due to health-seeking behavior, a follow-up study using an outcome more subject to health-seeking behavior bias may be employed. For example, a study of medically-attended RSV may be more impacted by health-seeking behavior bias.

4.6 Geographic Matching

The team may explore geographic matching of the vaccinated and unvaccinated comparator populations with as much granularity as feasible (e.g., census tract matching).

5. REFERENCES

1. Shi X, Miao W, Nelson JC, Tchetgen EJT. Multiply robust causal inference with double-negative control adjustment for categorical unmeasured confounding. J R Stat Soc Series B Stat Methodol. 2020;82(2):521-540. doi:10.1111/rssb.12361

2. Izurieta HS, Wu X, Forshee R, et al. Recombinant Zoster Vaccine (Shingrix): Real-World Effectiveness in the First 2 Years Post-Licensure. Clin Infect Dis. 2021;73(6):941-948. doi:10.1093/cid/ciab125

3. Kind AJ, Buckingham WR. Making Neighborhood-Disadvantage Metrics Accessible - The Neighborhood Atlas. New England Journal of Medicine. 2019;378(26):2456-2458.

4. Li K, Emerman I, Cook AJ, et al. Using double-negative controls to adjust for healthy-user bias in a recombinant zoster vaccine safety study. Am J Epidemiol. 2024:kwae439. https://doi.org/10.1093/aje/kwae439..

5. Shi X, Miao W, Tchetgen ET. A selective review of negative control methods in epidemiology. Curr Epidemiol Rep. 2020;7(4):190–202.

6. Miao W, Shi X, Tchetgen ET. A confounding bridge approach for double negative control inference on causal effects. arXiv preprint arXiv:1808.04945. 2018;

7. Miao W, Geng Z, Tchetgen Tchetgen EJ. Identifying causal effects with proxy variables of an unmeasured confounder. Biometrika. 2018;105(4):987–993.

8. Shi X, Wellman R, Heagerty PJ, et al. Safety surveillance and the estimation of risk in select populations: Flexible methods to control for confounding while targeting marginal comparisons via standardization. Stat Med. 2020;39(4):369–386.

9. Kummerfeld E, Lim J, Shi X. Data-driven Automated Negative Control Estimation (DANCE): search for, validation of, and causal inference with negative controls. arXiv preprint arXiv:2210.00528. 2022;