Modified HARmonized Protocol Template to Enhance Reproducibility – HARPER+

CMS has drafted this standardized real-world evidence (RWE) protocol template, called HARPER+, to be used by manufacturers or other sponsors when creating a study protocol using real-world data (RWD). The HARPER+ protocol template is based on the HARmonized Protocol Template to Enhance Reproducibility (HARPER), but adapted for medical devices and Medicare coverage criteria.

Below, the HARPER+ protocol template has been filled out with an example study to assist future protocol submissions. This HARPER+ example utilizes information from the following resources:

1) Longitudinal Assessment of Safety of Femoropopliteal Endovascular Treatment with Paclitaxel-Coated Devices Among Medicare Beneficiaries - PMC (nih.gov)
2) Study Details | Safety Assessment of Femoropopliteal Endovascular Treatment with PAclitaxel-coated Devices (SAFE-PAD Study) | ClinicalTrials.gov
3) Rationale and Design of the Safety Assessment of Femoropopliteal Endovascular treatment with PAclitaxel-coated Devices (SAFE-PAD Study) - PMC (nih.gov)

1. Title Page

Title	Safety Assessment of Femoropopliteal Endovascular Treatment with PAclitaxel-coated Devices (SAFE-PAD Study)
Research question & objectives	To provide a longitudinal assessment of the safety of femoropopliteal endovascular treatment with peripheral drug-coated devices (DCDs) among Medicare beneficiaries.
Protocol version	3
Last update date	2023-05-06
Contributors	**Primary Investigator contact information:** Eric A. Secemsky, MD and Robert W. Yeh, MD **Contributor names:** Acme, Inc.
Study registration in clinicaltrials.gov	**Site:** ClinicalTrials.gov **Identifier:** NCT04496544
Sponsor	**Organization:** Beth Israel Deaconess Medical Center **Contact:** PI@institution.edu
Conflict of interest: any real or perceived financial conflicts of interest (e.g., salary, consulting fees, ownership interests) that may influence the research outcomes	Dr. Secemsky reported receiving grants Acme, Inc. during the conduct of the study; and receiving grants from Acme, Inc., and Laminate Medical and personal fees from Acme, Inc. outside the submitted work. Dr. Schermerhorn reported receiving personal fees from Acme, Inc. outside the submitted work and participating in a scientific advisory board meeting without pay for Acme, Inc. Dr. Yeh reported receiving grants from Acme, Inc. during the conduct of the study; and receiving personal fees from Acme, Inc. outside the submitted work.

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2. Abstract

The SAFE-PAD Study aims to evaluate the long-term safety of paclitaxel-coated devices compared with non-paclitaxel-coated devices for femoropopliteal artery revascularization among a broad, real-world population of patients with peripheral artery disease. This multi-year analysis aims to create an ongoing mechanism to evaluate the safety of paclitaxel-coated devices in real-world practice. The null hypothesis is that the paclitaxel-coated devices are associated with an increase in mortality relative to the non-drug-coated devices beyond an acceptable magnitude (i.e., the non-inferiority margin), and the alternative hypothesis is that paclitaxel-coated devices are not associated with an increase in mortality relative to the non-drug-coated devices beyond the non-inferiority margin.

3. Amendments and Updates

Table 1. Documentation of the Amendments and Updates to the Study Protocol

Version date	Version number	Section of protocol	Amendment or update	Reason
2020-07-31	1	N/A	N/A	Initial version
2022-02-28	2	Milestones	Update on study status	Inform regulatory body of new anticipated dates of milestone completion
2023-05-4	3	Study identification and status	Update study identification identifier and study status	Inform regulatory body of new study identifiers and new anticipated dates of milestone completion

4. Milestones

Table 2. Milestones

Milestone	Date
IRB approval	July 2020
Obtain data use agreement	July 2020
Start enrollment	July 2020
Present interim results, including data quality checks, generalizability analysis, and enrollment/sample size update	December 2020
Enrollment and sample size update	January 2021
Publish study rationale and design paper	January 2021
Publish initial results paper	August 2021
Publish follow-on analysis paper	June 2022
Complete enrollment	June 2024
Perform final data quality checks and assessment of confounding adjustment	July 2024
Date when coverage under a Continued Access Study begins	October 2024
Review date with CMS	November 2024
Submit results for publication	December 2024

5. Rationale and Background

What is known about the condition (e.g., current standard of care including limitations, side effects):

Peripheral artery disease (PAD) affects 8.5 million Americans with combined annual costs exceeding $21 billion.[1–3] The current standard for treating symptomatic PAD includes bypass surgery and peripheral endovascular intervention (PVI).[4] The femoropopliteal artery, the most common site of lower extremity PAD, is characterized by high rates of restenosis after revascularization. Novel devices like paclitaxel-coated stents and balloons have been found to be effective at reducing the risk of restenosis by up to 50%.[5,6] Since FDA approval, paclitaxel-coated devices have experienced rapid uptake into clinical practice and are designated first-line therapies for femoropopliteal artery disease in society guidelines.[7–9]

What is known about the exposure of interest (e.g., expected benefits, indications/contraindications, subpopulations who benefit, mechanism of action, pertinent anatomy and physiology; in case of devices, performance metrics including battery life, failure rates):

A 2018 meta-analysis of randomized clinical trials found that paclitaxel-coated devices (drug-eluting stents [DES] and drug-coated balloons [DCB]) were associated with an increased risk of mortality at two years (risk ratio, 1.68; 95% CI, 1.15–2.47) and five years (risk ratio, 1.93; 95% CI, 1.27–2.93) compared with non-paclitaxel-coated peripheral devices (bare metal stents [BMS] and percutaneous transluminal angioplasty [PTA] with uncoated balloons).[10] The authors of that study postulated that the increased half-life and crystallinity of the paclitaxel found on these devices led to embolization in the systemic circulation, thus contributing to higher rates of amputation and mortality. The finding of increased long-term mortality associated with paclitaxel-coated devices was replicated by an internal analysis from the FDA.[11] The implications of these results have been vast: ongoing randomized trials were halted, and the FDA sent warnings to physicians recommending the use of these devices be restricted to “patients at particularly high risk for restenosis”.[12] In 2019, this led to a reduction in the sales of paclitaxel-coated devices by 50% and 30% in the U.S. and Europe, respectively, as well as a notable decline in use of these devices by a large U.S. healthcare system.[13–15]

The mechanism of action includes targeting the lesion with an antiproliferative agent (e.g., paclitaxel), which prevents restenosis (recurrent narrowing).

CMS-identified evidence deficiency and knowledge gaps:

Currently, the long-term safety of paclitaxel-coated devices compared with non-paclitaxel-coated devices for femoropopliteal artery revascularization among a broad, real-world population of patients with peripheral artery disease is not known.

What is the expected contribution of this study?

To evaluate the long-term safety of paclitaxel-coated devices compared with non-drug coated devices for femoropopliteal artery revascularization, with median follow-up time for the population surpassing five years.

6. Research Question and Objectives

Table 3. Primary and Secondary Research Questions and Objective

A. Primary research question and objective

Objective:	To provide a longitudinal assessment of the safety of femoropopliteal endovascular treatment with peripheral drug-coated devices (DCDs) among Medicare beneficiaries
Hypothesis:	Drug coated devices are as safe as non-drug-coated devices in the study population of interest
Population ***(mention key inclusion-exclusion criteria):***	Medicare fee-for-service beneficiaries (66+ years old) who underwent femoropopliteal artery revascularization. Patients needed at least one year of Medicare benefits prior to procedure.
Exposure(s):	Drug coated device (drug-eluting stent or drug-coated balloon)
Comparator(s):	Non-drug-coated device (NDCD) (bare metal stent or uncoated balloon)
Outcome:	All-cause mortality
Time ***(when follow up begins and ends):***	Median follow-up time of five years after exposure
Setting of exposure/intervention:	Outpatient or inpatient procedures
Main measure of effect:	Hazard ratio (HR)
Objective success criteria of powered endpoints:	Less than a 5% difference in all-cause mortality between the DCD and NDCD groups

7. Research Methods

7.1. Study Design

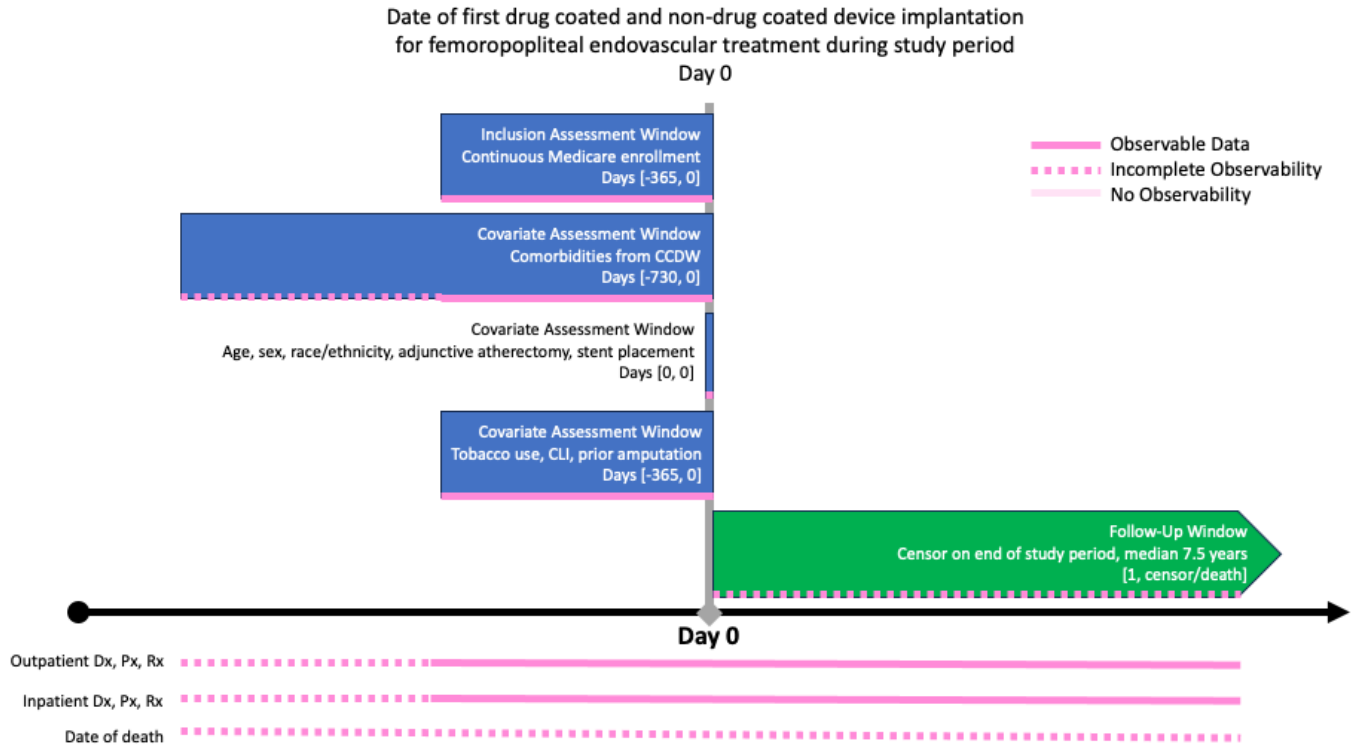
Research design (e.g., cohort, case-control):

Retrospective cohort study using claims data.

Rationale for study design choice:

The use of real-world data from a Medicare database will enable generalizability of the study population, larger sample sizes, and more diverse clinical settings to study the intervention.

7.2. Study Design Diagram



7.3. Setting

7.3.1. Context and Rationale for Definition of Time 0 (and Other Primary Time Anchors) for Entry to the Study Population

The date of intervention reported in the claims data will be used as time 0. We believe the date in the claims data to be sufficiently close to the true time 0.

Table 4. Operational Definition of Time 0 (Index Date) and Other Primary Time Anchors

Study population name(s)	Time anchor description (e.g., time 0)	Number of entries	Type of entry	Washout window	Care setting[1]	Code type[2]	Code position[3]	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
DCD	Date of the DCD procedure	Single	Incident	[-365, 0)	OP or IP	CPT, HCPCS, ICD-10-PCS	N/A	Prior 12 months of Medicare data	Sensitivity, specificity, PPV, and NPV reported in Secemsky et al. (2021)	Secemsky et al. (2021)
NDCD	Date of the NDCD procedure	Single	Incident	[-365, 0)	OP or IP	CPT, HCPCS, ICD-10-PCS	N/A	Prior 12 months of Medicare data	Sensitivity, specificity, PPV, and NPV reported in Secemsky et al. (2021)	Secemsky et al. (2021)

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] Use the appendix to list the clinical codes for each study parameter.
[3] Specify whether a code is required to be in the primary position (main reason for encounter).

7.3.2. Context and Rationale for Study Inclusion Criteria

N/A

Table 5. Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application	Assessment window	Care settings[1]	Code type[2]	Code position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Femoropopliteal artery revascularization	Treatment with either drug-coated or non-drug-coated devices	before	[0, 0]	IP, OP	CPT, HCPCS, ICD-10-PCS	N/A	DCD, NDCD	Sensitivity, specificity, PPV, and NPV reported in Secemsky et al. (2021)	Secemsky et al. (2021)
≥1 year of Medicare claims data prior to their index procedure	All patients with ≥1 year of Medicare claims data prior to their index procedure.	before	[-365, 0]	OT (MBSF)	N/A	N/A	DCD, NDCD	N/A	Investigators

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] Use the appendix to list the clinical codes for each study parameter.
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter).

7.3.3. Context and Rationale for Study Exclusion Criteria

N/A

Table 6. Operational Definitions of Exclusion Criteria

Criterion	Details	Order of application	Assessment window	Care settings[1]	Code type[2]	Code position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
<1 year of Medicare claims data prior to their index procedure	All patients with <1 year of Medicare claims data prior to their index procedure.	before	[-365, 0]	OT (MBSF)	N/A	N/A	DCD, NDCD	N/A	Investigators

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] Use the appendix to list the clinical codes for each study parameter.
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter).

7.3.4. Generalizability of Study Population

We believe our study population is going to be representative of the Medicare population who are candidates for DCD or NDCD given our broad inclusion criteria. At this time, we do not have statistics comparing the two populations.

7.4. Variables

7.4.1. Context and Rationale for Exposure(s) of Interest

We will use claim billing codes to identify both the exposure and comparator groups.

Algorithm to define duration of exposure effect:

Not relevant.

Table 7. Operational Definitions of Exposure

Exposure group name(s)	Details	Washout window	Assessment Window	Care setting[1]	Code type[2]	Code position[3]	Applied to study populations	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Exposure	Patients treated with paclitaxel-coated devices (drug-eluting stents [DES] and drug-coated balloons [DCB])	[-365, 0)	[0, 0]	OP or IP	CPT, HCPCS, ICD-10-PCS. See Table 15	N/A	DCD	Prior 12 months of Medicare data	Sensitivity, specificity, PPV, and NPV reported in Secemsky et al. (2021)	Secemsky et al. (2021)
Comparator	Patients treated with non-paclitaxel-coated peripheral devices (bare metal stents [BMS] and percutaneous transluminal angioplasty [PTA] with uncoated balloons)	[-365, 0)	[0, 0]	OP or IP	CPT, HCPCS, ICD-10-PCS. See Table 15	N/A	NDCD	Prior 12 months of Medicare data	Sensitivity, specificity, PPV, and NPV reported in Secemsky et al. (2021)	Secemsky et al. (2021)

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] Use the appendix to list the clinical codes for each study parameter.
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter).

7.4.2. Context and Rationale for Outcome(s) of Interest

Two studies have suggested that paclitaxel-coated devices were associated with increased risk of mortality. However, two analyses of CMS data have been published, which found no association between drug-coated device treatment and worsened survival. As an extension of this work, the Safety Assessment of Femoropopliteal Endovascular treatment with PAclitaxel-coated Devices (SAFE-PAD) study was designed to implement a prospective evaluation of five-year mortality of paclitaxel-coated devices among the U.S. population.

Table 8. Operational Definitions of Outcome

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care settings[1]	Code type[2]	Code position[3]	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
Death	Death observed within a median follow-up time of five years	Yes	Time-to-event	N/A	N/A	N/A	N/A	Exposure, comparator	99% of all deaths have been validated in Medicare data (ResDAC 2022)	Master Beneficiary Summary File

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[2] Use the appendix to list the clinical codes for each study parameter.
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter).

7.4.3. Context and Rationale for Follow Up

Per request by the FDA, the end of the study period will correspond with the projected median follow-up for the population of approximately five years, with a maximum follow-up of 7.5 years.

Table 9. Operational Definitions of Follow Up

Follow up start	Day 1	
	Below, indicate "Yes" or "No" to specify if event ends follow up[1]	**Specify additional details as relevant including code sets used to operationalize follow up that have not been previously referenced.**
Date of outcome	Yes	Outcome is death
Date of death	Yes	Outcome is death
End of observation in data	No	No censoring events
Day X following index date *(specify day)*	No	Will follow patients until study ends or death is observed
End of study period (specify date)	Yes	12-2024
End of exposure *(specify operational details, e.g., stockpiling algorithm, grace period)*	No	N/A
Date of add to/switch from exposure *(specify algorithm)*	No	N/A
Other date *(specify)*	No	N/A

[1] Follow up ends at the first occurrence of any of the selected criteria that end follow up.

7.4.4. Context and Rationale for Covariates (Confounding Variables and Effect Modifiers, e.g., Risk Factors, Comorbidities, Comedications)

Covariates were selected if they were identified by our clinical subject matter experts as potentially associated with either the exposure or outcome.

Table 10. Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care settings[1]	Code type[2]	Code position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Age	Age at time of procedure	Continuous	[0, 0]	All	N/A	N/A	Exposure, comparator	N/A	N/A
Sex	Sex of patient	Categorical	[0, 0]	All	N/A	N/A	Exposure, comparator	N/A	N/A
Race/ethnicity	Self-reported race/ethnicity using categories specified by CMS	Categorical	[0, 0]	All	N/A	N/A	Exposure, comparator	N/A	N/A
Acquired hypothyroidism	Comorbidity of acquired hypothyroidism	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Acute myocardial infarction	Comorbidity of acute myocardial infarction	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Alzheimer disease	Comorbidity of Alzheimer disease	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Alzheimer disease and related	Comorbidity of Alzheimer disease and related	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Anemia	Comorbidity of anemia	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Arthritis (RA/OA)	Comorbidity of arthritis (RA/OA)	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Asthma	Comorbidity of asthma	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Atrial fibrillation	Comorbidity of atrial fibrillation	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Benign prostatic hyperplasia	Comorbidity of benign prostatic hyperplasia	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW

Characteristic	Details	Type of variable	Assessment window	Care settings[1]	Code type[2]	Code position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Breast cancer	Comorbidity of breast cancer	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Colorectal cancer	Comorbidity of colorectal cancer	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Endometrial cancer	Comorbidity of endometrial cancer	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Lung cancer	Comorbidity of lung cancer	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Prostate cancer	Comorbidity of prostate cancer	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Cataract	Comorbidity of cataract	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Chronic kidney disease	Comorbidity of chronic kidney disease	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Congestive heart failure	Comorbidity of congestive heart failure	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
COPD/bronchiectasis	Comorbidity of COPD/bronchiectasis	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Critical limb ischemia	Comorbidity of critical limb ischemia	Categorical	[-365, 0]	All	ICD-10-CM, ICD-9-CM. See Table 16	N/A	Exposure, comparator	N/A	N/A
Depression	Comorbidity of depression	Categorical	[-365, 0]	All	OT, Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Diabetes	Comorbidity of diabetes	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Glaucoma	Comorbidity of glaucoma	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW

Characteristic	Details	Type of variable	Assessment window	Care settings[1]	Code type[2]	Code position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Hip/pelvic fracture	History of hip/pelvic fracture	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Hyperlipidemia	Comorbidity of hyperlipidemia	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Hypertension	Comorbidity of hypertension	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Ischemic heart disease	Comorbidity of ischemic heart disease	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Osteoporosis	Comorbidity of osteoporosis	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Prior amputation	History of prior amputation	Categorical	[-365, 0]	All	ICD-10-CM, ICD-9-CM. See Table 16	N/A	Exposure, comparator	N/A	N/A
Stroke/transient ischemic attack (TIA)	History of stroke/TIA	Categorical	[-365, 0]	All	OT: Variable from CCDW	N/A	Exposure, comparator	N/A	CCDW
Tobacco use	Tobacco use	Categorical	[-365, 0]	All	ICD-10-CM, ICD-9-CM. See Table 16	N/A	Exposure, comparator	N/A	N/A
Adjunctive atherectomy	Whether adjunctive atherectomy occurred during procedure	Categorical	[0, 0]	OP, IP	CPT, ICD-10-PCS. See Table 15.	N/A	Exposure, comparator	N/A	N/A
Inpatient procedure	Whether procedure was performed in the inpatient setting	Categorical	[0, 0]	IP	N/A	N/A	Exposure, comparator	N/A	N/A
Stent placement	Whether a stent was placed during procedure	Categorical	[0, 0]	OP, IP	CPT, ICD-10-PCS. See Table 15.	N/A	Exposure, comparator	N/A	N/A

Characteristic	Details	Type of variable	Assessment window	Care settings[1]	Code type[2]	Code position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Hospital femoropopliteal artery peripheral procedure volume	Hospital femoropopliteal artery peripheral procedure volume (per year)	Continuous	2016 American Hospital Association (AHA) Annual Survey File	N/A	N/A	N/A	Exposure, comparator	N/A	N/A
Teaching hospital	Indicator of whether the hospital where procedure was performed is a teaching hospital	Categorical	2016 American Hospital Association (AHA) Annual Survey File	N/A	N/A	N/A	Exposure, comparator	N/A	N/A
Hospital region	Geographical region of hospital where procedure was performed	Categorical	2016 American Hospital Association (AHA) Annual Survey File	N/A	N/A	N/A	Exposure, comparator	N/A	N/A
Hospital bed size	Hospital bed size where procedure was performed	Continuous	2016 American Hospital Association (AHA) Annual Survey File	N/A	N/A	N/A	Exposure, comparator	N/A	N/A

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[2] Use the appendix to list the clinical codes for each study parameter.
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter).

7.5. Data Analysis

7.5.1. Context and Rationale for Analysis Plan

The inverse probability weighting (IPW) method will be used as the primary analytic tool for the endpoints to correct potential confounding bias due to observed characteristics.[16,17] A propensity score model will first be fitted to connect group membership with patient and hospital characteristics. The Kaplan-Meier estimates of the cumulative incidence of survival and the log-rank test will then be computed. Statistical inference will be performed using the bootstrap method.

Table 11. Primary, Secondary, and Subgroup Analysis Specification

A. Primary Analysis

Hypothesis:	The hazard ratio of all-cause mortality of DCDs compared with NDCD is less than 1.05
Exposure contrast:	Exposure versus comparator
Outcome:	Death
Analytic software:	SAS, version 9.4
Model(s): *(provide details or code)*	Outcome model: Cox proportional hazards Followuptime*Status(0) = Exposure Propensity score model: logistic regression Exposure = Covariate1 + Covariate2 + … (see Table 9 for list of covariates included in propensity score model)
Confounding adjustment method	*Name method and provide relevant details, e.g., bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other. Describe the plans to quantitatively assess the performance of the confounding adjustment method (e.g., standardized mean differences in confounders between groups after adjustment).*
	We will use IPW to control for confounding. The performance of IPW will be evaluated by calculating covariate standardized mean differences (SMD) between the exposure and comparator groups. Post-weighting SMDs greater than 0.1 will be considered significant.
Missing data methods	*Identify assumed mechanisms of missingness (e.g., missing not at random, missing completely at random) and describe the method by providing relevant details, e.g., missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other. If possible, quantify the extent of missing data explicitly for key exposure, covariate, and outcome variables.*
	Complete case analysis. Missing covariates are believed to be independent of the outcome.
Subgroup analyses	*List all subgroups*

	We will perform multiple sub-group analyses to address residual questions. In order to examine a trial-like population, we will examine patients aged 66-70 years, with no critical limb ischemia and two or fewer comorbidities. We will also examine patients in the lowest quartile of total number of comorbidities. Additional subgroups will include procedural setting (inpatient or outpatient), disease severity (with or without history of critical limb ischemia) and device type (stent implantation or primary balloon angioplasty).

Table 12. Sensitivity Analyses – Rationale, Strengths, and Limitations

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Outcome Regression	A multivariable Cox model will be considered as an alternative and used to compare IPW estimates. The multivariable Cox model will include the main effects of group membership and the patient and hospital characteristics. The estimate of the hazard ratio associated with group membership will be compared to that generated by the IPW.	The IPW method could yield biased estimates if the propensity score model is mis-specified.	Checks if the propensity score is mis-specified.	Only the conditional association of the exposure on outcome can be assessed with covariate adjustment in a single model.
Simulation of Hypothetical Uncontrolled Confounders	The robustness of the inference with respect to uncontrolled confounding will be examined by artificially creating a confounder or multiple confounders and re-estimating the association between drug-coated device exposure and mortality including the simulated confounder(s). As the effect of multiple confounders can be mimicked by a single confounder in a linear model, one hypothetically uncontrolled confounder will be considered.[18]	By gradually varying the prevalence of the uncontrolled confounders and increasing their strength as measured by their association with group membership and the endpoint, the strength of the confounders needed to reverse the conclusion of the original analysis will be determined.	N/A	N/A

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Instrumental Variable Analysis	Another strategy to address unmeasured confounders will be to use instrumental variable (IV) methods. We will treat the percentage of drug-coated devices within each institution as the instrument since it has a causal effect on the exposure (drug-coated device or not). Most existing methods of instrumental variable-based causal inference for time-to-event outcomes are based on additive hazards models.[19,20] An alternative approach will be considered based on a Cox model, and will generate hazard ratios for comparison to the primary results.	To examine the relationship between exposure and outcome without the influence of unmeasured confounders.	N/A	N/A
Falsification Endpoints	Falsification endpoint testing will be used to assess the presence of unmeasured confounding. The pre-specified falsification endpoints will be hospitalized congestive heart failure, hospitalized myocardial infarction, and hospitalized pneumonia. See Table 17 for codes used as endpoints.	A confirmed falsification test—in this case, a significant association between paclitaxel-coated device use and a reduced risk of these outcomes—would suggest that an association of safety with these devices initially suspected to be causal is perhaps confounded by unobserved patient or physician characteristics.	N/A	N/A

7.6. Data Sources

7.6.1. Context and Rationale for Data Sources

Describe the data source(s):

This study will use Medicare FFS claims data, including inpatient Medicare Provider Analysis and Review (MedPAR) files, institutional outpatient files, Part B carrier claims, enrollment information, vital status data, Part D prescription drug information, and chronic conditions data. In addition, the 2016 American Hospital Association (AHA) Annual Survey File will be used to obtain institutional data.

Reason for selection:

The Medicare claims dataset is well-suited to evaluate the long-term association between the use of drug-eluting devices and all-cause mortality due to reasons listed below in “Strengths of data source(s).” We will utilize the 2016 AHA Annual Survey file because Institutional characteristics where the procedure is performed are important confounders for medical devices.

Strengths of data source(s):

First, Medicare is the largest insurer in the U.S., covering the majority of patients aged ≥65 years. Since PAD is more prevalent with age, Medicare insures a large proportion of patients with this disorder. This sample size allows for the needed analyses, including sensitivity and sub-group analyses, without requiring ongoing patient recruitment. This is critical since patients treated in 2019 onward, following the emergence of the safety signal and subsequent FDA warnings, differ substantially from those who were being treated before 2019. Furthermore, Medicare claims data contain specific device codes for femoropopliteal artery revascularization and drug-coated devices. As an early assessment of validity, we have demonstrated that these codes are both specific and sensitive for identifying drug-coated device treatment. The Medicare dataset includes procedures performed in both the inpatient and outpatient settings, collects data on a subset of patients with pharmacy coverage, and will enable tracking of patients’ utilization of the healthcare system, including repeat procedures and hospitalizations. Lastly, in contrast to other datasets that require external linkage to obtain mortality data, Medicare uses a number of sources to identify deaths of beneficiaries, with nearly 99% of all deaths validated.

Limitations of data source(s):

The limitations of using Medicare claims data are as follows. First, claims data lack certain granularity, including device specifications, lesion characteristics, and total paclitaxel treatment exposure. Second, there is potential for misclassification of the exposure using claims codes. However, this is attenuated by the association between procedural codes and compensation. Furthermore, we have now demonstrated that there is a high level of agreement between the device utilized and the claims code billed within our institutional data. Third, Medicare fee-for-service beneficiaries represent an older population of patients with higher rates of comorbidities compared with patients enrolled in the pivotal device trials, reducing the generalizability of our results.

Data source provenance/curation:

N/A

Table 13. Metadata about Data Sources and Software

	Data 1	Data 2
Data source(s):	CMS Medicare	2016 American Hospital Association (AHA) Annual Survey File
Study period:	4/1/2014 to 12/1/2023	2016
Eligible cohort entry period:	4/1/2015 to 12/31/2018	N/A
Data version (or date of last update):	Data will be updated semi-annually and continued until the median duration of follow-up surpasses five years	N/A
Data sampling/extraction criteria:	N/A	N/A
Type(s) of data:	Inpatient Medicare Provider Analysis and Review (MedPAR) files, institutional outpatient files, Part B carrier claims, enrollment information, vital status data, Part D prescription drug information, and chronic conditions data	N/A
Data linkage:	Medicare Provider ID/ CMS certification number	Medicare Provider ID/CMS certification number
Conversion to common data model (CDM)*:	No	No
Software for data management:	SAS	SAS

7.7. Data Management

Data will be collected and stored in a secure, centralized database, with appropriate access controls and backup systems in place to prevent unauthorized access and data loss. Regular data quality checks and validation procedures will be implemented to identify and address any data entry errors or discrepancies. Additionally, all data will be de-identified and anonymized to protect the privacy of the individuals involved in the study.

7.8. Quality Control

Data analysis will be conducted using well-documented and reproducible scripts or workflows, ensuring that the results can be easily verified and updated as needed. Upon completion of the study, the research team will prepare a data sharing plan, outlining the process for making the de-identified and anonymized datasets available to other researchers, subject to any necessary ethical approvals and data use agreements.

7.9. Study Size and Feasibility

The study population includes inpatient and outpatient procedures performed from 2015-2018. Through 2017, 155,032 femoropopliteal artery revascularization procedures were performed, with the following rates of device use: DCB 23.9% (N=36,410), DES 16.5% (N=25,097), PTA 37.2% (N=56,720), and BMS 22.5% (N=34,246). As such, we project 206,646 procedures will be included in the final cohort, with approximately 60% non-drug-coated devices and 40% drug coated devices. Per request by the FDA, the end of the study period will correspond with the projected median follow-up for the population of approximately five years, with a maximum follow-up of 7.5 years. There will be >99% power to reject the null hypothesis that drug-coated devices are associated with worsened survival.

Table 14. Power and Sample Size

Non-inferiority analysis	
Number of patients	
Exposed	82,658
Comparator	123,988
Non-inferiority margin (HR)	1.05
Power	>99%

8. Limitation of the Methods

Limitations of the data have been discussed in Section 7.6.1. In addition, the observational, non-randomized design may introduce unmeasured confounders. To address this, we have incorporated numerous sensitivity analyses to examine the impact of unmeasured confounding and to test whether results differ between alternative statistical approaches. Lastly, the study does not identify cause-specific mortality or assess for associations between paclitaxel exposure and specific causes of death.

9. Top Threats to Successful Completion of the Study Objectives

Table 15. Threats to Successful Completion of Study Objectives

Rank	Threat	Mitigation strategy
1	The observational, non-randomized design may introduce unmeasured confounders	We have incorporated numerous sensitivity analyses to examine the impact of unmeasured confounding and to test whether results differ between alternative statistical approaches.
2	Misclassification of the exposure using claims codes	This is attenuated by the association between procedural codes and compensation. Furthermore, we have now demonstrated that there is a high level of agreement between the device utilized and the claims code billed within our institutional data.
3	A randomized controlled trial emerges that demonstrates devices coated with a different drug has significantly lower complication rates than paclitaxel-coated devices.	We will immediately notify CMS to collaboratively develop a plan to address this issue.

10. Protection of Human Subjects/Governance

The study will be reviewed by the institutional review board of Beth Israel Deaconess Medical Center, where a waiver of informed consent due to using retrospective data analysis is anticipated.

11. Reporting of Adverse Events

We will report any suspected adverse events to the appropriate authority.

12. Applicable Federal Regulations

	Confirm/Agree
Sponsor/investigator attests that the study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals.	☒
Sponsor/Investigator commits to registering this study with ClinicalTrials.gov and to providing a complete final protocol to CMS prior to study initiation.	☒
Sponsor/Investigator commits to sharing data, methods, analytic code, and analytical output with CMS or with a CMS-approved third party if asked to do so.	☒
Sponsor/Investigator certifies that this study will comply with all applicable laws regarding subject privacy, including section 165.514 of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and 42 CFR, Part 2: Confidentiality of Substance Use Disorder Patient Records.	☒
Sponsor/Investigator commits to providing final results to CMS and to submit them for publication or to report them in a publicly accessible manner within 12 months of the study's primary completion date.	☒
Sponsor/Investigator commits to reporting the study using a reporting guideline appropriate for the study design and structured to enable replication.	☒
Sponsor/Investigator attests that any facts and statements made in this study or research protocol, or project plan submitted to CMS are complete and accurate. Additionally, all components will have been approved by CMS or other appropriate entities as CMS may determine.	☒
Sponsor/Investigator commits to maintaining data on a HIPAA-compliant server.	☒
Sponsor/Investigator commits to ensuring the integrity, security, and confidentiality of the data by complying with the terms of the agreement and applicable law, including the Privacy Act and HIPAA.	☒
Sponsor/investigator affirms that the data requested in this study is the minimum necessary to achieve the objectives of this study.	☒
Sponsor/Investigator affirms that data files will only be accessible and limited to the minimum necessary approved research personnel. Additionally, all personnel that will have access to the data will undergo HIPAA and or security training for access to sensitive data on the HIPAA-compliant server.	☒
Sponsor/Investigator certifies that remote login will require login from a personal computer or laptop, VPN authentication, and separate authentication to access the data on the server. Approved personnel may not download data onto their personal computers or laptops. Personal computers or laptops used to access the data will be encrypted, and will have their USB ports disabled, to prevent inadvertent disclosure of data. The server will be backed up regularly, and the backup will be encrypted and stored in a secure location.	☒

	Confirm/Agree
Sponsor/Investigator commits to ensuring the security programs, practices, and procedures comply with the HIPAA Security Rule and therefore, in the judgment of CMS and its independent third-party HIPAA auditor, provide a level and scope of security that is not less than the level and scope of security requirements set forth in (a) the Office of Management and Budget Circular No. A-130, Appendix III – Security of Federal Automated Information Resources; (b) Federal Information Processing Standard 200, "Minimum Security Requirements for Federal Information and Information Systems"; and (c) NIST Special Publication 800-53, "Recommended Security Controls for Federal Information Systems and Organizations."	☒
Sponsor/Investigator attests to the CMS cell suppression policy of not publishing or presenting tables with cell sizes less than 11.	☒
Sponsor/Investigator commits that at the end of this study and any follow-up period permitted under the Data Use Agreements or authorized by CMS in connection with a subsequent study, [Sponsor/investigator] copies of the data files (including both primary and archived files) will be destroyed consistent with National Institute of Standards and Technology (NIST) standards. Per NIH policy, all Medicare data will be retained at sponsor/investigator's research institution for two years following the termination of the study. Once this holding period has expired, sponsor/investigator will destroy all remaining data consistent with NIST standards and will certify the data's destruction to CMS. These procedures are governed by the Sponsor/investigator Data Use and Sharing Agreement.	☒
The sponsor/investigator hereby acknowledges that criminal penalties under §1106(a) of the Social Security Act (42 U.S.C. § 1306(a)), including a fine not exceeding $10,000 or imprisonment not exceeding five years, or both, may apply to disclosures of information that are covered by § 1106 and that are not authorized by regulation or by Federal law. The User further acknowledges that criminal penalties under the Privacy Act (5 U.S.C. § 552a(i) (3)) may apply if it is determined that the Requestor or Custodian, or any individual employed or affiliated therewith, knowingly and willfully obtained the file(s) under false pretenses. Any person found to have violated sec. (i)(3) of the Privacy Act shall be guilty of a misdemeanor and fined not more than $5,000. Finally, the sponsor/investigator acknowledges that criminal penalties may be imposed under 18 U.S.C. § 641 if it is determined that the sponsor/investigator, or any individual employed or affiliated therewith, has taken or converted to his own use data file(s), or received the file(s) knowing that they were stolen or converted. Under such circumstances, they shall be fined under Title 18 or imprisoned not more than 10 years, or both; but if the value of such property does not exceed the sum of $1,000, they shall be fined under Title 18 or imprisoned not more than 1 year, or both.	☒

13. Protocol Signatures

We, the undersigned, have reviewed and approved the clinical investigation plan specified above and agree on its content.

Sponsor Representative's Signature

_____ _____

Sponsor Representative Name Date (DD, MMM, YYYY)

_____

Sponsor Representative Signature

CMS Representative's Signature

_____ _____

CMS Representative Name Date (DD, MMM, YYYY)

_____

CMS Representative Signature

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15. Appendix A. Additional Statistical Considerations

NOTE: Most of the information relevant to the statistical analysis plan has been included in the main protocol above.

15.1. Multiple Testing

To control the family-wise type I error rate at 0.05, the Bonferroni approach will be applied so that each individual test will be performed at the level of 0.007 (one-sided).

16. Appendix B. Data Validation Output

The investigators will update this section when we get access to the data. Results of this analysis will be presented back to CMS by December 2020.

17. Appendix C. Data Use Agreement

See attached.

18. Appendix D. Data Dictionary

Please see https://www2.ccwdata.org/documents/10280/19022436/codebook-ffs-claims.pdf

19. Appendix E. Value Sets

Table 16. Procedure and Device Coding

Device & Procedure	CPT/ICD-10 Code
Drug-Coated Balloon	
Angioplasty, femoral, popliteal artery(ies), unilateral + catheter, transluminal angioplasty, drug-coated, non-laser	37224 + C2623*
Atherectomy, femoral, popliteal artery(ies), unilateral + catheter, transluminal angioplasty, drug-coated, non-laser	37225 + C2623*
Angioplasty with drug-coated balloon	047K3Z1, 047L3Z1, 047M3Z1, 047N3Z1
Angioplasty and stenting with drug coated balloon + bare-metal stent	047K3D1, 047L3D1, 047M3D1, 047N3D1
Drug-Coated Stent	
Stent placement(s), femoral, popliteal artery(ies), unilateral + stent, coated/covered, with or without delivery system	37226 + C1874 or C1875†
Stent placement(s) and atherectomy, femoral, popliteal artery(ies), unilateral + stent, coated/covered, with or without delivery system	37227 + C1874 or C1875†
Angioplasty and stenting with drug-coated balloon + drug-eluting stent	047K341, 047L341, 047M341, 047N341
Stenting with drug-eluting stent, with or without angioplasty with uncoated balloon	047K346, 047K34Z, 047K356, 047K35Z, 047K366, 047K36Z, 047K376, 047K37Z, 047L346, 047L34Z, 047L356, 047L35Z, 047L366, 047L36Z, 047L376, 047L37Z, 047M346, 047M34Z, 047M356, 047M35Z, 047M366, 047M36Z, 047M376, 047M37Z, 047N346, 047N34Z, 047N356, 047N35Z, 047N366, 047N36Z, 047N376, 047N37Z
Non-Drug-Coated Balloon Angioplasty (PTA)	
Angioplasty, femoral, popliteal artery(ies), unilateral +/- catheter transluminal angioplasty non laser	37224 +/- C1725‡
Atherectomy, femoral, popliteal artery(ies), unilateral +/- catheter transluminal angioplasty non laser	37225 +/- C1725‡
Angioplasty with uncoated percutaneous transluminal angioplasty balloon	047K3Z6, 047K3ZZ, 047L3ZZ, 047L3Z6, 047M3Z6, 047M3ZZ, 047N3Z6, 047N3ZZ
Bare Metal Stent (BMS)	
Stent placement(s), femoral, popliteal artery(ies), unilateral +/- stent non-coated/non covered with or without delivery system	37226 +/- C1876 or C1877§
Stent placement(s) and atherectomy, femoral, popliteal artery(ies), unilateral +/- stent non-coated/non covered with or without delivery system	37227 +/- C1876 or C1877§

Device & Procedure	CPT/ICD-10 Code
Stenting with bare metal stent, with or without angioplasty with uncoated balloon	047K3D6, 047K3DZ, 047K3E6, 047K3EZ, 047K3F6, 047K3FZ, 047K3G6, 047K3GZ, 047L3D6, 047L3DZ, 047L3E6, 047L3EZ, 047L3F6, 047L3FZ, 047L3G6, 047L3GZ, 047M3D6, 047M3DZ, 047M3E6, 047M3EZ, 047M3F6, 047M3FZ, 047M3G6, 047M3GZ, 047N3D6, 047N3DZ, 047N3E6, 047N3EZ, 047N3F6, 047N3FZ, 047N3G6, 047N3GZ

* C2623 is required with CPT code 37224 to define drug-coated balloon
† C1874 or C1875 is required with CPT 37226 or CPT 37227 to define drug-coated stent
‡ C1725 may not be present in dataset and is not necessary do define coding for non-drug-coated PTA
§ C1876 or C1877 may not be present in dataset and is not necessary to define coding for bare metal stent

Table 17. Claims Codes to Define Tobacco Use, Critical Limb Ischemia, and Prior Amputation

Comorbidity	ICD-10-CM Codes	ICD-9-CM Codes
Current or Prior Tobacco	F172, F1720, F17200, F17201, F17203, F17208, F1720, F1721, F17210, F17211, F17213, F17218, F17219, F1722, F17220, F17221, F17223, F17228, F17229, F1729, F17290, F17291, F17293, F17298, F17299, Z720, Z87891	305.1, 649.00–649.04, V15.82
Critical Limb Ischemia	I7022, I7023, I7024, I7026, I7032, I7033, I7034, I7036, I7042, I7043, I7044, I7046, I7052, I7053, I7054, I7056, I7062, I7063, I7064, I7066, I7072, I7073, I7074, I7076, E1052, E10621, E1152, E11621	440.20, 440.21, 440.22, 440.23, 440.24, 440.29, 440.30, 440.31, 440.32, 440.9, 440.0, 249.70, 249.71, 250.70, 250.71, 250.72, 250.73, 443.81, 443.9, 443.1, 444.22, 444.81, 785.4, or 440.4 **plus ≥1 of the following:** 440.22, 440.23, 707.10, 707.11, 707.12, 707.13, 707.14, 707.15, 707.19, 730.05, 730.06, 730.07, 730.15, 730.16, 730.17, 682.6, 682.7, 681.10, V49.70, V49.71, V49.72, V49.73, V49.74, V49.75, V49.76, V49.77
Prior Amputation	Z89.41, Z89.42, Z89.43, Z89.44, Z89.51, Z89.52, Z89.61, Z89.62	V49.70, V49.71, V49.72, V49.73, V49.74, V49.75, V49.76, V49.77

Table 18. Claim Codes to Define Falsification Endpoints

Condition	ICD-10-CM Codes	ICD-9-CM Codes
Congestive heart failure	I11.0, I13.0, I13.2, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, I50.810, I50.811, I50.812, I50.813, I50.814, I50.82, I50.83, I50.84, I50.89, I50.9	402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428, 428.1, 428.2, 428.21, 428.22, 428.23, 428.3, 428.31, 428.32, 428.33, 428.4, 428.41, 428.42, 428.43, 428.9
Myocardial infarction	I21.01, I21.02, I21.09, I21.11, I21.19, I21.21, I21.29, I21.3, I21.4, I21.9	410, 410.01, 410.1, 410.11, 410.2, 410.21, 410.3, 410.31, 410.4, 410.41, 410.5, 410.51, 410.6, 410.61, 410.7, 410.71, 410.8, 410.81, 410.9, 410.91
Pneumonia	A48.1, J09.X1, J10.00, J10.01, J10.08, J11.00, J11.08, J12.0, J12.1, J12.2, J12.3, J12.81, J12.89, J12.9, J13, J14, J15.0, J15.1, J15.20, J15.211, J15.212, J15.29, J15.3, J15.4, J15.5, J15.6, J15.7, J15.8, J15.9, J16.0, J16.8, J18.0, J18.1, J18.8, J18.9	480, 480.1, 480.2, 480.3, 480.8, 480.9, 481, 482, 482.1, 482.2, 482.3, 482.31, 482.32, 482.39, 482.4, 482.41, 482.42, 482.49, 482.81, 482.82, 482.83, 482.84, 482.89, 482.9, 483, 483.1, 483.8, 485, 486, 487, 488.11