NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Post Authorization Safety Study (PASS) information

Title	The acute effects of azithromycin use on cardiovascular mortality, as compared with amoxicillin in veterans
Protocol number	A0661211
Protocol version identifier	1.0
Date of last version of protocol	1 December 2016
European Union (EU) Post Authorisation Study (PAS) register number	Study not yet registered (estimated registration date: 21 Dec 2016)
Active substance	Azithromycin (AZT): J01FA10 Amoxicillin (AMX): J01CF05
Medicinal product	Azithromycin
Research question and objectives	The primary objectives are to estimate the relative and absolute risk of the following **adjudicated** outcomes for azithromycin users as compared to amoxicillin users, among persons aged 30-74 years old, within 5 days and within 6-10 days of dispensed prescription (Rx): 1. Cardiovascular death 2. Sudden cardiac death (a subset of CV death) Subgroup analyses: 3. Cardiovascular (CV) death among those with a history of cardiovascular disease (CVD) 4. Cardiovascular death among those with high baseline CV risk as defined by a CV risk score

	Secondary Objectives: The secondary objectives are to estimate the relative and absolute risk of the following outcomes for azithromycin users, as compared to amoxicillin users, among persons aged 30-74 years old; only reported (unadjudicated) outcome data will be used for these analyses: 1. Non-cardiovascular death and all-cause death, within 5 and within 6-10 days of dispensed prescription (Rx) 2. Cardiovascular death within 11-365 days of Rx dispensed: i. Among those with baseline CVD ii. Among those with high baseline CV risk according to a CV risk score iii. Among those with baseline CVD or with high baseline CV risk according to a CV risk score iv. Among those with chronic obstructive pulmonary disease (COPD) v. Among those with community acquired pneumonia (CAP)
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
AE	Adverse Event
AEM	Adverse Event Monitoring
AIDS	Acquired Immune Deficiency Syndrome
ALOC	Altered Level of Consciousness
AMX	Amoxicillin
ARB	Angiotensin Receptor Blocker
AZT	Azithromycin
BNP	B-type natriuretic peptide
CABG	Coronary Artery Bypass Grafting
CAP	Community acquired pneumonia
CARDIA	Coronary Artery Risk Development in Young Adults
CDW	Corporate Data Warehouse
CHF	Coronary Heart Disease
CHF	Congestive Heart Failure
CI	Confidence Intervals
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine Kinase
COD	Cause of Death
COPD	Chronic Obstructive Pulmonary Disease

CT	Computed Tomography
CV	Cardiovascular
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
EAC	Events Adjudication Committee
e-CRF	Electronic Case Report Form
ED	Emergency Department
EKG	Electrocardiogram
EMA	European Medicines Agency
EMM	Effect Measure Modifiers
EMR	Electronic Medical Record
EU PAS	European Union electronic register of Post-Authorisation Studies
FDA	Food and Drug Administration
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
HF	Heart Failure
HH	Homonymous Hemianopia
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICD	International Classification of Diseases
ICH	Intracerebral Hemorrhage
IEA	International Epidemiological Association
IEC	Independent Ethics Committee

IPH	Intraparenchymal Hemorrhage
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
JVD	Jugular Venous Distension
JVP	Jugular Venous Pressure
KP	Kaiser Permanente
MAH	Marketing Authorisation Holder
MI	Myocardial Infarction
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
NDI	National Death Index
NI	Non-Interventional
NIS	Non-Interventional Study
NLF	Nasolabial Fold
PET	Positron Emission Tomography
PI	Principal Investigator
PND	Paroxysmal Nocturnal Dyspnea
QA	Quality Assurance
Rx	Prescription
SAH	Subarachnoid Hemorrhage
SAP	Statistical Analysis Plan
SCD	Sudden Cardiac Death

SDH	Subdural Hemorrhage
ULN	Upper Limit of Normal
VA	Veterans Affairs
VHA	Veterans Health Administration

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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3. ABSTRACT

Title: The acute effects of azithromycin use on cardiovascular mortality, as compared with amoxicillin in veterans.

Version: 1.0 Date: 1 December 2016
Author: Mei Sheng Duh, ScD, MPH; Yinong Young-Xu, ScD, MS, MA; Eric Mortensen, MD, MSc; Niki Palmetto, PhD, MPH

Rationale & Background:

The purpose of this observational study is to examine the effects of azithromycin use on cardiovascular (CV) mortality. This observational study was preceded by four recently published retrospective cohort studies by Ray et al. (2012),[1] Svanstrom et al. (2013),[2] Rao et al. (2014),[3] and Mortensen et al. (2014),[4] which examined this, or a related research question. These studies have produced conflicting results, but taken together suggest a possible association between azithromycin use and acute CV risk, most notably in patients with pre-existing CV risk at baseline. Limitations of these studies included missing 'indication of use' information for some or all of the study populations, lack of death adjudication, limited power to examine associations in high CV risk subgroups, and varying generalizability. An additional observational study with sufficient power is required to further assess the potential CV signal. This observational study will be conducted in the Veterans Health Administration (VHA) database, as it closely resembles the study cohort in Ray et al. (2012), and will have sufficient power within high baseline CV risk subgroups, a population of particular interest for this research question.

Research Question & Objectives:

The primary objectives are to estimate the relative and absolute risk of the following **adjudicated** outcomes for azithromycin users as compared to amoxicillin users, among persons aged 30-74 years old, within 5 days and within 6-10 days of dispensed prescription (Rx):

1. CV death
2. Sudden cardiac death (a subset of CV death)

Subgroup analyses:

3. CV death among those with a history of cardiovascular disease (CVD)
4. CV death among those with high baseline CV risk as defined by a CV risk score

Secondary Objectives:

The secondary objectives are to estimate the relative and absolute risk of the following outcomes for azithromycin users, as compared to amoxicillin users, among persons aged 30-74 years old; only reported (unadjudicated) outcome data will be used for these analyses:

1. Non-CV death and all-cause death within 5 days and within 6-10 days of dispensed prescription (Rx)

2. CV death within 11-365 days of Rx dispensed:

    - Among those with baseline CVD
    - Among those with high baseline CV risk according to a CV risk score
    - Among those with baseline CVD or with high baseline CV risk according to a CV risk score
    - Among those with chronic obstructive pulmonary disease (COPD)
    - Among those with community acquired pneumonia (CAP)

Study design: Retrospective cohort study

Population: The study population will include veterans who received a prescription dispensing for azithromycin or amoxicillin between 2000 and 2014 (15 years).

Variables:

- Exposures: Antibiotic prescription dispensing for azithromycin and amoxicillin.
- Outcomes: CV death, sudden cardiac death, non-CV death, all-cause death, and cardiac death (sensitivity analysis only).
- Key covariates (potential confounders): The multivariate analyses will include indication of antibiotic use, CV conditions and medications, demographic factors (eg, age, gender, race/ethnicity, marital status), other medical co-morbidities (eg, respiratory, neurologic, and psychiatric conditions), other medications (eg, opioids and psychiatric drugs), and health care utilization variables (eg, number of CV-related office visits).
- Key effect measure modifiers: history of prior CVD, baseline CV risk according to a CV risk score, COPD, and CAP.

Data sources: This study will use data from the VHA's Corporate Data Warehouse (CDW), which is an integrated and unified electronic medical record (EMR) system with a centralized data warehouse that contains information on all outpatient visits, hospital stays, treatments, dispensed prescriptions, and laboratory results as well as billing and benefits information of veterans who seek care at a VHA facility (note: this EMR system does not include information on any care received outside of a VA facility). The CDW is updated daily to weekly, so there is little to no lag time. The VHA database captures exposure and outcome information during real-world practice encounters at VA-affiliated facilities. The study will also use information reported from the National Death Index (NDI) (in combination with

CDW data) to ascertain causes of death information to estimate cumulative incidence of CV cause-specific mortality outcomes among amoxicillin and azithromycin users in the VHA. All CV deaths and a sample of non-CV deaths will be confirmed by chart review through the efforts of an Event Adjudication Committee.

Study size: Based on a feasibility assessment conducted using data from the VHA from 2000-2011, the study will include over 1.5 million azithromycin exposures and over 2.6 million amoxicillin exposures.

Data analysis: The analysis will compare cumulative incidence for selected causes of death (CV, sudden cardiac, non-CV, and all-cause) occurring within 5 and within 6-10 days of azithromycin, and amoxicillin dispensation. Additional analyses will compare event rates within 11-365 days after antibiotic exposure. The event rates will be compared within a general population of azithromycin users and amoxicillin users, and among those with high baseline CV risk (as defined by a prior history of CV disease or a high CV risk score), COPD, and CAP. The detailed elements of the analysis plan are reported separately as part of the Statistical Analysis Plan (SAP). In brief, a regression analysis will be performed using propensity scores for confounder control.

Milestones:

- Final protocol: 16 December 2016
- Start of data collection: 31 January 2017
- End of data collection: 31 October 2017
- Final study report: 31 May 2018

4. AMENDMENTS AND UPDATES

None

5. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	19 September 2014
Final protocol	16 December 2016
Start of data collection	31 January 2017
End of data collection	31 October 2017
Registration in the EU PAS register	21 December 2016
Final study report	31 May 2018

6. RATIONALE AND BACKGROUND

The purpose of this observational study is to examine the effects of azithromycin use on cardiovascular (CV) mortality. This observational study was preceded by four recently published retrospective cohort studies by Ray et al. (2012),[1] Svanstrom et al. (2013),[2] Rao et al. (2014),[3] and Mortensen et al. (2014),[4] which examined this or a related research question.

Ray et al. (2012) examined the acute effects of azithromycin use on CV death within a population receiving health care coverage through Tennessee Medicaid and found that during the 5 days or 10 days from the start of therapy, patients taking azithromycin had an increased risk of CV death as compared with those who took amoxicillin (Hazard Ratio 2.49; 95% CI: 1.38-4.50 and Hazard Ratio 1.87; 95% CI: 1.16-3.01, for 5 and 10 day analyses, respectively). Further, it was estimated that there were 47 additional CV deaths per million prescriptions of azithromycin (when compared with amoxicillin), and 245 additional CV deaths among patients in the highest decile of CV risk score. The risk of CV death during the 5 days of azithromycin therapy was also higher when compared with ciprofloxacin, but did not differ significantly from that of levofloxacin. Ray et al. (2012) posited that the increased risk of CV death associated with azithromycin may be due to QT prolongation, resulting in ventricular arrhythmia and sudden cardiac death. The Ray et al. (2012) study had many methodological strengths, such as adequately powered analyses and stratification of effect by baseline CV risk (via a CV risk summary score), but was not without limitations, such as missing 'indication for use' information for 30% of the population, lack of death adjudication, and restricted generalizability of findings.

Using a different comparator and population, Svanstrom et al. (2013) did not find that Danish patients taking azithromycin had an increased risk of CV death compared with those taking penicillin V. When the risk of CV death associated with azithromycin use was examined among those with and without baseline cardiovascular disease (CVD), there was an increased, but non-significant effect among those with baseline CVD. Amoxicillin use was examined as an additional comparator group in a sensitivity analysis, and also yielded

non-significant findings. Strengths of the Svanstrom et al. (2013) study included a population-based sample, stratification of CV death risk according to baseline CVD status, and multiple sensitivity analyses (examination of cardiac-specific deaths, propensity score matching for main analyses, and an amoxicillin comparator group). However investigators did not adjudicate CV deaths or control for confounding by indication of use, and the analysis was likely underpowered to detect the small increase in risk found among those with prior CVD.

Rao et al. (2014) conducted a retrospective cohort study among United States (US) veterans to examine the acute effects of azithromycin use, compared with amoxicillin, on all-cause death and serious arrhythmias. Follow-up times were separated into the first 5 days and 6-10 days after antibiotic dispensation. There was an increased likelihood of all-cause death (HR 1.48; 95% CI 1.05-2.09), and serious arrhythmia (HR 1.77; 95% CI 1.20-2.62) associated with the use of azithromycin, compared with amoxicillin use, within the first 5 days after drug dispensation; these effects were attenuated and not statistically significant for the 6-10 day period. The primary strength of the Rao et al. (2014) publication was adequate power for the outcomes examined. However, Rao et al. (2014) also had several limitations, including no examination of CV death as an outcome, no subgroup analyses by baseline CV risk, potential residual confounding by indication of use (only 66% of patients had a recorded "indication for use"), and limited generalizability to the larger US population.

A study conducted by Mortensen et al. (2014)[4] also used a retrospective cohort study design among US veterans to compare outcomes associated with azithromycin use to other antibiotic therapy use. Primary outcomes were 30-day and 90-day all-cause mortality and cardiovascular events within 90 days of admission to a hospital. Among those who received azithromycin, 30-day mortality (OR 0.77, 95% CI 0.73-0.81) and 90-day mortality (OR 0.73, 95% CI 0.70-0.76) were significantly lower as compared to those not on azithromycin. However, there was also a significantly increased odds of myocardial infarction (OR 1.17, 95% CI 1.08-1.25) for those exposed to azithromycin, but non-significant associations with other outcomes. This study had the same limitations as Rao et al. (2014).

While mixed, taken together, the findings from Ray et al. (2012), Svanstrom et al. (2013), and Rao et al. (2014) suggest the possibility of an increased acute risk of CV and/or all-cause death associated with azithromycin, particularly among patients with high baseline CV risk. Mortensen et al. demonstrated an increased risk of myocardial infarction but decreased risk of all-cause mortality associated with azithromycin use. Though no studies have reported longer-term CV effects associated with azithromycin use, there have been 2 studies which have found longer-term CV effects associated with clarithromycin, another with macrolide.[5,6]

Jespersen et al. (2005) conducted a randomized controlled trial (CLARICOR trial), which randomized patients with stable coronary heart disease to either a two week treatment of clarithromycin or placebo, and found an increased risk CV mortality associated with clarithromycin, 3 years post treatment (HR: 1.45; 95% CI 1.09 – 1.92).[5] Schembri et al. (2013) conducted two observational cohort analyses among patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease (COPD) and community acquired pneumonia (CAP), treated with either clarithromycin or no macrolide during

hospitalization.[6] Among those with COPD, clarithromycin was associated with an increased risk of CV mortality (HR: 1.52; 95% CI 1.02-2.26) 1 year post treatment. Among those with CAP, clarithromycin was not associated with increased CV mortality, however was associated with an increased risk of CV events (acute coronary syndrome, cardiac failure, serious arrhythmia, or sudden cardiac death) (HR: 1.68; 95% CI 1.18-2.38).

Additional observational studies, with sufficient power and adequate control of confounding are therefore required to further assess the potential CV signal. Pfizer is currently conducting such a study with Kaiser Permanente (KP). While the merits of the KP database include capabilities inherent to a comprehensive closed-network EMR system, including large sample size, and the ability to link to death certificates, as well as enhanced "indication of use" capture, the KP membership population may represent a different population segment than the Tennessee Medicaid population used in Ray et al. (2012). The KP cohort is hypothesized to be of higher socioeconomic status, have better access to health care, and importantly, have lower CV risk than the Tennessee Medicaid population. These differences lead to difficulties in comparability between the results from Ray et al. (2012) and those from the KP population and may limit the power of the KP study to detect CV mortality risks associated with azithromycin within the highest CV risk populations.

Due to these differences, Pfizer is conducting a separate study using data from the VHA, as veterans are more similar to the Medicaid population with regards to cardiovascular risk, as compared to the commercial insurance population.[7] Patients with high CV risk may be the subgroup at greatest risk for experiencing CV death associated with azithromycin, and this subgroup is a focus of both the KP and VHA studies. Other than the high CV risk profile of the population, the VHA EMR system includes the necessary elements to examine this research question, including a sufficient sample size (and therefore sufficient power) for the high CV risk subgroup, the ability to identify and adjudicate CV-specific mortality, and the ability to link various sources of data on hospitalizations, outpatient visits, and pharmacy dispensings for each individual. The study will follow Ray et al.'s methodology to the extent feasible.

This non-interventional observation study is designated as a PASS and is a post marketing requirement of the Food and Drug Administration (FDA) that will serve to provide additional information about the potential association between azithromycin and incremental risk for CV deaths.

7. RESEARCH QUESTION AND OBJECTIVES

Primary Objectives:

The primary objectives are to estimate the relative and absolute risk of the following **adjudicated** outcomes (see Table 1) for azithromycin users as compared to amoxicillin users, among persons aged 30-74 years old, within 5 days and within 6-10 days of dispensed prescription (Rx):

1. CV death

2. Sudden cardiac death (a subset of CV death, see Table 1)

Subgroup analyses:

3. CV death among those with a history of CVD

4. CV death among those with high baseline CV risk as defined by a CV risk score

Secondary Objectives:

The secondary objectives are to estimate the relative and absolute risk of the following outcomes (see Table 1) for azithromycin users, as compared to amoxicillin users, among persons aged 30-74 years old; only reported (unadjudicated) outcome data will be used for these analyses:

1. Non-CV death and all-cause death, within 5 and within 6-10 days of dispensed Rx

2. CV death within 11-365 days of Rx dispensed:

   - Among those with baseline CVD
   - Among those with high baseline CV risk according to a CV risk score
   - Among those with baseline CVD or with high baseline CV risk according to a CV risk score
   - Among those with chronic obstructive pulmonary disease (COPD)
   - Among those with community acquired pneumonia (CAP)

8. RESEARCH METHODS

8.1. Study design

This study will employ a retrospective cohort design to examine the effects of azithromycin on CV and sudden cardiac mortality (primary endpoints, see Table 1). Subgroup analyses will examine CV death among those with a history of CVD and CV death among those with high baseline CV risk as defined by a CV risk score as primary endpoints. Cumulative incidence will be compared among a population of azithromycin users and amoxicillin users, and among those with high baseline CV risk. The secondary endpoints will include non-CV mortality and all-cause mortality. The main measures of effect will be hazard ratios. The study will follow Ray et al. (2012)'s methodology to the extent feasible.

8.2. Setting

This study will be conducted among veterans enrolled in the VHA.

The VHA has about 8 million patients with outpatient encounters and 1 million patients with inpatient encounters each year. The VHA EMR system has several advantages for pharmacoepidemiology studies. The VHA EMR system contains information on all outpatient visits, hospital stays, treatments, dispensed prescriptions, and laboratory results

rendered in VHA medical facilities, and can be linked to the NDI to obtain mortality data. Any prescription dispensing of azithromycin or amoxicillin use during the study time period of January 01, 2000 – December 31, 2014 will be identified. January 1, 2000 will be the start date of the study as this is the date by which the VHA had a nationwide, fully functioning EMR system. December 2014 will be the end date for this study because data from the NDI are necessary to identify the primary outcome of CV-specific mortality, and these data have a two-year lag time. Furthermore, using data from January 2000 to December 2014 will allow for sufficient overlap of the years of data from the study by Ray et al. (2012), which included data from 1992 to 2006, and the study by Svanstrom et al. (2013), which included data from 1997 to 2010. Additionally, the study conducted by KP used data spanning from 1998-2014, 17 years of data, which will be similar to the length of time that will be used for the current analysis (15 years, from 2000-2014).

8.2.1. Inclusion criteria

Patients must meet the following inclusion criteria to be eligible for inclusion in the study:

Inclusion Criteria:

1. Dispensation of an outpatient or inpatient prescription for azithromycin or amoxicillin between 01 Jan 2000 and 31 Dec 2014. If a patient had more than one prescription dispensing within this period, each exposure will be counted separately (thus, individuals may contribute multiple prescription dispensings to the analysis), and the index date of each exposure will be identified as the first day the exposure meets the inclusion criteria. The second prescription fill will be excluded if it occurs <10 days from the first dispensing.

2. Only oral prescription dispensings will be included (not intravenous or ophthalmic) and amoxicillin-clavulanate prescription dispensings will also be included in the amoxicillin group.[1,2]

3. Patients with regular use of VHA medical care, defined as at least two outpatient (excluding emergency department [ED], as ED visits may not be considered regular) or inpatient encounters in the one year prior to index antibiotic prescription dispensing will be included. The encounters must be separated by >30 days (for inpatient, by admission date), and at least one must be within 6 months prior to the index antibiotic prescription dispensing. This will ensure that patients have ongoing health care encounters, particularly near the index date, and regularly receive their healthcare from VHA facilities, rather than outside facilities, which may be financially covered/ reimbursed by the VHA, but will not be captured in the VHA EMR system.

8.2.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

Exclusion Criteria:

1. Missing date of birth or gender.
2. Age < 30 or >74 years on the index date (the date of the index antibiotic prescription dispensing).
3. Not enrolled in/disenrolled from VHA benefits during the 365 days prior to the index date. This criterion ensures capture of potential confounders and effect measure modifiers.
4. No pharmacy dispensings (other than the index antibiotic) during the one year prior to the index date. This criterion ensures patients use VHA to fill prescriptions.
5. More than one type of study antibiotic prescribed on the index date, or within 10 days prior (ie, wash-out period).
6. Residing in a nursing home or other residential institution on the index date or at any time in the preceding 365 days, except for stays of <30 days following hospital discharge. Since the VHA contains data only on VHA-paid nursing homes and nursing home residency in patients with Medicare, this definition also includes inferred nursing home stays. Inferred nursing home stays will be defined as 2 or more outpatient encounters in the year leading up to the index prescription dispensing date with procedure codes indicating nursing home place of service separated by at least 28 days. It also includes external cause of injury diagnosis code indicating place of residence was an institution. This criterion considers that the cause of death information recorded on death certificates, and therefore the NDI, within a nursing home setting may be less accurate.

8.3. Variables

8.3.1. Exposure

Outpatient or inpatient prescription dispensings for azithromycin or amoxicillin occurring between 01 Jan 2000 and 31 Dec 2014. If a patient had more than one prescription dispensing within this period, each exposure will be counted separately (thus, individuals may contribute multiple prescription dispensings to the analysis). For the second antibiotic dispensing, event follow-up for the first exposure will be censored at the date of the second prescription fill.

8.3.2. Outcomes

The following outcomes, which are defined in Table 1, will be examined in this study: 1) CV death, 2) sudden cardiac death, 3) non-CV death, 4) all-cause death, 5) cardiac death (sensitivity analysis only). All outcomes will be identified through cause of death information as captured by the NDI. See Table 1 below for outcome variable database programming definitions and database sources. Any confirmed deaths with missing cause of death information will be classified as "unknown cause of death" and not considered a CV death or a non-CV death (but will be included in the all-cause mortality analyses). Deaths identified through database programming will be referred to as reported (unadjudicated). Reported deaths that are adjudicated will be referred to as "adjudicated."

Table 1. Outcome variable definitions (by database programming)

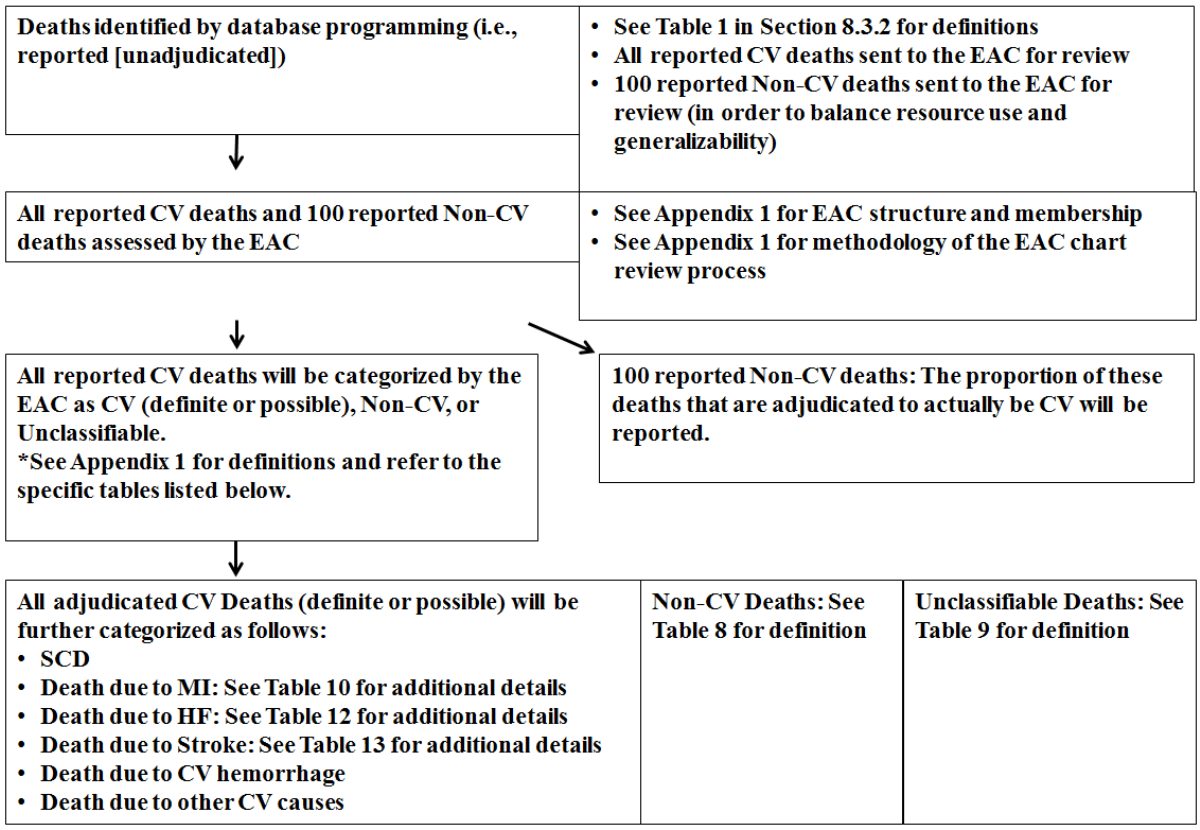
Variable	Role	Data Source	Operational Definition
CV death	Outcome (primary objective)	NDI	Underlying cause of death consistent with a CV cause, such as myocardial infarction, heart failure, arrhythmia, and stroke. The death certificate must thus include any of the following codes, which define all possible causes of CV death: ▪ ICD-9 codes:390.xx-459.xx, 798.1x, 798.2x, 798.9x, 799.9x *or* ▪ ICD-10 codes: I00.xx-I99.xx, R96.0x, R96.1x
Sudden Cardiac Death (SCD), using the methods and specific codes used by Chung and colleagues.[9] (subset of CV death)	Outcome (primary objective)	NDI	Deaths meeting the following three criteria applied in this order: 1. (exclusion): No evidence of terminal institutional stay. Thus, deaths will not be counted as SCD if the member was hospitalized or in a nursing home on the date of death or if the place of death indicates hospital or nursing home. 2. (inclusion): Underlying cause of death code consistent with SCD: ▪ ICD-9 codes: 401.9x, 402.xx, 410.xx-414.xx, 425.4x, 427.5x, 427.1x, 427.4x, 427.8x, 427.9x, 429.2x, 429.9x, 440.9x, 798.2x, 798.9x *or* ▪ ICD-10 codes: I10.xx, I11.9x, I20.xx-25.xx, I42.9x, I42.8x, I46x, I47.0x, I47.2x, I49.0x, I49.8x, I49.9x, I51.6x, I51.9x,

Variable	Role	Data Source	Operational Definition
			I70.9x, R96.1x, R98xx 3. (exclusion): No evidence of procedure codes which would not be expected in the clinical setting of cardiac arrest. Thus, deaths will not be considered SCD if any the following procedures were performed or treatments were received on the day of death: ▪ Radiology: X-Ray (except chest x-ray), CT (computed tomography), MRI (magnetic resonance imaging), MRA (magnetic resonance angiography), ultrasound, fluoroscopy, angiography, mammography, nuclear medicine scan, PET (positron emission tomography). **See** Appendix 1 for the specific Radiology procedure codes used for this variable ▪ Thrombolytic drugs (ED or hospital encounters): alteplase (Activase), reteplase (Retavase), tenecteplase (TNKase), streptokinase (Kabikinase, Steptase), urokinase (Abbokinase) ▪ Use of general anesthesia (as determined by variable indicating general anesthesia was planned)

Variable	Role	Data Source	Operational Definition
Non-CV death	Outcome (secondary objective)	NDI	All deaths that are not categorized as CV deaths but which can be attributed to a specific medical condition or condition(s) (thus, not an unknown cause of death)
All-cause death	Outcome (secondary objective)	NDI	Death confirmed by NDI
Cardiac death (subset of CV death)	Outcome (sensitivity analysis)	NDI	▪ Underlying cause of death consistent with cardiac cause ICD-9 codes: 402.xx, 404.xx, 410.xx-414.xx, 416.8x, 416.9x, 420.xx-429.xx *or* ▪ ICD-10 codes: I11.xx, I13.xx, I20.xx-25.xx, I27.xx, I30.xx-52.xx

Endpoints for the primary objective (ie, CV death and SCD within 5 and within 6-10 days of antibiotic dispensation) will then be adjudicated by the Events Adjudication Committee (EAC). For this study's primary objective, the primary analyses will include only deaths adjudicated to be either definitely or possibly CV in nature (or, either definitely or possibly SCD for the SCD outcome). All analyses of the secondary objectives will be conducted using reported (unadjudicated) endpoints (See Section 7 above). The process of death outcome determination is summarized in Figure 1, below.

Figure 1. Overview of death outcome determination and adjudication methodology



8.3.3. Effect Measure Modifiers (EMM)

The following subgroups will be examined for the risk of CV death within 5 days, within 6-10 days, and within 11-365 days of azithromycin dispensation, compared to amoxicillin use: 1) baseline CVD and 2) baseline CV risk as defined by a CV risk score. The following subgroups will be examined for the risk of CV death within 11-365 days of azithromycin dispensation, compared to amoxicillin use: 1) COPD and 2) CAP.

8.3.3.1. Baseline CVD

Individuals with baseline CVD will be defined by an in- or out-patient encounter with one of the component CVD diagnostic codes (Table 2) within one year prior to the index antibiotic dispensing (t_0). This will include emergency department (ED) encounters. The Corporate Data Warehouse (CDW) includes both ICD-9 and Current Procedural Terminology (CPT) procedure codes, which are shown in Table 2 below. These codes have been used and validated in previous publications.[8,9-21]

Table 2. Component CVD diagnoses

Variable	Role	Data Source	Operational definition
Acute coronary syndrome	Component of CVD diagnosis (EMM)	CDW	ICD-9 codes: 411.1x or 410.xx
Other ischemic heart disease	Component of CVD diagnosis (EMM)	CDW	ICD-9 codes: 411.8x, 412.xx, 413.xx, 414.xx
Percutaneous or surgical coronary revascularization	Component of CVD diagnosis (EMM)	CDW	Percutaneous coronary intervention (PCI) ▪ ICD-9 procedure codes: 36.01, 36.02, 36.05, 36.06, 36.07, 36.09, 00.66 ▪ *or* CPT 4 codes: 92980, 92981, 92982, 92984, 92995, 92996 Coronary artery bypass grafting (CABG) ▪ ICD-9 procedure codes: 36.03, 36.1x ▪ *or* CPT 4 codes: 33533, 33534, 33535, 33536, 33572, 33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33521, 33522, 33523, 33530
Heart failure or cardiomyopathy	Component of CVD diagnosis (EMM)	CDW	ICD-9 codes: 428.xx, 402.01, 402.11, 402.91, 425.xx
Valvular heart disease or heart valve surgery	Component of CVD diagnosis (EMM)	CDW	ICD-9 codes: 424.0x-3x, 424.90, 429.5x, 429.6x, 394.xx, 395.xx, 396.xx, 397.xx *or* ICD-9 procedure codes: 35.0, 35.1, 35.2, 35.31, 35.32, 35.33, 35.96, 35.99
Congenital heart disease	Component of CVD diagnosis (EMM)	CDW	ICD-9 codes: 745.xx, 746.xx, 747.xx *or* ICD-9 procedure codes: 35.34, 35.35, 35.39, 35.4x, 35.5x, 35.6x,

Variable	Role	Data Source	Operational definition
			35.7x, 35.8x, 35.9x
Cerebrovascular disease	Component of CVD diagnosis (EMM)	CDW	ICD-9 codes: 430.xx-438.xx (inclusive)
Peripheral arterial disease	Component of CVD diagnosis (EMM)	CDW	ICD-9 codes: 440.xx-443.xx (inclusive)
Arrhythmia (all types)	Component of CVD diagnosis (EMM)	CDW	ICD-9 codes: 426.xx, 427.xx (except 427.6)

8.3.3.2. High Baseline CV Risk according to CV Risk Score

Individuals with a high baseline CV risk will be determined by a CV risk summary score, using the validated methodology of Ray and colleagues,[1,22,23,24] which statistically summarizes the effects of numerous CV variables. The CV risk score output provides a continuous indicator variable which is then categorized into deciles of CV risk. The Statistical Analysis Plan describes the detailed CV risk score methodology. **High baseline CV risk will be defined as individuals among the top decile of CV risk**. The CV risk score will include all CVD diagnoses (detailed in Table 2 above), as well as the elements shown in Table 3 below, including various CV medications (at least one dispensed prescription of one of the drug types within one year prior to the index antibiotic prescription dispensing (t_0); except as noted below). Only oral forms of medication will be included, with the exception of nitroglycerin and insulin. CV emergency room visits and current smoking status will also be included. Other CV variables not shown in Table 2 and Table 3, such as a history of hypertension, hyperlipidemia, and diabetes mellitus will be treated as covariates in the study's regression models (see Section 8.3.4 below).

Table 3. Other component CV risk summary score variables

Variable	Role	Data Source	Operational definition[1]
ACE inhibitor	Component of CV risk score (EMM)	CDW	Drug names: ramipril, benazepril, captopril, enalapril, enalaprilat, fosinopril, lisinopril
ARB	Component of CV risk score (EMM)	CDW	Drug names: losartan, valsartan,

Variable	Role	Data Source	Operational definition[1]
Antiarrhythmic	Component of CV risk score (EMM)	CDW	Drug names: quinidine, procainamide, flecainide, propafenone, amiodarone, sotalol, dofetilide
Anticoagulant	Component of CV risk score (EMM)	CDW	Drug names: warfarin, dabigatran, rivaroxaban, apixaban, heparin, enoxaparin
Beta-Blocker	Component of CV risk score (EMM)	CDW	Drug names: atenolol, betaxolol, bisoprolol, carvedilol, propranolol, metoprolol succinate, metoprolol tartrate Requires: oral dosing only (not ophthalmic)
Calcium channel blocker	Component of CV risk score (EMM)	CDW	Drug names: verapamil, diltiazem, amlodipine, felodipine, nicardipine, nifedipine
Digoxin	Component of CV risk score (EMM)	CDW	Drug names: digoxin
Diabetes medication	Component of CV risk score (EMM)	CDW	Drug names: insulin, metformin, saxagliptin, pioglitazone, glipizide, acarbose *NOTE: injection forms of insulin are accepted.
Cholesterol-modifying medication	Component of CV risk score (EMM)	CDW	Drug names: simvastatin, atorvastatin, lovastatin, pravastatin, niacin, gemfibrozil, cholestyramine, colestipol
Loop diuretic	Component of CV risk score (EMM)	CDW	Drug names: furosemide, torsemide, bumetanide, ethacrynic acid
Nitroglycerin	Component of CV risk score (EMM)	CDW	Drug names: nitroglycerin, isosorbide mononitrate, isosorbide dinitrate

Variable	Role	Data Source	Operational definition[1]
			*NOTE: topical forms are accepted in this drug class (in addition to oral forms)
Platelet inhibitor	Component of CV risk score (EMM)	CDW	Drug names: clopidogrel
Thiazide diuretic	Component of CV risk score (EMM)	CDW	Drug names: hydrochlorothiazide, indapamide, metolazone, chlorthalidone
CV emergency room visit	Component of CV risk score (EMM)	CDW	Requires: an emergency room visit with an associated ICD-9 code for one of the types of CV disease defined above: acute coronary syndrome (ACS), other ischemic heart disease, coronary revascularization, heart failure or cardiomyopathy, valve disease, congenital heart disease, cerebrovascular disease, peripheral artery disease, or arrhythmia
Smoking	Component of CV risk score (EMM)	CDW	Requires: An inpatient or outpatient encounter with one of the codes (below) within one year prior to the index antibiotic prescription dispensing (t_0) ICD-9 codes: 305.1x or V15.82

8.3.3.3. Individuals with COPD and CAP

Individuals in the COPD and CAP subgroups will be identified based on the diagnosis codes shown in Table 4 below.

Table 4. Diagnosis codes for COPD and CAP

Variable	Role	Data Source	Operational definition
COPD	EMM	CDW	ICD-9 codes: 491.xx 496.xx
CAP	EMM	CDW	ICD-9 codes: 480.xx - 488.xx, 500.xx- 508.xx, 510.xx - 511.xx, 513.xx, 515.xx, 010.xx 012.xx, 073.xx, 517.1x

8.3.4. Covariates

In addition to the variables described in the tables above and based on availability, clinical relevance, and collinearity considerations, the statistical analysis will include adjustment for indication of antibiotic use (see Section 8.4.2), CV conditions and medications, demographic factors (eg, age, gender, race/ethnicity, marital status), other medical co-morbidities (eg, respiratory, neurologic, and psychiatric conditions), other medications (eg, opioids and psychiatric drugs), and health care utilization variables (eg, number of CV-related office visits). The definitions of any specific variable not described above as well as the timing of the covariates relative to the index antibiotic prescription dispensing date is included in the Statistical Analysis Plan (SAP).

8.4. Data sources

8.4.1. VHA EMR Database and NDI

This study will use the EMR datacut downloaded from the CDW at study initiation. The datacut will then be considered "frozen", and will not be updated. The study will also use information reported from the NDI to the VHA in combination with CDW data to identify the study primary endpoint: deaths due to CV causes and SCD.

VHA EMR Database

The VHA is an integrated healthcare system that provides comprehensive services, including primary, specialty and inpatient care, rehabilitation, long-term and home care, and other services, to military veterans. As of September 2016, the VA Healthcare System was comprised of 168 medical centers and 1,053 outpatient sites of care of varying complexity, serving more than 8.9 million veterans each year. In 2011, greater than 84% of these veterans were at least 45 years old, and over 72% were at least 55 years of age. Female veterans represented about 10% of the VHA population.

The VHA's EMR system, called the CDW, contains information on all outpatient visits, hospital stays, treatments, dispensed prescriptions, and lab results as well as billing and benefits information for healthcare encounters that take place at VHA facilities (note: although the VA may financially cover/reimburse care provided at non-VHA facilities, this EMR system does not capture information on such visits). It is updated daily to weekly so

there is little to no lag time. The CDW stores data in separate databases, one for each type of clinical information (eg, inpatient medication, inpatient admission, outpatient medication, outpatient visit). Each patient is assigned a unique patient identification number to allow for longitudinal follow-up as well as to cross-reference to the various separate databases. For example, in each inpatient admission record, there is information on primary discharge diagnosis (and as many as 15 secondary diagnoses), date of admission, date of discharge, and length of stay. This record can then be linked to other information of that inpatient stay located in other files, including procedures that the patient underwent during the hospitalization, medical specialty of the provider, and prescriptions dispensed. Other files are structured similarly, and therefore may be linked together to provide comprehensive information about the patient and his/her medical encounters.

NDI Data

The NDI is a centralized database that contains death record information from all US states and was established by the National Center for Health Statistics as a resource to aid epidemiologists and other researchers in mortality ascertainment. Records are currently available from 1979 through 2014. The NDI service is available to investigators for statistical analysis in medical and health research and can be obtained through an application process. Variables available in the NDI include social security number, date of birth, age at death, date of death, sex, marital status, race, state of residence, and state of birth. The NDI Plus file contains cause of death information, and will be used for this study. The cause of death codes are recorded as ICD-9 and ICD-10 codes.

8.4.2. Antibiotic Indication Assessments

One important limitation of some of the prior research is the largely missing data on indications for prescription antibiotic use, possibly resulting in residual confounding by prophylactic versus therapeutic use as well as by underlying infectious diseases.[1-4] To indirectly capture indication of antibiotic use (as done in Ray et al. (2012)[1] – see "Antibiotic indication" section), we will identify diagnostic codes (see Table 5 below) recorded for the visit that occurred within a specific date range around the date of antibiotic dispensing. Antibiotic dispensings with a temporally-associated infection diagnosis will be categorized as having that specific type of infection as the indication of use. Prophylactic antibiotic dispensings (eg, dental/procedural, surgical prophylaxis or traveler's diarrhea prophylaxis) will be considered as a separate category, contingent on data availability. The feasibility of identifying prophylactic antibiotic use depends on whether dental or surgical procedures of interest are mostly performed at VHA facilities, and will be assessed after gaining data access. If there is no infection or prophylaxis code associated with the prescription dispensing, the indication of use will be categorized as "missing."

The ICD-9 codes listed in Table 5 below (adapted from Ray et al. (2012)[1]) will be considered infection indications for an antibiotic dispensing. Ray et al. (2012) provides the specific types of infection shown in Table 5 but does not provide the codes. Instead, for the current study we propose to take infectious disease diagnosis codes from the Chrisendres coding manual (icd9.chrisendres.com), similar to the KP study approach (protocol #A0661209). In conducting the other PASS, KP investigators reviewed numerous charts of members

prescribed azithromycin or amoxicillin and found additional appropriate infection codes which have been added to Table 5. During the processes of data investigation, additional codes may be discovered that are deemed indicative of infection by the study investigators, and will be added to the list of potential indications if the numbers are sizable (or added to the "other" infection coding if rare). The infection severity prioritization shown in Table 5 below duplicates Ray's methodology.[1]

Table 5. ICD codes used to define infections for antibiotic indications of use

Infectious Disease Indication	ICD-9 Coding Plan	Infection Severity Priority
Pneumonia	480.xx-488.xx, 500.xx -508.xx, 510.xx -511.xx, 513.xx, 515.xx, 010.xx -012.xx, 073.xx, 517.1x	High
COPD	491.xx -496.xx	High
Pyrexia unknown origin	780.60	High
Other serious infections		High
➢ Cardiac infections	036.42, 093.2x, 420.xx -422.xx, 424.9xx	High
➢ Brain/spinal infections	320.xx -326.xx, 013.xx	High
➢ Blood infections	995.9x, 996.6x, 038.xx, 790.7x, 018.xx, 449.xx, 634.5x, 635.5x, 636.5x, 637.5x, 638.5x, 639.5x	High
➢ Other serious infections	030.xx -037.xx, 039.xx -041.xx, 020.xx -027.xx, 017.xx	High
Ear-nose-throat	380.1x-2x, 382.xx -384.xx, 472.xx -476.xx, 460.xx -464.xx, 289.1x-3x	Low
Bronchitis	465.xx -466.xx, 490.xx	Low
Respiratory symptoms	786.xx	Low
Other respiratory	478.xx	Low
Gastrointestinal	530.1x-2x, 530.4x, 530.86, 531.xx -535.xx, 540.xx -543.xx, 551.xx, 562.01, 562.03, 562.11, 562.13, 565.1x, 566.xx, 567.xx, 572.0x, 572.1x, 574.0x, 574.1x, 574.3x, 574.4x, 574.6x-8x, 575.xx, 576.1x, 577.0x-2x, 001.xx -009.xx, 014.xx	Low
Genitourinary	590.xx, 595.xx, 597.xx, 599.0x, 604.xx, 608.0x, 608.4x, 614.xx -616.xx, 670.xx, 672.xx, 639.0x, , 601.xx, 016.xx, 634.0x, 635.0x, 636.0x, 637.0x, 638.0x, 639.0x	Low
Sexually transmitted diseases	090.xx -099.xx	Low
Skin/soft tissue/joint/bone	680.xx -686.xx, 711.xx, 730.xx, 015.xx	Low

Infectious Disease Indication	ICD-9 Coding Plan	Infection Severity Priority
Wounds	870.xx -897.xx	Low
Other Infection (not otherwise specified)	675.xx, 076.xx -088.xx, 100.xx -104.xx, 120.xx -139.xx, 363.0x-2x, 370.xx, 372.xx -373.xx, 379.xx, 390.xx -393.xx, 451.xx, 522.xx, 523.xx, 526.4x, 527.2x-3x, 528.0x-5x, 529.0x, 611.0x	Low

The process of determining antibiotic indication of use is summarized in the two figures below and further detailed in the text that follows. Figure 2 describes the general process, which is largely adapted from Ray et al. (2012)'s methodology, and Figure 3 describes the algorithm to be employed to resolve "ties" among competing infection diagnosis codes, thus selecting only one infection diagnosis as the indication of use in all cases.

Figure 2. Flow diagram describing antibiotic indication of use determination

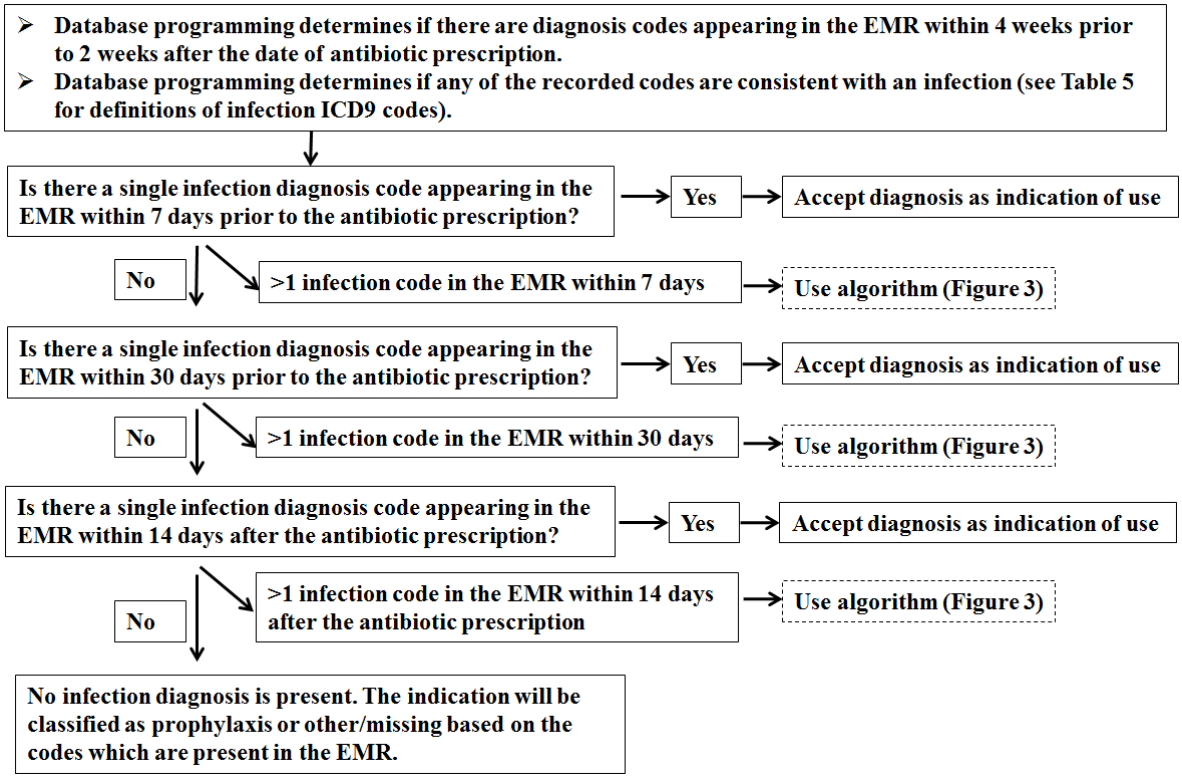
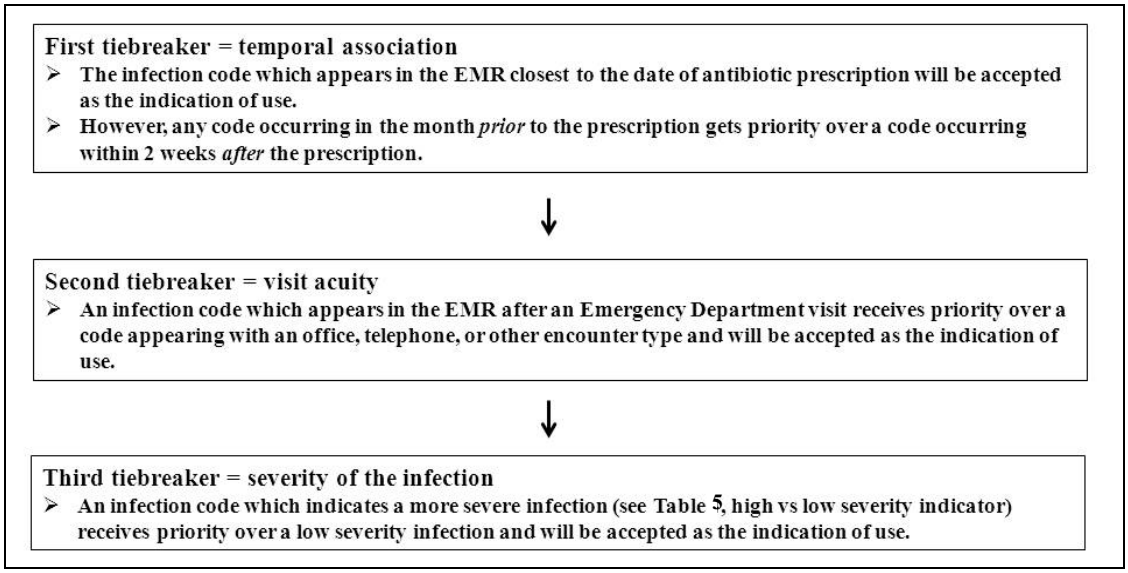


Figure 3. Algorithm to determine antibiotic ion of use among competing infection diagnoses



Indication for antibiotic use will be determined via the methodology outlined in the table and figures above. Accepted encounter types for the diagnosis codes in the EMR will include ED visits, hospitalization, and outpatient visits. Both primary and secondary codes will be used. If the VHA data are deemed sufficiently complete to identify prophylactic antibiotic use, the methodology adopted from the KP study above will be used with the addition of the prophylaxis category.

The proportion of antibiotic prescription dispensings with a prophylaxis (if data allow for the identification of this indication) or missing indication will be compared according to antibiotic type (azithromycin vs amoxicillin) to determine if there are any significant differences. A sensitivity analysis will be performed which will restrict the primary analyses to include only those prescription dispensings with an infection indication of use (see Section 8.7.4 below).

8.4.3. Cardiovascular Death Adjudication

All primary objective analysis endpoints will be adjudicated according to the CV Event Adjudication Committee Charter (see Appendix 2).

8.5. Study size

A comprehensive feasibility analysis conducted within the VHA database, submitted to the FDA in 2014 revealed a projected sample size of about 1.5 million azithromycin dispensings and >2.6 million amoxicillin dispensings among those aged 30-75[2] between the years of

[2] The feasibility analysis submitted to the FDA used an age cut-off of 75 years which is a very close approximation of methodology used in the current study. The Ray et al. methodology (considering ages 30-74) was not replicated exactly in error.

2000-2011, after application of the study's planned exclusion criteria. In comparison, the corresponding numbers for the KP feasibility analysis were 1.4 million and >5.4 million, respectively, and for the study by Ray et al. (2012) were about 350,000 and 1.3 million, respectively.

The VHA feasibility assessment found a cumulative incidence of 129.1 CV deaths per million prescription dispensings among amoxicillin users, a number over twice as high as that (52.6) reported in Ray et al. (2012).

Sample size calculations were performed based on information from the VHA feasibility assessment. Assuming that the cumulative incidence of CV death was 129.1 per million prescriptions (as reported for amoxicillin users in the feasibility assessment) the sample sizes listed in Table 6 below would be required to detect the specified hazard ratios with 80% and 90% power (assuming a two-sided alternative hypothesis, alpha of 0.05, and exposure standard deviation of 0.25). A minimum hazard ratio of 1.7 would be detectable with 80% power with a total sample size of <3.5 million prescriptions, which is lower than the total of 4.2 million amoxicillin and azithromycin prescriptions observed in the feasibility study conducted using data from 2000-2011. Similarly, a hazard ratio of 1.8 would be detectable with 90% power with a sample size of <3.8 million prescriptions. Data from 2000-2014 for a total of 15 years (ie, 3 additional years) will be included in the current study, and thus it is anticipated that the sample size achieved will be larger than that determined in the feasibility assessment, even after accounting for additional exclusion criteria that have been added since the feasibility assessment.

Table 6. Sample size estimation

Hazard Ratio	Sample Size Estimate to Achieve 90% Power	Sample Size Estimate to Achieve 80% Power
1.5	7,916,692	5,915,885
1.6	5,895,142	4,403,579
1.7	4,625,466	3,455,151
1.8	3,769,041	2,815,414
1.9	3,160,496	2,360,841
2.0	2,710,805	2,024,929
2.1	2,365,916	1,767,302
2.2	2,094,530	1,564,581

Based on the literature, we expect to lose approximately 50% of the reported CV deaths due to the adjudication process (either reported CV deaths adjudicated to be non-CV deaths, or reported CV deaths with insufficient information to adjudicate),[25,26] for a cumulative incidence of 64.5 per million dispensings, and a minimum detectable HR of 1.98 (assuming a sample size of approximately 4.2 million, power of 80%, alpha of 0.05, cumulative incidence of CV death of 64.5 per million, and exposure standard deviation of 0.25) which is still below Ray et al.'s (2012) main effect HR of 2.49 (95% CI: 1.38, 4.50).

Power calculations for the association among high CV risk subgroups have not been performed, as it is necessary to first construct the CV risk score.

8.6. Data management

Detailed methods for data collection are described in Section 8.4. Data for this study will be extracted from the VHA EMR and NDI database (previously described) that contain information about patient demographics, dispensed prescriptions, procedures, diagnoses, and death. Additional data will be collected during the endpoints adjudication process (for primary outcomes) by medical record analysts using a standardized form. The adjudication data, including the adjudicated outcome, will be entered into an Excel or SAS dataset.

8.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study are documented in the SAP, which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

The SAP is authored by study statisticians and investigators. An overview of the major components is detailed below.

8.7.1. Regression model

The regression analysis will allow for heterogeneity in association between exposures and study endpoints over time (eg, 1 – 5 days vs. 6 – 10 days vs. 11-365 days) and use Cox proportional hazards model with treatment * time interaction term, both allowing for occasional right-censoring; separate azithromycin/amoxicillin hazard ratios will be estimated for time intervals of interest (eg, 1 – 5 days vs. 6 – 10 days vs. 11-365 days).

8.7.2. Confounder control methods

Given the number of potential confounders, propensity scores will be used. Variables for inclusion in the propensity score logistic regression model(s) will be determined a priori, and will include those covariates hypothesized to be associated with exposures and study outcomes, and not mediating the potential effects of interest. Standard approaches to covariate balance diagnostics will be used to assess adequacy of the propensity score model specification. The propensity score will be included in the model as a covariate, categorized based on deciles. Further details are described in the SAP.

8.7.3. CV Risk Score development

The summary CV risk score will be generated for both the azithromycin and amoxicillin cohorts using methodology similar to that used by Ray and colleagues.[1,22] The CV risk score equation will be developed based on antibiotic non-users. Non-users will be identified similar to Ray et al. (2012), with patients in the control group (the study antibiotic non-user group) being required to meet all eligibility criteria on the day the control period began but not having used either azithromycin or amoxicillin during the prior 30 days. Specifically, the first date of the control period will be defined as the first day on which the period meets the criteria defined. Unexposed periods will be matched to exposed periods based on bins

defined by age, gender, index month. The first date on which exposure to azithromycin or amoxicillin 60 days prior to or 30 days after did not occur will be used, and the exposed and nonexposed periods will be matched on the index date. Some risk score elements were not explicitly defined using ICD codes by Ray et al. (2012), and therefore as a result, the ICD codes implemented may differ slightly in the present study. If details of the methods Ray et al. (2012) used to sample nonusers cannot be determined, the following stratified random sampling methods (which were used in the feasibility analysis of VHA data for studying cardiac safety of azithromycin) will be used:

- For each month of index dates, the exposed population (ie, patients treated with azithromycin) will be broken down into two gender and nine age groups (30-34, 35-39, …, 70-74), and the number of prescription dispensings in each month-gender-age bin will be calculated (eg, 1,000 azithromycin/amoxicillin prescription dispensings with index date March 2009 who were male and belong to the 51-55 age group).

- For each specific bin identified, individuals with calendar date, age, and gender characteristics corresponding to the specific bin and who do not have exposure to study antibiotics (ie, azithromycin and amoxicillin) 30 days prior to the index month will be selected from the VHA population. In order to reduce the number of program run cycles (loops), 20,000 prescription dispensings that meet the characteristics of each bin will be randomly selected. A random selection of four matches per prescription dispensing in the bin will then be made. Based on Ray et al.'s (2012) methodology, patients will be matched based on their index date, age, sex, having more than 10 outpatient visits with a non-CV diagnosis in the past year, a prescription dispensing for beta agonist in the past year, an ED visit in the past 30 days, or any prescription dispensing (other than azithromycin or amoxicillin) in the past 30 days.

The CV risk score will be developed from a logistic regression analysis of the effects of each contributing variable on the probability of CV death. The sequential steps involved in the generation of the CV risk score are summarized below and full details are detailed in the SAP.

1. Define the exposed population time periods
2. Define the unexposed population time periods, if determined to be appropriate by the study statisticians (defined above for non-users)
3. Determine the presence/absence of the CV risk score elements (variables) for the population time periods
4. Determine the presence or absence of the outcome (CV death) for the population time periods
5. Quantify the associations between all of the CV risk score variables and the outcome (CV death, unadjudicated for the unexposed population) through a logistic regression model in the unexposed population
6. Apply the CV risk score variable coefficients to the exposed population

7. Divide the population time periods into low, intermediate, and high-risk groups based on the CV risk score results: The CV risk score results will also be divided into three groups of increasing risk for the exposed population time periods: the low risk group (deciles 1-5), the intermediate risk group (deciles 6-9), and the high risk group (decile 10). The primary analysis will focus on outcomes for the top decile of risk (ie, high baseline CV risk).

8.7.4. Sensitivity Analyses

1. Conduct primary analysis (CV death within 5 days and 6-10 days) using propensity score decile as a stratifying variable as an alternative method (ie, estimating 1 HR per decile) and summarizing across strata using inverse-variance weighting or Mantel-Haenszel estimation, after assessment of the heterogeneity across strata

2. Conduct primary analysis (CV death within 5 days and 6-10 days) using propensity score as a continuous covariate

3. Examine the association between azithromycin use and cardiac death (as defined in Section 8.3.2) within 5 days, and 6-10 days, as compared to amoxicillin.

4. Conduct primary analysis (CV death within 5 days and 6-10 days), according to number of antibiotic Rxs (both study and non-study antibiotics) within the prior 30-day period:

    a. among those with no antibiotic Rx within the prior 30-day period (ie, "new users")

    b. among those with 1 antibiotic Rx within the prior 30-day period

    c. among those with > 1 antibiotic Rx within the prior 30-day period

5. Conduct primary analysis (CV death within 5 and 6-10 days) according to antibiotic dose and duration of therapy. The detailed methodology for modeling antibiotic dose as an effect modifier variable will be developed as part of the Statistical Analysis Plan.

6. Conduct primary analysis (CV death within 5 days and 6-10 days) with alternative CV death definition, to include Definite, Possible, and Unclassifiable CV deaths (will exclude deaths classified as "Non-CV")

7. Conduct primary analysis (CV death within 5 days and 6-10 days) with an alternative CV death definition, to include all reported (unadjudicated) deaths meeting CV death criteria by database programming/death certificate data. Thus, this analysis will include reported (unadjudicated), programmatic CV deaths determined to be non-CV deaths by chart review/adjudication.

8. Conduct primary analysis (CV death within 5 and 6-10 days) with alternative CV risk score cut-off points for low, medium, and high CV risk categories. Specifically, the high CV risk group will be created to reflect Ray et al.'s (2012) high CV risk group profile as closely as possible. Therefore, a high CV risk category will be created to reflect the CV mortality cumulative incidence of approximately 160 CV deaths per million amoxicillin prescriptions, as reported by Ray et al. (2012)

9. Conduct primary analysis (CV death within 5 days and 6-10 days) restricted to antibiotic prescription dispensings which have an infection indication of use and thus excluding prescription dispensings given for prophylaxis (if data allow for this indication to be assessed) or missing/other indications (see Section 8.4.2 above).

10. Conduct primary analysis (CV death within 5 days and 6-10 days) restricting to patients who are in the Priority 1 veteran subgroup. These patients have the highest levels of service-connected disability and therefore are the highest priority for VHA care. This subgroup is deemed to have most complete data in the VHA system, as they receive virtually all care from VHA.

11. Estimate the distribution of infection severity according to the type of antibiotic exposure. Because infection severity is extremely resource-intensive to measure with existing VHA data, the study will use a proxy for infection severity that captures each patient's health care utilization after study antibiotic exposure. This method is not yet validated, though it will be applied in the corresponding KP study. Within each 10 day interval after antibiotic exposure, the patients' utilization status will be categorized as: 0 (no emergency department visits or hospital admissions), 1 (any emergency department visit but no hospital admissions), or 2 (any hospital admission). The distribution of this utilization "score" will be compared between antibiotic exposure groups, after excluding those antibiotic prescriptions dispensed for prophylactic indications (as opposed to active infections). If the score is imbalanced between the two antibiotic exposure groups and is also found to be a potential confounder (associated with CV death), it will be added as a variable within the propensity score used for the primary analysis.

12. Instead of treating the number of previous study antibiotic exposures as an ordinary confounder, conduct primary analysis with the Cox regression model stratified on this covariate, allowing for separate, unspecified baseline hazard functions within each stratum. The number of study antibiotics filled prior to each antibiotic fill date is a time-varying covariate, and will be assessed at each index date with look-back from that date to the earliest available calendar date of data collection (January 1, 1999 [one year prior to earliest possible index date for study inclusion], or VHA healthcare membership enrolment date, whichever is latest). In addition to examining number of prior exposures across the full range (0, 1, 2, 3…..), we will also broadly categorize this Cox stratification variable as: 0 and ≥ 1 previous study antibiotic fills.

8.8. Quality control

Data for the study will be extracted from electronic databases in the CDW of the VHA and NDI. Each data content area in the CDW is subjected to similar checks, from high level variable name/type checks, to detailed trending comparisons. As an example, the diagnostic data is subject to the following checks:

- Referenced table exists.
- Diagnosis type correctly assigned by codes defining the diagnosis.
- Percentages, rates, are as expected (check ranges and for missing).
- Both inpatient and outpatient diagnosis codes are captured. Referenced variables exist and are of appropriate length and type.

Data retrieval will be coordinated by an experienced programmer/analyst. The analyst will write programming for retrieval of each data element from the electronic databases. Data quality checks will include comparisons of observed vs. expected numbers of prescription dispensings, outcomes, and patients, comparisons of electronic coding (pharmacy codes) with text string searches of drug names to confirm complete acquisition of medications of interest, and comparisons of estimates of person time from membership files with actual calculated membership time. All tables will be reviewed by the project manager and the principal investigator to evaluate for internal consistency of counts and totals. All calculated variables will be checked against the component variables (cross-tabs) to ensure accuracy. For example, categorical age would be compared with continuous age to confirm that each category of age contained only persons of the expected age ranges within that category.

8.9. Strengths and Limitations of the research methods

The strengths of the proposed study include the adjudication of primary endpoints (unlike prior studies examining this research question, apart from the ongoing KP study), a large sample size with adequate power to detect small effect sizes, the ability to estimate hazards rather than odds, and a population with a high chronic disease risk and similar to the Medicaid population analyzed in Ray et al, (2012)'s study as compared to other populations like the Military Health System and those on commercial health plans.[7] In addition, the study will include comprehensive analytic methods, including many planned sensitivity analyses, a wider range of outcomes and time periods to be examined compared to prior studies. Additionally, similar to KP's analysis, this study will not censor patients after hospitalization, as information about dispensed prescriptions and other health care provided during inpatient stays are captured in the VHA database for hospitalizations at VHA hospitals.

Several limitations of this study should be noted. First, although the VHA CDW has many strengths in its comprehensive structure, variety of variables, and electronic accessibility, there are also gaps in the data since veterans may receive health care services outside of the VHA, which will not be recorded in the CDW. For example, veterans with secondary insurance or veterans who are 65 years of age or older who have Medicare may receive

health care services outside of VHA facilities. One study on VHA enrollees in seven different states found that of all patients admitted to VHA hospitals in 2007, one-fifth also had a non-VHA hospitalization during that year.[27] Another study reported that about 53% of veterans 65 years of age and older who were dually eligible for VHA and Medicare services in 2003-2004 used both.[28] Any care that patients receive outside of VHA facilities will not be captured in the VHA EMR system. KP facilities, however, often are able to keep their patients within their system and do not face this complication. In order to address this concern and ensure that the patient is receiving the majority of his care at the VHA, one of the study inclusion criteria requires that patients have at least two inpatient or outpatient (except ED) encounters and at least 1 dispensing of a medication other than amoxicillin or azithromycin recorded in the database during the year preceding the index antibiotic dispensing date. In this way, the patient included will have made regular use of VHA services, to a reasonable degree of certainty. Additionally, a sensitivity analysis including only Priority Group 1 patients will ensure the cohorts under examination will virtually receive all care at the VHA because of the generous and comprehensive medical benefits package patients in this group receive; however, the number of patients belonging to Priority Group 1 may be too small for making any conclusive inferences.

Furthermore, the VHA population is largely male and the study population is retricted to patients aged 30 – 74. These criteria limit the generalizability to the broader female population and an older population respectively. However, the intention is not necessarily to generalize to the general population, but to follow Ray et al. (2012)'s methods as closely as feasible.

Another possible limitation of the study includes missing indication of antibiotic use information given the indirect method of capturing associated diagnoses for antibiotic prescription dispensings. Furthermore, it may not be possible to completely assess prophylactic antibiotic indication as dental procedures may be handled separately from the veteran's benefits or patients may opt to receive dental or surgical procedures outside of the VHA system. The limited ability of identifying antibiotic prophylaxis may introduce confounding as amoxicillin may be used more frequently for prophylaxis purposes than azithromycin. There may also be some degree of missing data for some of the variables that will be used to calculate the CV risk score as veterans may choose to seek specialty care outside of VHA facilities. However, given the subsequent algorithm refinement after examining the data, the degree of missing information should be limited.

Additionally, veterans may elect to fill prescriptions outside of the VHA, especially if the medications are inexpensive, such as the generic antibiotics to be studied in this analysis. Although this cannot be controlled for, incorporating the inclusion criterion that there are at least two inpatient or outpatient (except ED) encounters and at least 1 pharmacy dispensing for a medication other than amoxicillin or azithromycin will capture the veterans who proactively seek healthcare through the VHA.

Lastly, the VHA pharmacy dispensing data indicate the date on which a prescription was dispensed to a patient but does not guarantee that the medication was taken exactly as prescribed and does not provide data on the exact days that patients are taking their medications. This is a limitation common to all secondary data collection studies.

8.10. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

Informed consent is not required for this study as it is a secondary data collection study, with no patient contact. We anticipate that the VHA Institutional Review Board (IRB) will approve the waiving of informed consent.

9.2. Patient withdrawal

Not Applicable.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the principal investigators to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (eg, recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

This protocol is expected to be approved by the Institutional Review Board of the Veterans Affairs Medical Center, White River Junction, VT on December 21, 2016.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study uses existing health care databases, in which it is generally not possible to link (ie, identify a potential association between) a particular product and medical event for any individual.

In addition, this study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AE) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to any Pfizer drug that appear in the reviewed information must be recorded on the eCRF and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these safety events with an explicit attribution to or associated with use of, respectively, a Pfizer product, the data captured in the medical record will constitute all clinical information known regarding these adverse events. No follow-up on related adverse events will be conducted.

All research staff members will complete the Pfizer requirements regarding training on the following: "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)"* and any relevant Your Reporting Responsibilities supplemental training. This training must be completed by research staff members prior to start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The final study report will be submitted to the FDA according to the timetable outlined in Section 5.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

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13. LIST OF TABLES

14. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

[Not Required.]

ANNEX 3. ADDITIONAL INFORMATION

Not applicable

Appendix 1. Radiology procedures and codes used in the Sudden Cardiac Death (SCD) programmatic algorithm.

The presence of any of these codes on the day of death prevents the death from being classified as SCD.

PROCEDURE NAME	CPT PROCEDURE CODE
3D RENDERING W/INTERP & POSTPROCESS SUPERVISION	76376
3D RENDERING W/INTERP&POSTPROC DIFF WORK STATION	76377
ACUTE GASTROINTESTINAL BLOOD LOSS IMAGING	78278
ACUTE VENOUS THROMBOSIS IMAGING PEPTIDE	78456
ADRENAL IMAGING CORTEX &/MEDULLA	78075
ANGIOGRAPHY ADRENAL BILATERAL SLCTV RS&I	75733
ANGIOGRAPHY ADRENAL UNILATERAL SLCTV RS&I	75731
ANGIOGRAPHY ARTERIOVENOUS SHUNT RAD S&I	75790
ANGIOGRAPHY CAROTID CEREBRAL BILATERAL RS&I	75671
ANGIOGRAPHY CAROTID CEREBRAL UNILATERAL RS&I	75665
ANGIOGRAPHY CAROTID CERVICAL BILATERAL RS&I	75680
ANGIOGRAPHY CAROTID CERVICAL UNILATERAL RS&I	75676
ANGIOGRAPHY CERVICOCEREBRAL CATHETER RS&I	75650
ANGIOGRAPHY EXTERNAL CAROTID BI SLCTV RS&I	75662
ANGIOGRAPHY EXTERNAL CAROTID UNI SLCTV RS&I	75660
ANGIOGRAPHY EXTREMITY BILATERAL RS&I	75716
ANGIOGRAPHY EXTREMITY UNILATERAL RS&I	75710
ANGIOGRAPHY INTERNAL MAMMARY RS&I	75756
ANGIOGRAPHY PELVIC SLCTV/SUPRASLCTV RS&I	75736
ANGIOGRAPHY PULMONARY BILATERAL SLCTV RS&I	75743
ANGIOGRAPHY PULMONARY UNILATERAL SLCTV RS&I	75741
ANGIOGRAPHY SPINAL SELECTIVE RS&I	75705
ANGIOGRAPHY VERTEBRAL/CERVICAL/&/INTRACRAN RS&I	75685
ANGIOGRAPHY VISCERAL SLCTV/SUPRASLCTV RS&I	75726
ANGIOGRPHY AV SHUNT COMPLETE EVAL FLUOR S&I	75791
ANGRPH CATH F/U STUDY THER/EMBOLIZATION/INFUSION	75805
ANGRPH CATH F-UP STD TCAT OTHER THAN THROMBYLSIS	75898
ANGRPH PULMONARY NONSLCTV CATH/VEN NJX RS&I	75746
ANGRPH RNL BI SLCTV W/FLUSH AORTOGRAM RS&I	75724
ANGRPH RNL UNI SLCTV W/FLUSH AORTOGRAM RS&I	75722
ANGRPH SLCTV EA VSL STUDIED AFTER BASIC XM RS&I	75774
ANIOGRAPHY BRACHIAL RETROGRADE RS&I	75658
AORTOGRAPHY ABDL BI ILIOFEM LOW EXTREM CATH RS&I	75630
AORTOGRAPHY ABDOMINAL SERIALOGRAPHY RS&I	75625
AORTOGRAPHY THORACIC SERIALOGRAPHY RS&I	75605

AORTOGRAPHY THORACIC W/O SERIALOGRAPHY RS&I	75600
BASIC RADIATION DOSIMETRY CALCULATION	77300
BONE &/JOINT IMAGING 3 PHASE STUDY	78315
BONE &/JOINT IMAGING LIMITED AREA	78300
BONE &/JOINT IMAGING MULTIPLE AREAS	78305
BONE &/JOINT IMAGING TOMOGRAPHIC SPECT	78320
BONE &/JOINT IMAGING WHOLE BODY	78306
BONE AGE STUDIES	76020
BONE AGE STUDIES	77072
BONE DENSITY 1/> SITES 1 PHOTON ABSORPTIOMETRY	78350
BONE DENSTY 1/> SITES DUAL PHOTON ABSORPTIOMETR	78351
BONE LENGTH STUDIES	77073
BONE LENGTH STUDIES	76040
BONE MARROW BLOOD SUPPLY	77084
BONE MARROW IMAGING LIMITED AREA	78102
BONE MARROW IMAGING MULTIPLE AREAS	78103
BONE MARROW IMAGING WHOLE BODY	78104
BRACHYTHERAPY ISODOSE PLAN COMPLEX	77328
BRACHYTHERAPY ISODOSE PLAN INTERMEDIATE	77327
BRACHYTHERAPY ISODOSE PLAN SIMPLE	77326
BRAIN IMAGING <4 STATIC VIEWS	78600
BRAIN IMAGING <4 STATIC VIEWS W/VASCULAR FLOW	78601
BRAIN IMAGING MIN 4 STATIC VIEWS W VASCULAR FLOW	78606
BRAIN IMAGING MINIMUM 4 STATIC VIEWS	78605
BRAIN IMAGING PET METABOLIC EVALUATION	78608
BRAIN IMAGING PET PERFUSION EVALUATION	78609
BRAIN IMAGING TOMOGRAPHIC SPECT	78607
BRAIN IMAGING VASCULAR FLOW ONLY	78610
BRONCHOGRAPY BILATERAL RS&I	71060
BRONCHOGRAPY UNILATERAL RS&I	71040
CARD BL POOL GATED 1 STDY REST RT VENT EJCT FRCT	78496
CARD BL POOL GATED MLT STDY WAL MOTN EJECT FRACT	78473
CARD BL POOL GATED SPECT REST WAL MOTN EJCT FRCT	78494
CARD BL POOL PLANAR 1 STDY WAL MOTN EJECT FRACT	78481
CARD BL POOL PLNR MLT STDY WAL MOTN EJECT FRACT	78483
CARD BLOOD POOL GATED PLANAR 1 STUDY REST/STRESS	78472
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CARDIAC SHUNT DETECTION	78428
CARD-VASC HEMODYNAM W/WO PHARM/EXER 1/MLT DETERM	78414
CEPHALOGRAM ORTHODONTIC	70350
CEREBRAL VASCULAR FLOW	78615
CEREBROSPINAL FLUID FLOW W/O MATL CISTERNOGRAPHY	78630
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CEREBROSPINAL FLUID FLOW W/O MATL TOMOG SPECT	78647
CEREBROSPINAL FLUID FLOW W/O MATL VENTRICLGRAPHY	78635
CEREBROSPINAL FLUID LEAK DETECTION&LOCALIZATIO	78650
CHANGE PRQ TUBE/DRAINAGE CATH W CONTRAST RS&I	75984
CHELATABLE IRON ESTIMATION OF TOTAL BODY IRON	78172
CHOLANGIO&/PANCREATOGRAPHY ADDL SET INTRAOP RS	74301
CHOLANGIO&/PANCREATOGRAPHY THRU CATH RS&I	74305
CHOLANGIO&/PANCREATOGRAPHY TRANSHEPATC RS&I	74320
CHOLANGIOGRAPHY&/PANCREATOGRAPHY NTRAOP RS&I	74300
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CHOLECYSTOGRAPHY ORAL CONTRST	74290
CINERADIGRPH/VIDEORADIOGRAPHY NO WHERE SPEC INCL	76120
CINERADIOGRAPY/VIDRADIOGRAPY ROUTINE EXAMINATION	76125
CISTERNOGRAPHY POSITIVE CONTRAST RS&I	70015
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CT ABDOMEN W/CONTRAST MATERIAL	74160
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CT ANGIOGRAPHY PELVIS W/CONTRAST/NONCONTRAST	72191
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CT BN MINERL DNSITY STDY 1/MORE SITE; AXIAL SKEL	76070
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CT UPPER EXTREMITY W/O CONTRAST MATERIAL	73200
CTA ABDL AORTA&BI ILIOFEM W/CONTRAST&POSTP	75635
CTA HRT CORNRY ART/BYPASS GRFTS CONTRST 3D POST	75574
CYSTOGRAPHY MINIMUM 3 VIEWS RS&I	74430
DACRYOCSTOGRAPY NASOLACRIMAL DUCT RS&I	70170
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DOPPLER ECHO FETAL SPECTRAL DISPLAY COMPLETE	76827
DOPPLER VELOCIMETRY FETAL MIDDLE CEREBRAL ART	76821
DOPPLER VELOCIMETRY FETAL UMBILICAL ARTERY	76820
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DXA B1 DNS STD 1+ SITS APPND SKEL PRPH	76076
DXA B1 DNS STD 1+ SITS AXIAL SKEL	76075
DXA B1 DNS STD 1+ SITS VRT FX ASSMT	76077

DXA BONE DENSITY STUDY 1/> SITES AXIAL SKEL	77080
DXA BONE DENSITY STUDY 1/>SITES APPENDICLR SKEL	77081
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KIDNEY IMAGING MORPHOOGY W/VASCULAR FLOW	78701
KIDNEY IMAGING; WITH FUNCTION STUDY	78704
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KIDNEY IMG MORPHOLOGY VASCULAR FLOW 1 W/RX	78708
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MR IMAG BRST W/O &OR W/CONTRST MATERIAL; UNI	76093
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MRA HEAD W/CONTRAST MATERIAL	70545
MRA HEAD W/O & W/CONTRAST MATERIAL	70546
MRA HEAD W/O CONTRST MATERIAL	70544
MRA LOWER EXTREMITY W/WO CONTRAST MATERIAL	73725
MRA NECK W/CONTRAST MATERIAL	70548
MRA NECK W/O &W/CONTRAST MATERIAL	70549
MRA NECK W/O CONTRST MATERIAL	70547
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MRI ABDOMEN W/O & W/CONTRAST MATERIAL	74183
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MRI ANY JT LOWER EXTREM W/O CONTRAST MATRL	73721
MRI ANY JT UPPER EXTREMITY W/CONTRAST MATRL	73222
MRI ANY JT UPPER EXTREMITY W/O & W/CONTR MATRL	73223
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MRI BRAIN OPEN INTRACRANIAL PX W/O CONTRAST MATL	70557
MRI BREAST BILATERAL	77059
MRI BREAST UNILATERAL	77058
MRI CHEST W/CONTRAST MATERIAL	71551
MRI CHEST W/O & W/CONTRAST MATERIAL	71552
MRI CHEST W/O CONTRAST MATERIAL	71550
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MRI LOWER EXTREM OTH/THN JT W/O & W/CONTR MATR	73720
MRI LOWER EXTREM OTH/THN JT W/O CONTR MATRL	73718
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MRI ORBIT FACE & NECK W/CONTRAST MATERIAL	70542
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MRI PELVIS W/O & W/CONTRAST MATERIAL	72197
MRI PELVIS W/O CONTRAST MATERIAL	72195
MRI SPINAL CANAL CERVICAL W/CONTRAST MATRL	72142
MRI SPINAL CANAL CERVICAL W/O & W/CONTR MATRL	72156
MRI SPINAL CANAL CERVICAL W/O CONTRAST MATRL	72141
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MRI SPINAL CANAL LUMBAR W/O & W/CONTR MATRL	72158
MRI SPINAL CANAL LUMBAR W/O CONTRAST MATERIAL	72148
MRI SPINAL CANAL THORACIC W/CONTRAST MATRL	72147
MRI SPINAL CANAL THORACIC W/O & W/CONTR MATRL	72157
MRI SPINAL CANAL THORACIC W/O CONTRAST MATRL	72146
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MRI UPPER EXTREM OTHER THAN JT W/O & W/CONTRAS	73220
MRI UPPER EXTREMITY OTH THAN JT W/CONTR MATRL	73219
MRI UPPER EXTREMITY OTH THAN JT W/O CONTR MATRL	73218
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MYELOGRAPY THORACIC RS&I	72255
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MYOCARD PERFUS IMAG; SPECT 1 STDY AT REST/STRSS	78464
MYOCARD PERFUS IMAG; SPECT MX STDY REST&/STRESS	78465
MYOCARD PERFUS STDY W/WALL MOTION QUAL/QUAN STDY	78478
MYOCARDIAL IMAG PLANAR; W/EJECT FRACT-1ST PASS	78468
MYOCARDIAL IMAGING INFARCT AVID PLANAR QUAL/QUAN	78466
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OPH US DX B-SCAN&QUAN A-SCAN SM PT ENCTR	76510
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PET IMAGING LIMITED AREA CHEST HEAD/NECK	78811
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PET IMAGING WHOLE BODY	78813
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PLASMA VOL RADIOPHARM VOL DILUTE SPX MULT SMPLES	78111
PLASMA VOL RADIOPHARM VOL DILUTION SPX 1 SAMPLE	78003
PLASMA VOL RADIOPHARM VOL DILUTION SPX 1 SAMPLE	78110
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PLMT PROX XTN PRSTH EVASC DESC THORAC AORTA RS&I	75958
PLMT XTN PROSTH EVASC RPR INFRARENAL RS&I	75953
POSTOP BILIARY STONE RMVL PRQ T-TUBE RS&I	74327
PROTON TX DELIVERY COMPLEX	77525
PROTON TX DELIVERY INTERMEDIATE	77523
PROTON TX DELIVERY SIMPLE W/COMPENSATION	77522
PROTON TX DELIVERY SIMPLE W/O COMPENSATION	77520
PROVISION OF DIAGNOSTIC RADIOPHARMACEUTICAL	78990
PROVISION OF THERAPEUTIC RADIOPHARMACEUTICAL	79900
PRQ PLMT INT/EXT BILIARY DRNG CATH/STENT RS&I	75982
PRQ PLMT IVC FILTER RS&I	75940
PRQ TRANSHEPATC BILIARY DRG W/CONTRAST MNTR RS&I	75980
PRQ TRANSHEPATC DILAT BILIARY DUCT STRICTRE RS&I	74363
PRQ TRANSHEPATC PORTOGRAPY HEMODYN EVAL RS&I	75885
PRQ TRANSHEPATC PORTOGRAPY W/O HEMODYN EVL INTRP	75887
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PULM PERF IMAG-PARTICULATE W/VENT IMAG-AEROSOL	78588
PULM PERFUS IMAG PARTICULATE W/VENT; 1 BREATH	78584
PULM PERFUS PARTICULATE W/VENT; REBREATH & WASH	78585
PULM VI AERSL 1 PROJECTION	78586
PULM VI AERSL MLT PRJCJ	78587
PULM VI GASEOUS 1 PRJCJ	78591
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PULM VI GASEOUS RBRTHING&WSHOT MLT PRJCJ	78594
PULMONARY PERFUSION IMAGING PARTICULATE	78580
PULMONARY QUANTITATIVE DIFF FUNCTION STUDY	78596
PULMONARY VENTILATION & PERFUSION IMAGING	78582
PULMONARY VENTILATION IMAGING	78579
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QUANT DIFFERENTIAL PULM PERFUSION W/WO IMAGING	78597
RAD EXAM COMPLX MOTION BODY SECT-NOT UROG; BIL	76102
RAD EXAM COMPLX MOTION BODY SECT-NOT UROG; UNI	76101
RAD EXAM SM INTESTINE; VIA ENTEROCLYSIS TUBE	74251
RAD EXAM; PHARYNX/LARYNX INCL FLUORO &/OR MAGNIF	70370
RAD S&I PERQ VRTPLS/SACRPLSTY PER VRT BODY CT	72292
RAD S&I PERQ VRTPLS/SACRPLSTY PR VRT BODY FLUO	72291
RAD TX DELIV-1 TX AREA-1 PORT-SMPL BLOC; 6-10MEV	77403
RAD TX DELIV-1 TX AREA-1 PORT-SMPL BLOC; TO 5MEV	77402
RAD TX DELIV-2 TX AREAS-3/MORE PORTS; 11-19 MEV	77409
RAD TX DELIV-2 TX AREAS-3/MORE PORTS; 20 MEV/GRT	77411
RAD TX DELIV-2 TX AREAS-3/MORE PORTS; 6-10 MEV	77408
RAD TX DELIV-2 TX AREAS-3/MORE PORTS; TO 5 MEV	77407
RAD XM SI JT ARTHG RS&I	73542
RADEX 1 PLNE BODY SECTION OTH/THN W/UROGRAPY	76100
RADEX ABD COMPL AQT ABD W/S/E/D VIEWS 1 VIEW CH	74022
RADEX ABDOMEN 1 ANTEROPOSTERIOR VIEW	74000
RADEX ABDOMEN COMPL W/DCBTS&/ERC VIEWS	74020
RADEX ABSCESS/FISTULA/SINUS TRACT RS&I	76080
RADEX A-C JOINTS BI W/WO WEIGHTED DISTRCJ	73050
RADEX ANKLE ARTHROGGRAPHY RS&I	73615
RADEX ANKLE COMPLETE MINIMUM 3 VIEWS	73610
RADEX CH 2 VIEWS FRNT & LAT APICAL LORDOTIC PX	71021
RADEX CH 2 VIEWS FRONTAL & LATERAL OBLIQUE PRJCJ	71022
RADEX CH 2 VIEWS FRONTAL & LATERAL W/FLUORO	71023
RADEX CHEST COMPLETE MINIMUM 4 VIEWS	71030
RADEX CHEST COMPLETE MINIMUM 4 VIEWS W/FLUORO	71034
RADEX CHEST SPECIAL VIEWS	71035
RADEX CLAVICLE COMPLETE	73000
RADEX COLON BARIUM ENEMA W/WOKUB	74270
RADEX COLON W/SPEC HI DNS BARIUM W/WO GLUCAGON	74280
RADEX ELBOW 2 VIEWS	73070
RADEX ELBOW ARTHROGRAPHY RS&I	73085
RADEX ELBOW COMPLETE MINIMUM 3 VIEWS	73080
RADEX ESOPHAGUS	74220
RADEX FACIAL BONES < 3 VIEWS	70140
RADEX FACIAL BONES COMPLETE MINIMUM 3 VIEWS	70150
RADEX FINGR MINIMUM 2 VIEWS	73140
RADEX FOOT COMPLETE MINIMUM 3 VIEWS	73630
RADEX FOREARM 2 VIEWS	73090
RADEX FROM NOSE RECTUM FOREIGN BODY 1 VIEW CHLD	76010
RADEX GI TRACT UPPER W/WO DELAYED FILMS W/KUB	74241
RADEX GI TRACT UPPER W/WO DELAYED FILMS W/O KUB	74240

RADEX GI TRACT UPR W/SM INT W/MULT SERIAL FLMS	74245
RADEX GI UPR W/WO GLUCOSE W/SM INTEST FOLLW-THRU	74249
RADEX HIP ARTHROGRAPHY RS&I	73525
RADEX HIP OPERATIVE PROCEDURE	73530
RADEX HIP UNILATERAL 1 VIEW	73500
RADEX HIP UNILATERAL COMPLETE MINIMUM 2 VIEWS	73510
RADEX HIPS BILATERAL 2 VIEWS ANTEROPOST PELVIS	73520
RADEX HUMERUS MINIMUM 2 VIEWS	73060
RADEX INTERNAL AUDITORY MEATI COMPLETE	70134
RADEX LOWER EXTREMITY INFANT MINIMUM 2 VIEWS	73592
RADEX NASAL BONES COMPLETE MINIMUM 3 VIEWS	70160
RADEX ORBITS COMPLETE MINIMUM 4 VIEWS	70200
RADEX PHARYNX&/CERVICAL ESOPHAGUS	74210
RADEX RENAL CYST STUDY TRANSLUMBAR RS&I	74470
RADEX RIBS BI W/POSTEROANT CH MINIMUM 4 VIEWS	71111
RADEX RIBS BILATERAL 3 VIEWS	71110
RADEX RIBS UNI W/POSTEROANT CH MINIMUM 3 VIEWS	71101
RADEX RIBS UNILATERAL 2 VIEWS	71100
RADEX SACRUM & COCCYX MINIMUM 2 VIEWS	72220
RADEX SCAPULA COMPLETE	73010
RADEX SHOULDER 1 VIEW	73020
RADEX SHOULDER ARTHROGRAPHY RS&I	73040
RADEX SHOULDER COMPLETE MINIMUM 2 VIEWS	73030
RADEX SINUSES PARANASAL <3 VIEWS	70210
RADEX SINUSES PARANASAL COMPL MINIMUM 3 VIEWS	70220
RADEX SMALL INTESTINE W/MULTIPLE SERIAL FILMS	74250
RADEX SPINE 1 VIEW SPECIFY LEVEL	72020
RADEX SPINE CERVICAL 3 VIEWS OR LESS	72040
RADEX SPINE CERVICAL 4 OR 5 VIEWS	72050
RADEX SPINE CERVICAL 6 OR MORE VIEWS	72052
RADEX SPINE ENTIRE SURVEY STD ANTEROPOST & LAT	72010
RADEX SPINE LUMBOSACRAL 2/3 VIEWS	72100
RADEX SPINE LUMBOSACRAL MINIMUM 4 VIEWS	72110
RADEX SPINE LUMBOSACRAL ONLY BENDING 2/3 VIEWS	72120
RADEX SPINE LUMBSCRL COMPL W/BENDING VIEWS MIN 6	72114
RADEX SPINE SCOLIOS STUDY W/SUPINE & ERECT STUDY	72090
RADEX SPINE THORACIC 2 VIEWS	72070
RADEX SPINE THORACIC 3 VIEWS	72072
RADEX SPINE THORACIC MINIMUM 4 VIEWS	72074
RADEX SPINE THORACOLMBR STANDING SCOLIOSIS	72069
RADEX SPINE THORACOLUMBAR 2 VIEWS	72080
RADEX STERNOCLAVICULAR JT/JTS MINIMUM 3 VIEWS	71130
RADEX STERNUM MINIMUM 2 VIEWS	71120
RADEX TEMPOROMANDBLE JT OPN & CLSD MOUTH BILAT	70330

RADEX TEMPOROMANDBLE JT OPN & CLSD MOUTH UNILAT	70328
RADEX UPPER EXTREMITY INFANT MINIMUM 2 VIEWS	73092
RADEX UPPER GI W/WO GLUCAGON/DELAY FILMS W/O KUB	74246
RADEX UPPER GI W/WO GLUCAGON/DELAY FLMS W/KUB	74247
RADEX WRIST 2 VIEWS	73100
RADEX WRIST ARTHROGRAPHY RS&I	73115
RADEX WRIST COMPLETE MINIMUM 3 VIEWS	73110
RADIAT TX DELIV-1 TX AREA-1 PORT; 20 MEV/GREATER	77406
RADIATION DELIVERY STEREOTACTIC CRANIAL COBALT	77371
RADIATION DELIVERY STEREOTACTIC CRANIAL LINEAR	77372
RADIATION THERAPY MGMT 1/2 FRACTIONS ONLY	77431
RADIATION TREATMENT MANAGEMENT 5 TREATMENTS	77427
RADIATION TX DELIV-1 TX AREA-1 PORT; 11-19 MEV	77404
RADIATION TX DELIVERY SUPERFICIAL&/ORTHO VOLTA	77401
RADIOGRAPHIC ABSORPTIOMETRY 1+ SITS	77083
RADIOGRAPHIC ABSORPTIOMETRY ONE OR MORE SITES	76078
RADIOIRON ORAL ABSORPTION	78162
RADIOIRON RED CELL UTILIZATION	78170
RADIOLOG EXAM MANDIBLE COMPL MINIMUM 4 VIEWS	70110
RADIOLOGIC EXAM ABD; AP&ADD OBLIQUE&CONE VIEWS	74010
RADIOLOGIC EXAM BOTH KNEES STANDING ANTEROPOST	73565
RADIOLOGIC EXAM CHEST 2 VIEWS FRONTAL&LATERAL	71020
RADIOLOGIC EXAM KNEE ARTHROGRAPHY RS&I	73580
RADIOLOGIC EXAM KNEE COMPLETE 4/MORE VIEWS	73564
RADIOLOGIC EXAM MASTOIDS < 3 VIEWS PER SIDE	70120
RADIOLOGIC EXAM MASTOIDS; CMPL MINI 3 VIEWS-SIDE	70130
RADIOLOGIC EXAM PELV&HIPS INFNT/CHLD MINI 2 VIEW	73540
RADIOLOGIC EXAM PELVIS COMPL MINIMUM 3 VIEWS	72190
RADIOLOGIC EXAM SACROILIAC JOINTS 3/MORE VIEWS	72202
RADIOLOGIC EXAM SKULL COMPLETE MINIMUM 4 VIEWS	70260
RADIOLOGIC EXAM TEETH COMPLETE FULL MOUTH	70320
RADIOLOGIC EXAM TEETH PRTL EXAM < FULL MOUTH	70310
RADIOLOGIC EXAMINATION ANKLE 2 VIEWS	73600
RADIOLOGIC EXAMINATION CHEST SINGLE VIEW FRONTAL	71010
RADIOLOGIC EXAMINATION CHEST STERO FRONTAL	71015
RADIOLOGIC EXAMINATION EYE DETECT FOREIGN BODY	70030
RADIOLOGIC EXAMINATION FEMUR 2 VIEWS	73550
RADIOLOGIC EXAMINATION FOOT 2 VIEWS	73620
RADIOLOGIC EXAMINATION HAND; MINIMUM THREE VIEWS	73130
RADIOLOGIC EXAMINATION HAND; TWO VIEWS	73120
RADIOLOGIC EXAMINATION KNEE 1/2 VIEWS	73560
RADIOLOGIC EXAMINATION KNEE 3 VIEWS	73562
RADIOLOGIC EXAMINATION MANDIPLE PRTL <4 VIEWS	70100

RADIOLOGIC EXAMINATION NECK SOFT TISSUE	70360
RADIOLOGIC EXAMINATION OSSEOUS SURVEY COMPL	77075
RADIOLOGIC EXAMINATION OSSEOUS SURVEY INFANT	77076
RADIOLOGIC EXAMINATION OSSEOUS SURVEY INFANT	76065
RADIOLOGIC EXAMINATION OSSEOUS SURVEY LIMITED	77074
RADIOLOGIC EXAMINATION OSSEOUS SURVEY; COMPLETE	76062
RADIOLOGIC EXAMINATION OSSEOUS SURVEY; LIMITED	76061
RADIOLOGIC EXAMINATION PELVIS 1/2 VIEWS	72170
RADIOLOGIC EXAMINATION SACROILIAC JNTS <3 VIEWS	72200
RADIOLOGIC EXAMINATION SALIVARY GLAND CALCULUS	70380
RADIOLOGIC EXAMINATION SELLA TURCICA	70240
RADIOLOGIC EXAMINATION SKULL 4/> VIEWS	70250
RADIOLOGIC EXAMINATION TEETH 1 VIEW	70300
RADIOLOGIC EXAMINATION TIBIA & FIBULA 2 VIEWS	73590
RADIOLOGIC EXAMINATION; CALCAN MINIMUM 2 VIEWS	73650
RADIOLOGIC EXAMINATION; OPTIC FORAMINA	70190
RADIOLOGIC EXAMINATION; TOE MINIMUM OF TWO VIEWS	73660
RADIOLOGICAL EXAMINATION SURGICAL SPECIMEN	76098
RADIOLOGICAL GUIDANCE PRQ DRG W/PLMT CATH RS&I	75989
RADIOPHARMACEUTICAL ABLAT GLAND THYROID CA	79030
RADIOPHARMACEUTICAL DACRYOCYSTOGRAPHY	78660
RADIOPHARMACEUTICAL THERAPY METS THYROID CA	79035
RADJ DLVR 3/> AREAS CUSTOM BLKING <5MEV	77412
RADJ DLVR 3/> AREAS CUSTOM BLKING 11-19MEV	77414
RADJ DLVR 3/> AREAS CUSTOM BLKING 20MEV/<	77416
RADJ DLVR 3/> AREAS CUSTOM BLKING 6-10MEV	77413
RADOPHRM LOC INFLAM PROCESS; TOMOGRAPHIC	78807
RADOPHRM TX HYPER-THYROIDISM; INIT INCL EVAL PT	79000
RADOPHRM TX HYPER-THYROIDISM; SUBSEQUENT EA TX	79001
RADOPHRM TX NONTHYROID NONHEMATOLOGIC IV INJ	79400
RADOPHRM TX THYROID SUPPRESSION INCL EVAL PT	79020
RADPHRM TX POLYCYTHEM VERA CHRON LEUKEM EA TX IV	79100
RBC SURVIVAL STUDY DIFFERNTL ORGAN/TISS KINETICS	78135
RED CELL SURVIVAL STUDY	78130
RED CELL VOLUME DETERMINATION SPX 1 SAMPLING	78120
RED CELL VOLUME DETERMINATION SPX MULT SAMPLINGS	78121
REIMB GI NUCLEAR PROCEDURE-FACILITY.	78229
REIMB MUSCULOSKELETAL NUCLEAR EXAM PC.	78339
REMOTE AFTERLOAD BRACHYTHERAP 5-8 SOURCE POSIT	77782
REMOTE AFTERLOAD BRACHYTHERAP; > 12 SOURCE POSIT	77784
REMOTE AFTERLOAD BRACHYTHERAP; 1-4 SOURCE POSIT	77781
REMOTE AFTERLOAD BRACHYTHERAP; 9-12 SOURCE POSIT	77783

REMOTE AFTLD RADIONUCLIDE BRACHYTX > 12 CHANNEL	77787
REMOTE AFTLD RADIONUCLIDE BRACHYTX 1 CHANNEL	77785
REMOTE AFTLD RADIONUCLIDE BRACHYTX 2-12 CHANNEL	77786
RMVL FB ESOPHAGEAL W/USE BALLOON CATH RS&I	74235
RP LOCLZJ INFLAMMATORY PROCESS LIMITED AREA	78805
RP LOCLZJ INFLAMMATORY PROCESS WHOLE BODY	78806
RP LOCLZJ TUMOR/DSTRBJ AGENT LIMITED AREA	78800
RP LOCLZJ TUMOR/DSTRBJ AGENT MULTIPLE AREAS	78801
RP LOCLZJ TUMOR/DSTRBJ AGENT TOMOG SPECT	78803
RP LOCLZJ TUMOR/DSTRBJ AGENT WHOLE BDY 1 DAY	78802
RP LOCLZJ TUMOR/DSTRBJ AGT WHOL BDY REQ 2/> DAY	78804
RP THER RADIOLBLD MONOCLONAL ANTIBODY IV INFUS	79403
RP THERAPY INRACAVITARY ADMINISTRATION	79200
RP THERAPY INTERSTITIAL RADIOACTIVE COLLOID ADMN	79300
RP THERAPY INTRA-ARTERIAL PARTICULATE ADMN	79445
RP THERAPY INTRA-ARTICULAR ADMINISTRATION	79440
RP THERAPY INTRAVENOUS ADMINISTRATION	79101
RP THERAPY ORAL ADMINISTRATION	79005
RP THERAPY UNLISTED PROCEDURE	79999
RS&I PRQ VRTPLS/VRT AGMNTJ PR VRT BDY CT	76013
RS&I PRQ VRTPLS/VRT AGMNTJ PR VRT BDY FLUOR	76012
SALINE INFUS SONOHYSTEROGRAPHY W/COLOR DOPPLER	76831
SALIVARY GLAND FUNCTION STUDY	78232
SALIVARY GLAND IMAGING	78230
SALIVARY GLAND IMAGING SERIAL IMAGES	78231
SCREENING MAMMOGRAPHY BILATERAL	77057
SCREENING MAMMOGRAPHY BILATERAL	76092
SHUNTOGRAM INDWELLING NONVASCULAR SHUNT RS&I	75809
SIALOGRAPHY RAD S&I	70390
SPCL DOSIMETRY ONLY WHEN PRSC TREATING PHYSICIAN	77331
SPCL TELETX PORT PLAN PARTICLES HEMIBDY TOT BDY	77321
SPECIAL MEDICAL RADIATION PHYSICS CONSULTATION	77370
SPECIAL TREATMENT PROCEDURE	77470
SPLEEN IMAGING ONLY W/WO VASCULAR FLOW	78185
SPLENOPORTOGRAPY RS&I	75810
STEREOTACT GUID BRST BX/NEEDLE PLCMT-EA LES-RS&I	76095
STEREOTACTIC BODY RADIATION DELIVERY	77373
STEREOTACTIC BODY RADIATION MANAGEMENT	77435
STERETCTC RADIATION TX MANAGEMENT CRANIAL LESION	77432
STRSC X-RAY GDN LOCLZJ TARGET VOL DLVR RADJ THER	77421
STRTCTC LOCLZJ GID BREAST BX/NEEDLE PLACEMENT	77031
SUBTRACTION IN CONJUNCTION WITH CONTRAST STUDIES	76350
SUPERVISION HANDLING LOADING RADIATION SOURCE	77790

SURFACE APPLICATION RADIATION SOURCE	77789
SWALLOWING FUNCJ W/CINERADIOGRAPY/VIDRADIOG	74230
TCAT RETRIEVAL PRQ IV FOREIGN BODY RS&I	75961
TCAT STENT ILIAC/LOW EXT ART PRQ/OPN RSI EA VSL	75960
TELETHERAPY ISODOSE PLAN COMPLETE	77315
TELETHERAPY ISODOSE PLAN INTERMEDIATE	77310
TELETHERAPY ISODOSE PLAN SIMPLE	77305
TEMPOROMANDBLE JT ARTHROGRAPHY RS&I	70332
TESTICULAR IMAGING WITH VASCULAR FLOW	78761
TESTICULAR IMAGING;	78760
THER RAD SIMULAJ-AIDED FIELD SETTING COMPLEX	77290
THER RAD SIMULAJ-AIDED FIELD SETTING INTERMED	77285
THER RAD SIMULAJ-AIDED FIELD SETTING SIMPLE	77280
THER RAD SIMULAJ-AIDED FLD SETTING 3-DIMENSIONAL	77295
THERAPEUTIC ENEMA RDCTJ INTUSSUSCEPTION/OBSTRCJ	74283
THERAPEUTIC RADIOLOGY PORT FILMS	77417
THERAPEUTIC RADIOLOGY TX PLANNING COMPLEX	77263
THERAPEUTIC RADIOLOGY TX PLANNING INTERMEDIATE	77262
THERAPEUTIC RADIOLOGY TX PLANNING SIMPLE	77261
THYROID CARCINOMA METASTASES IMG ADDL STUDY	78016
THYROID CARCINOMA METASTASES IMG LMTD AREA	78015
THYROID CARCINOMA METASTASES IMG WHOLE BODY	78018
THYROID CARCINOMA METASTASES UPTAKE	78020
THYROID IMAGING ONLY	78010
THYROID IMAGING W/UPTAKE MULT DETERMINATIONS	78007
THYROID IMAGING W/UPTAKE SINGLE DETERMINATION	78006
THYROID IMAGING W/VASCULAR FLOW	78011
THYROID IMAGING WITH VASCULAR FLOW	78013
THYROID UPTAKE MULTIPLE DETERMINATIONS	78001
THYROID UPTAKE SINGLE DETERMINATION	78000
THYROID UPTAKE SINGLE/MULTIPLE QUANT MEASUREMENT	78012
THYROID UPTAKE W/BLOOD FLOW SNGLE/MULT QUAN MEAS	78014
TRANSCATHETER BIOPSY RS&I	75970
TRANSCATHETER EMBOLIZATION ANY METH RS&I	75894
TRANSCATHETER INFUSION OTHER THAN THROMBOLYSIS	75896
TRANSCERVICAL CATHJ FALLOPIAN TUBE RS&I	74742
TRANSLUMINAL ATHERECT EA ADD PERIPH ART RAD S&I	75993
TRANSLUMINAL ATHERECTOMY PERIPHERAL ART RAD S&I	75992
TRANSLUMINAL ATHERECTOMY RENAL RAD S&I	75994
TRANSLUMINAL ATHERECTOMY VISCERAL RAD S&I	75995
TRANSLUMINAL BALLOON ANGIOPLASTY VENOUS RS&I	75978
TRANSLUMINAL BALLOON ANGPLSTY PERIPH ART RAD S&I	75962

TRLUML BALO ANGIOPLASTY EA VISCERAL ART RS&I	75968
TRLUML BALO ANGIOPLASTY RENAL/OTH VISC ART RS&	75966
TRNSLUM ATHERECT EA ADD VISCERAL ART RAD S&I	75996
TRNSLUM BALLN ANGPLSTY EA ADD PERIPH ART RAD S&I	75964
TUMR IMAG POSITRON EMISSION TOMOGRPH METAB EVAL	78810
TX DEVICES DESIGN & CONSTRUCTION COMPLEX	77334
TX DEVICES DESIGN & CONSTRUCTION INTERMEDIATE	77333
TX DEVICES DESIGN & CONSTRUCTION SIMPLE	77332
ULTRASONIC GUIDANCE INTRAOPERATIVE	76986
ULTRASONIC GUIDANCE INTRAOPERATIVE	76998
ULTRASOUND ABDOMINAL REAL TIME W/IMAGE LIMITED	76705
ULTRASOUND SCROTUM & CONTENTS	76870
ULTRASOUND SPINAL CANAL & CONTENTS	76800
ULTRASOUND TRANSRECTAL	76872
ULTRASOUND TRANSVAGINAL	76830
UNLIS PX THER RADIOL CLINICAL TX PLANNING	77299
UNLIST HEMATOPOIETIC & LYMPHATIC PROC-DX NUCLEAR	78199
UNLIST PROC MED RAD PHYSICS/DOSIMETRY & TX DEVIC	77399
UNLISTED CARDIOVASCULAR PX DX NUCLEAR MEDICINE	78499
UNLISTED COMPUTED TOMOGRAPHY PROCEDURE	76497
UNLISTED DIAGNOSTIC RADIOGRAPHIC PROCEDURE	76499
UNLISTED ENDOCRINE PX DX NUCLEAR MEDICINE	78099
UNLISTED FLUOROSCOPIC PROCEDURE	76496
UNLISTED GASTROINTESTINAL PX DX NUCLEAR MEDICINE	78299
UNLISTED GENITOURINARY PX DX NUCLEAR MEDICINE	78799
UNLISTED MAGNETIC RESONANCE PROCEDURE	76498
UNLISTED MISCELLANEOUS PX DX NUCLEAR MEDICINE	78999
UNLISTED MUSCULOSKELETAL PX DX NUCLEAR MEDICINE	78399
UNLISTED NERVOUS SYSTEM PX DX NUCLEAR MEDICINE	78699
UNLISTED PROCEDURE CLINICAL BRACHYTHERAPY	77799
UNLISTED PROCEDURE THERAPEUTIC RADIOLOGY TX MGMT	77499
UNLISTED RESPIRATORY PX DX NUCLEAR MEDICINE	78599
UNLISTED ULTRASOUND PROCEDURE	76999
UREA BREATH TEST C-14 ISOTOPIC ACQUISJ ANALYSIS	78267
UREA BREATH TEST C-14 ISOTOPIC ANALYSIS	78268
URETERAL REFLUX STUDY RP VOIDING CYSTOGRAM	78740
URETHROCYSTOGRAPHY RETROGRADE RS&I	74450
URETHROCYSTOGRAPHY VOIDING RS&I	74455
URINARY BLADDER RESIDUAL STUDY	78730
UROGRAPHY ANTEGRADE RS&I	74425
UROGRAPHY INFUSION DRIP &/BOLUS TECHNIQUE	74410
UROGRAPHY IV W/WO KUB W/WO TOMOGRAPHY	74400
UROGRAPY INFUSION DRIP &/BOLUS TECHQ W/WO TOMO	74415

US &MNTR PARENCHYMAL TISSUE ABLATION	76940
US ABDOMINAL REAL TIME W/IMAGE DOCUMENTATION	76700
US BONE DENSITY MEAS & INTERP PERIPH ANY METHO	76977
US BREAST REAL TIME W/IMAGE DOCUMENTATION	76645
US CHEST REAL TIME W/IMAGE DOCUMENTATION	76604
US ENDOMYOCARDIAL BIOPSY RS&I	76932
US EXTREMITY NON-VASC REAL-TIME IMG	76880
US EXTREMITY NON-VASC REAL-TIME IMG COMPL	76881
US EXTREMITY NON-VASC REAL-TIME IMG LMTD	76882
US FETAL NUCHAL TRANSLUCENCY 1ST GESTATION	76813
US FETAL NUCHAL TRANSLUCENCY EA ADDL GESTATION	76814
US GUID COMPRS REPAIR ART PSEUDO-ANEUR/AV FISTE	76936
US GUID INUTERO FETAL TRANSFUS/CORDOCEN IMAG S&I	76941
US GUIDANCE AMNIOCENTESIS RS&I	76946
US GUIDANCE ASPIRATION OVA RS&I	76948
US GUIDANCE CHORIONIC VILLUS SAMPLING RS&I	76945
US GUIDANCE INTERSTITIAL RADIOELMENT APPLICATION	76965
US GUIDANCE NEEDLE PLACEMENT RS&I	76942
US GUIDANCE PERICARDIOCENTESIS RS&I	76930
US GUIDANCE PLACEMENT RADIATION THERAPY FIELDS	76950
US GUIDANCE, & MONITORING, TISSUE ABLATION	76490
US INFT HIPS R-T IMG DYNAMIC REQ PHYS/QHP MANJ	76885
US INFT HIPS R-T IMG LMTD STATIC PHYS/QHP MANJ	76886
US PELVIC NONOBSTETRIC IMAGE DCMTN LIMITED/F/U	76857
US PELVIC NONOBSTETRIC REAL-TIME IMAGE COMPLETE	76856
US PREG UTERUS > 1ST TRIMESTER ABDL EA GESTATIO	76810
US PREG UTERUS 14 WK TRANSABDL EACH GESTATION	76802
US PREG UTERUS AFTER 1ST TRIMEST 1/1ST GESTATION	76805
US PREG UTERUS DETAIL FETAL ANAT EXAM EA GESTAT	76812
US PREG UTERUS REAL TIME F/U TRNSABDL PER FETUS	76816
US PREG UTERUS REAL TIME W/IMAGE DCMTN TRANSVAG	76817
US PREG UTERUS W/DETAIL FETAL ANAT 1ST GESTATION	76811
US PREGNANT UTERUS 14 WK TRANSABDL 1/1ST GESTAT	76801
US PREGNANT UTERUS LIMITED 1/> FETUSES	76815
US RETROPERITONEAL REAL TIME W/IMAGE COMPLETE	76770
US RETROPERITONEAL REAL TIME W/IMAGE LIMITED	76775
US SOFT TISSUE HEAD & NECK REAL TIME IMGE DOCM	76536
US STUDY FOLLOW UP	76970
US TPLNT KIDNEY B-SCAN &OR REAL TM W/IMAG DOC	76778
US TRANSRCT PRSTATE VOL BRACHYTX PLNNING SPX	76873
US TRNSPLNT KIDNEY REAL TIME W/IMAGE DOCMTN	76776
US VASC ACCESS SITS VSL PATENCY NDL ENTRY	76937
VASOGRAPY VESICULOGRAPY/EPIDIDYMOGRAPY RS&I	74440
VENOGRAPHY ADRENAL BILATERAL SELECTIVE RS&I	75842

VENOGRAPHY ADRENAL UNILATERAL SELECTIVE RS&I	75840
VENOGRAPHY CAVAL INFERIOR SERIALOGRAPHY RS&I	75825
VENOGRAPHY CAVAL SUPERIOR SERIALOGRAPHY RS&I	75827
VENOGRAPHY EPIDURAL RS&I	75872
VENOGRAPHY EXTREMITY BILATERAL RS&I	75822
VENOGRAPHY EXTREMITY UNILATERAL RS&I	75820
VENOGRAPHY ORBITAL RS&I	75880
VENOGRAPHY RENAL BILATERAL SELECTIVE RS&I	75833
VENOGRAPHY RENAL UNILATERAL SELECTIVE RS&I	75831
VENOGRAPHY SUPERIOR SAGITTAL SINUS RS&I	75870
VENOGRAPHY VENOUS SINUS/JUGULAR CATH RS&I	75860
VENOUS SAMPLING THRU CATH W/WO ANGIOGRAPHY RS&	75893
VENOUS THROMBOSIS IMAGING VENOGRAM BILATERAL	78458
VENOUS THROMBOSIS IMAGING VENOGRAM UNILATERAL	78457
VENOUS THROMBOSIS STUDY	78455
VITAMIN B-12 ABSRPJ STDY W/WO INTRINSIC FACT	78272
VITAMIN B-12 ABSRPJ STUDY W/INTRINSIC FACTOR	78271
VITAMIN B-12 ABSRPJ STUDY W/O INTRINSIC FACTOR	78270
WHOLE BLOOD VOLUME DETERM PLASMA&RED CELL VOLU	78122
XERORADIOGRAPY	76150
X-RAY URINARY TRACT EXAM WITH CONTRAST MATERIAL	74420

Appendix 2. Event Adjudication Committee Charter

1. EVENT ADJUDICATION COMMITTEE (EAC)

This study will employ an EAC whose primary purpose will be to perform a blinded adjudication of all identified CV deaths (including sudden cardiac deaths), and a random sample (N=100) of non-CV deaths. The EAC will review all reported CV deaths occurring within 10 days after the index antibiotic (azithromycin or amoxicillin) exposure dates. For each event, the EAC will classify death as definitely CV, possibly CV, non-CV, or unclassifiable, using the hierarchical approach recommended by the American Heart Association (method of Luepker and Apple, 2003).[29] For this study, the primary analyses will include all deaths adjudicated to be either definitely or possibly CV in nature. The EAC will be supported by at least 3 data abstractors who will obtain the required medical record documents (for CV death adjudication) and redact those documents so as to blind the adjudicators to the study antibiotic exposure. The EAC will consist of at least 3 qualified adjudicators (VHA Cardiologists). The adjudicators will be cardiologists independent of the study.

2. PERSONNEL

Data abstractors

Staff members from Analysis Group will perform the data abstraction for this project.

Adjudicators (Committee Members)

TBD.

3. EAC METHODS

The specific methodology for the cause of death categorization (by medical records review adjudication) is based on the definitions published by Leupker and Apple (2003),[29] as well as those recommended by Hicks et. al. in a draft guideline for the FDA (Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials),[30] and those utilized by the CARDIA (Coronary Artery Risk Development in Young Adults) observational study.[31,32] The FDA draft guideline's methodology is primarily used for the present study's outcome definitions, but in some cases lacks specific details. In those cases, methodology from Leupker and the CARDIA study are used. For the present study, the fraction of CV deaths attributed to sudden cardiac death is also of interest, and therefore defining the other sub-types of CV death will facilitate the EAC's chart review process. Thus, every death found by database programming of death certificate data to be CV will be reviewed and defined by the EAC as either CV (non-SCD types), SCD, non-CV death, or unclassifiable.

All death outcomes will initially be identified via database programming using the CDW and NDI's ICD-9/10 diagnostic codes for cause of death.

3.1 Outcome Definitions

Definition of CV (non-SCD) death

CV death includes death resulting from acute myocardial infarction (MI), death due to heart failure (HF), death due to stroke, death due to CV hemorrhage, death to other CV causes, and SCD (see separate definition below). For the purposes of this study, death directly due to complications of CV or other medical procedures will not be considered CV deaths. Definitions for the definite and possible CV death subtypes are provided in the table below.

Table 7. Definition of CV death subtypes

Subtype of CV Death	Chart review definition
Definite sudden cardiac death	Requires: Documentation that death occurred unexpectedly, not following an acute MI, and including the following kinds of deaths: ▪ Death witnessed and instantaneous without new or worsening symptoms ▪ Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest an acute MI. ▪ Death witnessed and attributed to an identified arrhythmia (eg, captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review). ▪ Death after unsuccessful resuscitation from cardiac arrest ▪ Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac etiology (Post-Cardiac Arrest Syndrome) ▪ Unwitnessed death (may or may not be sudden) where a death certificate may not be available or death is not attributable to another cause (information regarding the subject's clinical status preceding death should be provided, if available). Exclusions: The presence in the medical record of any of the following suggests that death was due to acute MI and should not be classified as SCD: ▪ Preceding acute MI/ischemia symptom such as chest discomfort or shortness of breath. ▪ EKG changes consistent with ischemia/MI (see table below) ▪ Fresh coronary thrombus seen at coronary angiography or autopsy ▪ A prior history of cardiomyopathy with chronically impaired left ventricular systolic function (ejection fraction).

Possible SCD	Requires: ▪ Evidence that death was due to presumed SCD that did not meet "definite" criteria above *and* ▪ A death certificate ICD-9 code consistent with SCD without other underlying or immediate cause. Underlying cause of death codes c/w SCD include: o ICD-9 codes: 401.9x, 402.xx, 410.xx -414.xx, 425.4x, 427.5x, 427.1x, 427.4x, 427.8x, 427.9x, 429.2x, 429.9x, 440.9x, 798.2x, 798.9x *or* ICD-10 codes: I10xx, I11.9x, I20.xx -25.xx, I42.9x, I42.8x, I46.xx, I47.0x, I47.2x, I49.0x, I49.8x, I49.9x, I51.6x, I51.9x, I70.9x, R96.1x, R98.xx
Definite Fatal Myocardial Infarction (MI) /fatal coronary heart disease (CHD)	Requires: Either documentation of definite or probable MI during the 30 days preceding death and no evidence of a non-coronary cause of death *Or* Autopsy evidence of a recent coronary occlusion or MI within the 30 days preceding death. Note: Death by any CV mechanism (eg, arrhythmia, sudden death, heart failure, stroke, pulmonary embolus, peripheral arterial disease) is accepted as MI-related if occurring ≤ 30 days after a MI and judged to be an immediate consequence of the MI, such as progressive heart failure or recalcitrant arrhythmia. See section below for the definition of Definite MI (Table 10 & Table 11). Death will be considered to be due to Definite fatal CHD if there is a lack of sufficient evidence to diagnose Definite Fatal MI but BOTH of the following criteria are present: ▪ No known non-atherosclerotic or non-cardiac atherosclerotic process or event that was probably lethal *and* ▪ Presence of one OR both of the following findings: o Chest pain within 72 hours of death o A history of ever having had chronic ischemic heart disease (such as definite or possible MI, coronary insufficiency or angina pectoris) in the absence of valvular heart disease or non-ischemic cardiomyopathy.
Possible Fatal MI/CHD	Requires: A lack of sufficient evidence to diagnose Definite Fatal MI or Definite Fatal CHD and plus *all* of the following

	criteria: ▪ Evidence consistent with probable or possible MI (see table below) ▪ No known non-atherosclerotic or non-cardiac atherosclerotic process or event that was probably lethal *and* ▪ Death certificate with consistent underlying MI cause, ICD-9-CM codes 410.xx -414.xx, 427.5x, 429.2x and/or 799.xx *or* ICD-10 codes I20.xx -25.xx and I46.xx. See section below for the definition of Definite MI (Table 10 **&** Table 11).
Definite Fatal Heart Failure (HF)	Requires: Documentation that death was associated with clinically worsening symptoms and/or signs of heart failure or cardiogenic shock regardless of HF etiology but in the absence of an acute myocardial infarction within 30 days prior to death. Such deaths must meet the standard of definite decompensated HF (see section below). Sudden deaths occurring within 30 days of symptoms consistent with decompensated HF in patients with reduced left ventricular ejection fraction will be attributed to HF and not SCD. Heart failure can have various etiologies, including single or recurrent (but remote) myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, alcoholism, valvular disease, prior myocarditis, or from idiopathic/unknown mechanisms. See section below and Table 12 for the definition of definite heart failure exacerbation.
Possible Fatal Heart Failure	Requires: ▪ Documentation that death was associated with HF that does not meet the definition of definite decompensated HF but does meet the definition of possible decompensated HF (see section below), *and* ▪ Death certificate code consistent with underlying HF cause, including ICD-9 codes 428.xx, 402.01, 402.11, 402.91, and 425.xx *or* ICD-10 codes I50.xx, I11.0x, I13.0x, I13.2x, I97.13x, and I09.81 See section below and Table 12 for the definition of possible heart failure exacerbation.
Definite Fatal Stroke	Requires: Evidence that death was due to definite stroke (hemorrhagic, ischemic, or unknown type) with consistent imaging, surgical, or autopsy evidence.

	Definition of definitive vs possible stroke: See section below and Table 13
Possible Fatal Stroke	Requires: ▪ Evidence that death was due to presumed stroke (hemorrhagic, ischemic, or unknown type) that did not meet criteria for definite stroke *and* ▪ A death certificate code consistent with stroke without other underlying or immediate cause, including ICD-9 codes 430.xx -438.xx.
Definite Fatal CV Hemorrhage	Requires: Evidence that death was related to hemorrhage such as a non-procedural or non-traumatic vascular rupture (eg, aortic aneurysm), or pericardial hemorrhage causing cardiac tamponade with consistent imaging, surgical, or autopsy evidence.
Possible Fatal CV Hemorrhage	Requires: ▪ Evidence that death was due to presumed CV hemorrhage that did not meet "definite" criteria above *and* ▪ A death certificate ICD-9 code consistent with CV hemorrhage without other underlying or immediate cause, including ICD-9 codes 441.0x-1x, 441.3x, 441.5x-6x, 420.xx, 423.0x, & 423.3x.
Definite death due to other CV causes	Requires: Evidence that death was due to other types of CV disease not included in the types described above. Examples include death due to pulmonary embolism, peripheral arterial disease (eg, fatal limb ischemia) or dissection and/or rupture of an aortic aneurysm. The diagnosis should be supported by consistent imaging, surgical, or autopsy evidence
Possible death due to other CV causes	Requires: ▪ Death due to a presumed other type of CV disease not included in the types described above that does not meet criteria for definite (see row above) *and* ▪ Death certificate consistent with CV disease without other underlying or immediate cause.

Table 8. Definition of non-CV death

Non-CV Death	Chart review definition
Fatal Non-CV Disease and Other Reasons of Death	Requires: Documentation that death was due to fatal non-CV diseases and other reasons of death, including the following categories: HIV/AIDS; other infections; cancer; diabetes; kidney disease; liver disease; asthma; other lung disease; homicide; suicide; unintentional injury; hemorrhage, death due to complications of medical procedures (including CV procedures); other; ambiguous.

Table 9. Definition of unclassifiable death

Unclassifiable Death	Requires: That insufficient information is available in the available documentation to determine whether the death was CV related or due to a specific non-CV cause.

Definitions of Definite, Probable, and Possible Myocardial Infarction (MI)

The documentation required to diagnose MI, and thus support a diagnosis of fatal MI, will include elements of the medical history, results of cardiac enzyme blood tests, and electrocardiogram (EKG) readings. The diagnostic criteria for MI are similar to those recommended by Luepker and Apple, have also been used in the CARDIA observational study, and are defined in the table below.

Table 10. History, EKG, and oratory data to be used to define MI

Data Element	Definition
Anginal symptoms	Presence of acute chest, epigastric, neck, jaw, or arm pain or discomfort or pressure without apparent non-cardiac cause. Symptoms of breathlessness, nausea, or vomiting can be accepted as angina if there is documentation that a health care provider interpreted those symptoms to be cardiac/angina in nature.
EKG findings	Any EKG obtained during a fatal hospitalization should be reviewed (report/tracing) and the summarized EKG results for each patient will be categorized and defined as follows: ▪ Evolving diagnostic: ST segment elevation or depression in at least 2 contiguous EKG leads measuring ≥1 mm in amplitude that are dynamic, improving as symptoms resolved. The development of new Q waves in at least 2 contiguous leads also qualifies. Contiguous EKG groupings include the inferior (II, III, aVF), lateral (I, aVL, V5-V6) and anterior (V1-V4) distributions. ▪ Positive: ST segment elevation or depression in at least 2 contiguous EKG leads measuring ≥1 mm in amplitude that are not documented to change during the hospital admission. ▪ Non-specific: ST segment elevation or depression in at least 2 contiguous EKG leads measuring < 1 mm in amplitude or abnormal T waves (flattening, inversion, or hyperacute) in at least two contiguous leads. Q waves that are known to old also qualify. ▪ Normal or other: The absence of abnormal ST deviation, T wave abnormalities, or Q waves on EKG s obtained during the hospitalization.
Cardiac enzyme levels	Any cardiac enzyme levels obtained during a potential MI hospitalization should be reviewed and based on the most abnormal result, categorized as follows:

	▪ Diagnostic o Cardiac troponin (C, I, or T) level >2x upper limit of normal (ULN) or >3x ULN if within 48 hours after percutaneous coronary intervention, or >5x ULN if within 48 hours of heart surgery, *or* o Creatine Kinase MB fraction (CK-MB) >2x ULN or ≥10% of total CK level or described as "abnormal" (or similar language) in the documentation without quantification. Requires a level >3x ULN within 48 hours after percutaneous coronary intervention or >5x ULN if within 48 hours of heart surgery, *or* o Total Creatine Kinase (CK) >2x ULN o Myoglobin level >2x ULN ▪ Equivocal o Cardiac troponin 1-2x ULN o CK-MB 1-2x ULN or 5-9% of total CK or described as "mildly abnormal" (or similar language) o Total CK 1-2x ULN and cardiac troponin 1-2x ULN o Myoglobin level ULN ▪ Missing (no data available) ▪ Normal o Cardiac troponin within normal limits (WNL) o CK-MB WNL or <5% of total CK o Total CK 1-2x WNL o Myoglobin level WNL

The three elements above (symptoms, EKG findings, and enzyme levels) will be interpreted using the three-way interactive approach defined below:

Table 11. Interactive approach to incorporate EKG and cardiac enzyme data to define MI

If anginal symptoms **are present**				
EKG findings	Cardiac Enzyme Levels			
	Diagnostic	Equivocal	Missing	Normal
Evolving diagnostic	*Definite*	*Definite*	*Definite*	*Definite*
Positive	*Definite*	*Probable**	*Probable*	*No*
Non-specific	*Definite*	*Possible*	*No*	*No*
Normal or other EKG	*Definite*	*Possible*	*No*	*No*
If anginal symptoms **are absent**				
EKG findings	Cardiac Enzyme Levels			
	Diagnostic	Equivocal	Missing	Normal
Evolving diagnostic	*Definite*	*Definite*	*Definite*	*Definite*
Positive	*Definite*	*Probable*	*Probable*	*No*
Non-specific	*Definite*	*Possible*	*No*	*No*
Normal or other EKG	*Definite*	*No*	*No*	*No*

**Probable* status will be considered equivalent to *Definite* status during adjudication.

Definitions of Definite and Possible Decompensated Heart Failure (HF)

The documentation required to diagnose HF, and thus support a diagnosis of fatal HF, will include elements of the medical history, physical exam, and laboratory data. The diagnostic criteria for HF are similar to those used by the KP PI in a recent observational study of CV outcomes in cancer patients and also draw from the methodology of the CARDIA observational study. The criteria are defined in the table below. A diagnosis of Definite HF requires documentation of a HF symptom plus at least one abnormality on exam or laboratory results, as defined below. A diagnosis of Possible HF requires the presence of a co-morbid condition (such as lung disease) which could explain the potential HF symptom(s) plus at least one abnormality on exam or laboratory results, as defined below.

Table 12. History, exam, and laboratory data to be used to define HF

Data Element	Definition
HF symptoms	Symptoms consistent with acute decompensated HF include new or worsening shortness of breath (or dyspnea), orthopnea (shortness of breath lying flat), paroxysmal nocturnal dyspnea (PND, waking from sleep due to shortness of breath), abdominal distension, or edema (leg/foot swelling).
Physical exam findings	Any of the following exam findings would support a diagnosis of acute decompensated HF: ▪ Elevated jugular venous pressure or distension (JVP, JVD). If this is quantified on the exam documentation, a level >7 cm or mmHg will be considered abnormal. ▪ Bilateral lower extremity edema (swelling of legs, ankles, or feet). The edema should be bilateral but does not have to be symmetrical in severity. ▪ Hypoxia: A description of hypoxia (or hypoxemia) in a source document. If this is quantified on the exam documentation, an oxygen saturation < 90% while breathing room air will be considered abnormal. Documentation that supplement oxygen is required will also be considered evidence of hypoxia.
Laboratory data	Laboratory evidence of HF acute decompensated HF requires <u>one</u> of the following: ▪ <u>Abnormal chest imaging:</u> Will be considered abnormal if a diagnosis of HF if pulmonary edema is documented in the report of at least one CXR or chest CT or related documentation. If the text of the report is not definitive, language such as "probable, likely, or consistent with" pulmonary edema will be considered laboratory evidence of HF. Synonyms for pulmonary edema include: heart failure, congestive heart failure, CHF, alveolar edema, interstitial edema, pulmonary congestion, and pulmonary vascular congestion. ▪ <u>Abnormal blood level of B-type natriuretic peptide (BNP):</u> A single BNP level >2x ULN will be considered abnormal.

<u>Definition of Definite Stroke</u>

The documentation required to diagnose stroke, and thus support a diagnosis of fatal stroke, will include elements of the medical history, physical exam, and laboratory data. The diagnostic criteria for stroke are similar to those used PI in a recent observational study of CV outcomes in cancer patients conducted by KP and also draw from the methodology of the CARDIA observational study. The criteria are defined in the table below. A diagnosis of definite ischemic stroke requires documentation of a stroke symptom plus at least one abnormality on exam or imaging. A diagnosis of definite hemorrhagic stroke requires documentation of a stroke symptom plus at least one abnormality on brain imaging or an abnormal lumbar puncture showing evidence of bleeding in the spinal fluid or cerebrospinal

fluid (CSF), as described in the documentation as follows: bloody fluid, elevated red blood cell (RBC) count or obvious blood in the sample that is not felt to be due to traumatic lumbar puncture, xanthochromia (a pink or yellow tint due to hemoglobin degradation), or abnormal spectrophotometry.

Table 13. History, exam, and imaging data to be used to define stroke

Data Element	Definition
Stroke symptoms	Symptoms consistent with acute stroke include any of the following noted in the source documents with a duration >1 hour: weakness or paralysis of an extremity or the face (facial droop), neck pain or stiffness, incoordination of a leg and/or arm, gait problem (difficulty walking, unsteady gait, falls), numbness or tingling of an extremity of the face, speech problem (dysarthria, slurred speech, aphasia, trouble speaking, difficulty getting words out or the wrong words are chosen), difficulty understanding speech or responding inappropriately, dysphagia (difficulty swallowing), confusion (altered mental status, delirium, acute memory problems, disorientation), coma/unresponsiveness, seizures/convulsion, visual disturbance (double vision), hemianopia (visual field cut)), vertigo (spinning sensation, dizziness), or acute headache (different in character vs any chronic headache symptoms).
Physical exam findings	Any of the following exam findings would support a diagnosis of acute stroke: ▪ Altered mental status, altered level of consciousness (ALOC), coma, obtund, unresponsive, delirium, memory problems, disorientation, agitation. ▪ Trouble speaking: can't get the words out (Broca's aphasia), wrong words come out (Wernicke's aphasia), trouble understanding, inappropriate response. ▪ Visual field cut, homonymous hemianopia (HH), or diplopia (double vision) ▪ Difficulty swallowing, dysarthria, slurred speech, dysphonia, tongue deviation. ▪ Facial droop, or decrease in the nasolabial fold (NLF). ▪ Extremity weakness, incoordination, pronator drift (weakness of arm), hemiparesis, hemiplegia, monoparesis, monoplegia, paresis, paralysis of limb(s). ▪ Numbness, tingling, burning, prickly sensation, paresthesia, hemianesthesia, dysthesia, or sensation deficit anywhere on the face or an extremity. ▪ Difficulty walking, ataxic, staggering, impaired gait, wobbly, fell down and couldn't get up, positive Romberg.
Imaging data	The presence of ischemic infarction on a CT or MRI scan of the brain supports the clinical diagnosis of ischemic stroke. An abnormal finding on a brain imaging study any time after the development of stroke

Data Element	Definition
	symptoms is acceptable. A CT obtained during acute stroke often shows no findings but a follow-up CT may show findings. MRI is more likely to be abnormal during the acute phase. Imaging will be considered abnormal if at least one MRI or CT scan was obtained during the stroke admission or at the time of outpatient diagnosis and the scan report or related documentation describe ischemic infarction, ischemic cerebrovascular accident (CVA), ischemic stroke, low density lesions in a typical vascular pattern, or lacunae. Imaging will also be considered abnormal if there is evidence of a hemorrhagic stroke, such as hemorrhagic infarction, hemorrhagic cerebrovascular accident (CVA), hemorrhagic stroke, bleeding anywhere in the brain (cerebral, cerebellar, brainstem), intracerebral hemorrhage (ICH), intraparenchymal hemorrhage (IPH), subarachnoid hemorrhage (SAH), or subdural hemorrhage (SDH).

3.2 Data abstraction and adjudication processes

The steps for data abstraction and death adjudication are the following:

a. The data analyst/programmer supplies the medical record numbers, name, birth date, sex, date of death, and death data (coded underlying causes of death) via a Microsoft Excel database.® A chart review case number will be assigned to each death.

b. The data abstractors will acquire the available medical chart documentation that provides potentially useful information to aid cause of death (COD) determination, including but not limited to the types of documentation listed below. In general, all documented information occurring within 30 days prior to death and any time after death will be potentially useful and thus abstracted/redacted. However, any information relevant to the patients' CV status charted within 3 years prior to the date of death, or as specified below, will be abstracted/redacted in order to maximize the adjudicators understanding of each individuals burden of CV disease prior to death.

Data to be obtained and timing relative to the date of death:

- NDI cause of death information.

- Data to be extracted when present in the chart **within 30 days** prior to or any time after the date of death. For certain neurologic and CV diseases (including, but not limited to coronary artery disease, myocardial infarction, congestive heart failure, cardiac arrhythmias, stroke (hemorrhagic or ischemic)) we will search the medical record for 3 years prior to the date of death, or as specified below. After the date of death, looking specifically for autopsy reports or other information related to the death

- Patients with healthcare encounters after the date of death should be flagged and brought to the attention of the Study Coordinator and/or Site PI

Hospital chart data:

- Non-CV Hospitalizations (based on primary discharge diagnosis code) and Emergency Department (ED) Visits
  - All hospitalizations/ED visits occurring within 30 days of the date of death
    - Admission History and Physical
    - Emergency Department notes
    - Surgical notes
    - Discharge summaries
- CV Hospitalizations (based on primary discharge diagnosis code) and ED Visits
  - The three most recent CV hospitalizations occurring within the past 3 years
    - Emergency Department Notes
    - Admission History and Physical
    - Cardiology and/or Neurology consult notes
    - Cardiology and/or Neurology procedure notes
      - CT/MRI (cardiac and neuro)
      - Chest X-ray
      - Echo (cardiac)
      - Coronary interventions (CABG, Stent)
      - Coronary angiography
      - Cardiac catheterization
      - Myocardial perfusion scans
      - EKG reports (1st and last for a particular hospitalization if more than 1)
      - Others not mentioned above, but that seem relevant

    - Cardiac enzymes (troponin, CK, CKMB) and B-type natriuretic peptide (BNP) laboratory results

- Outpatient chart data:
    - Administrative encounter notes containing relevant clinical information
    - Three most recent clinic visits occurring in the 30 days prior to the date of death
    - Outpatient surgery visits (three most recent visits prior to the date of death occurring within the previous 3 years)
    - Cardiology procedure reports/notes (three most recent visits prior to the date of death occurring within the previous 3 years)
        - Cardiac Stress Tests
        - Cardiac ultrasound (echo)
        - Cardiac MRI/CR
        - Chest X-ray
        - EKG reports
        - Others not mentioned above, but that seem relevant
    - Cardiology clinic visits
        - Three most recent visits prior to the date of death occurring within the previous 3 years)
    - Neurology test reports (three most recent visits prior to the date of death occurring within the previous 3 years)
        - Brain CT/MRI
    - Neurology clinic visits
        - Three most recent visits prior to the date of death occurring within the previous 3 years)
    - Notes from a nursing home or extended care facility (within the 30 days prior to the date of death)

- Any other information deemed possibly relevant to the patients' CV status charted within 3 years prior to the date of death.

  Any entries which are present in the paper or electronic medical records may be selected by the abstractors if deemed pertinent for the cause of death adjudication process. If a report/finding not specifically listed above is found and the record abstractor is unsure of whether to include they should send a summary of the information to the project manager, who will consult with the PI as needed.

a. All documentation will be redacted such that no personal identifying information is visible (eg, patient names, provider names, MRNs, dates, locations) and no information is available regarding which type of antibiotic (amoxicillin or azithromycin) was prescribed prior to the death outcome. For electronic documents, the relevant information will be printed as a pdf and redacted using Adobe Acrobat Pro. The study ID will be added electronically to each document included for review of cause of death or indication of use. Whenever possible, the information will be organized in reverse chronological order (from date of death). The files will be saved in a secure project folder that is accessible only to project staff at the VHA.

b. The project manager at AG will review each file for completeness, enter into a tracking database, and assign each case number to two adjudicators.

c. In each case, the adjudicator will review the redacted documents and fill out an electronic case report form (e-CRF) connected to the Microsoft Excel database® residing on the shared VHA project folder. The form will be pre-populated with the chart review case number and will include the following fields to be filled out by the adjudicator:

   - Cause of death: Definite CV death, Possible CV death, Non-CV death, and Unclassifiable.

   - If CV death, define subtype: SCD, MI/CHD, HF, Stroke, CV hemorrhage, or other CV death type.

d. The two adjudicators will review all cases independently. If the two adjudicators are in agreement regarding all cause of death categorizations (CV death vs. Non-CV death vs Unclassifiable; CV death subtype), their adjudicated results will be accepted as final. If the two adjudicators are not in agreement regarding at least one of the categorizations, the project managers will assign the case to a third adjudicator. If the third adjudicator is in agreement with either of the two initial adjudicators, the third adjudicated results will be accepted as final. If there is no agreement between the third adjudication and either of the two initial adjudications, the case will be decided by consensus during a teleconference including all 3 adjudicators. The project managers will complete an additional e-CRF describing the final determination of cause of death.

3.3 Adjudication of Non-CV Deaths

In order to estimate the false negative rate for determining CV vs non-CV death, the EAC will adjudicate a random sample (n=100) of non-CV deaths (by programmatic determination/death certificate codes). In each case the adjudicators will use the same classification scheme described above: Definite CV death, Possible CV death, Non-CV death, and Unclassifiable). Any deaths adjudicated to be CV will be further classified as above: SCD, MI/CHD, HF, Stroke, CV hemorrhage, or other CV death type. For a sample size of 100, the error in estimation is approximately 9%, 6%, and 6% if the true proportion of non-CV deaths is 70%, 80%, and 90%, respectively. The processes of data management, adjudicator assignment, and cause of death finalization will be identical to those described above for the adjudication of CV deaths.

If it is determined that 80% or greater are indeed non-CV deaths, then the adjudication of non-CV deaths will be complete. If it is determined that less than 80% are true non-CV deaths, than an additional random sample of 100 non-CV deaths will be adjudicated, after modifications to the programming based on any uncovered errors. These steps will be repeated until 80% accuracy or greater is attained, or the collaborating investigators have determined that the reported accuracy rate is stable and adequately precise.

3.4 Quality Assurance (QA) Processes

Before beginning the adjudication process, all EAC members plus the project managers and data abstractors will convene to review the relevant sections of the study protocol, the processes of care, and the types of documentation which will be reviewed, the electronic databases, and the e-CRF. The importance of blinding the adjudicators to the study antibiotic will be emphasized during this meeting. During the initial QA meetings, sample cases not obtained from the study population will be reviewed to provide examples of Definite and Possible CV death cases including SCDs, non-CV deaths, and examples of unclassifiable and non-CV deaths. Each adjudicator will then undergo an independent test review of additional sample cases (not from the study population). If a perfect score (for cause of death determination) is not achieved on the test, educational feedback will be given and additional testing performed until a perfect score is achieved. Once the EAC begins to review study deaths, the EAC will convene monthly to review the results of the adjudication process with a particular focus on resolving any problems, such as confusion about death definitions, problems with document access, and any issues with e-CRF completion. During these meetings, the PI will provide feedback to the other adjudicators regarding cases in which a third adjudication was required.

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