# NON-INTERVENTIONAL (NI) STUDY PROTOCOL

## PASS information

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| **Title** | The acute effects of azithromycin use on cardiovascular mortality, as compared with amoxicillin |
| **Protocol number** | A0661209 |
| **Protocol version identifier** | 1.0 |
| **Date of last version of protocol** | 19 March 2015 |
| **EU Post Authorisation Study (PAS) register number** | Study not yet registered |
| **Active substance** | Azithromycin (AZT): J01FA10<br><br>Amoxicillin (AMX): J01CF05 |
| **Medicinal product** | Azithromycin |
| **Product reference** | Appendix 1 |
| **Procedure number** | EPITT Ref No 16156 |
| **Marketing Authorisation Holder (MAH)** | Pfizer Limited |
| **Joint PASS** | No |
| **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<br><br>Subgroup analyses:<br><br>2. Sudden cardiac death<br>3. Cardiovascular death among those with a history of cardiovascular disease (CVD)<br>4. Cardiovascular death among those with high baseline CV risk as defined by a CV risk score<br><br>Secondary Objectives:<br><br>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 un-adjudicated outcome data will be used for these analyses:<br><br>1. Non-cardiovascular death and all-cause death, within 5 and within 6-10 days of dispensed prescription (Rx)<br><br>2. Cardiovascular death within 11-365 days of Rx dispensed.<br>i. Among those with baseline CVD<br>ii. Among those with high baseline CV risk according to a CV risk score<br>iii. Among those with baseline CVD or with high baseline CV risk according to a CV risk score<br>iv. Among those with chronic obstructive pulmonary disease (COPD)<br>v. Among those with community acquired pneumonia (CAP) |

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| **Country(-ies) of study** | US |
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**Marketing Authorisation Holder(s)**

| | |
|---|---|
| **Marketing Authorisation Holder(s)** | See Appendix 1 |
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## 1. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ACE | Angiotensin Converting Enzyme |
| ACS | Acute Coronary Syndrome |
| AIDS | Acquired Immune Deficiency Syndrome |
| ALOC | Altered Level of Consciousness |
| ARB | Angiotensin Receptor Blocker |
| BNP | B-type natriuretic peptide |
| CAP | Community acquired pneumonia |
| CARDIA | Coronary Artery Risk Development in Young Adults |
| CHF | Coronary Heart Disease |
| CHF | Congestive Heart Failure |
| CI | Confidence Intervals |
| CK | Creatine Kinase |
| COD | Cause of Death |
| COPD | Chronic Obstructive Pulmonary Disease |
| CT | Computed Tomography |
| CV | Cardiovascular |
| CVA | Cerebrovascular Accident |
| CVD | Cardiovascular Disease |
| DOR | Division of Research |
| DOR | KPNC Division of Research |
| 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 |
| FDA | Food and Drug Administration |
| FDA | Food and Drug Administration |
| HF | Heart Failure |
| HH | Homonymous Hemianopia |
| HIV | Human Immunodeficiency Virus |
| HR | Hazard Ratio |
| ICD | International Classification of Diseases |
| ICH | Intracerebral Hemorrhage |
| IPH | Intraparenchymal Hemorrhage |
| IRB | Institutional Review Board |
| JVD | Jugular Venous Distension |
| JVP | Jugular Venous Pressure |
| KASIS | Kaiser surgical procedures database |
| KPNC | Kaiser Permanente Northern California |
| KPSC | Kaiser Permanente Southern California |
| MI | Myocardial Infarction |
| MRA | Magnetic Resonance Angiography |
| MRA | Medical Record Analysts |

| | |
|---|---|
| MRI | Magnetic Resonance Imaging |
| NLF | Nasolabial Fold |
| ORSOS | Kaiser anesthesia database |
| PET | Positron Emission Tomography |
| PI | Principal Investigator |
| PIMS | Kaiser pharmacy database |
| PND | Paroxysmal Nocturnal Dyspnea |
| QA | Quality Assurance |
| Rx | Prescription |
| SAH | Subarachnoid Hemorrhage |
| SAP | Statistical Analysis Plan |
| SCD | Sudden Cardiac Death |
| SDH | Subdural Hemorrhage |
| TRRS | Kaiser radiology database |
| ULN | Upper Limit of Normal |
| VDW | Virtual Data Warehouse |

## 2. RESPONSIBLE PARTIES

### Principal Investigator(s) of the Protocol

| Name, degree(s) | Title | Affiliation | Address |
|---|---|---|---|
| Jonathan Zaroff, MD | Principal Investigator | Kaiser Permanente Northern California (KPNC) | 2200 O'Farrell Street<br>4th Floor Cardiology Department<br>San Francisco, CA 94115 |
| Niki Palmetto, PhD, MPH | Principal Investigator | Pfizer | 235 East 42nd Street, MS 219/9/01<br>New York, NY 10017-5703 |
| Douglas Corley, MD PhD | Co-Investigator | KPNC Division of Research (DOR) | Division of Research<br>2000 Broadway<br>Oakland, CA 94612-2304 |
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## 3. ABSTRACT

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

Version: 1.0 Date: 19 March 2015
Author: Jonathan Zaroff, MD. Kaiser Permanente Northern California

Rationale & Background:

The purpose of this observational study is to examine the effects of azithromycin use on cardiovascular mortality. This observational study is 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 cardiovascular (CV) risk, most notably in patients with pre-existing cardiovascular 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 variable generalizability. An additional observational study, with sufficient power, adequate control of confounding, and a broadly generalizable population is required to further assess the potential cardiovascular signal. Pfizer's feasibility assessment, submitted to the FDA and the EMA, proposed using a combined Kaiser Permanente Northern California and Kaiser Permanente Southern California (KPNC-KPSC) database as an appropriate data source based on numerous strengths, including its electronic medical record system (EMR) and large sample size, as well as its ability to link to death certificates, directly capture 'indication of use' for a subset of participants (allowing for algorithm validation), and allow for CV death adjudication.

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. Cardiovascular death

Subgroup analyses:

2. Sudden cardiac death
3. Cardiovascular 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 un-adjudicated outcome data will be used for these analyses*:

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

2. Cardiovascular 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)

* Individual secondary objective analyses which merit further investigation will be adjudicated. These analyses will be submitted to regulatory authorities (FDA/PRAC), according to a later, agreed upon timeframe.

Study design: Retrospective cohort study

Population: The study population will include members of both KPNC and KPSC who received a prescription for azithromycin or amoxicillin between 1998 – 2012.

Variables:

- Exposures: Antibiotic prescription for azithromycin and amoxicillin
- Outcomes: Cardiovascular death, sudden cardiac death, non-cardiovascular death, and all-cause death.
- Key covariates (potential confounders): The models will include indication of use, cardiovascular conditions and medications, demographic factors (eg, age, gender, race/ethnicity), 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 cardiovascular disease, baseline cardiovascular risk according to a CV risk score, COPD, and CAP.

Data sources: The study will use multiple KPNC/KPSC databases including the Virtual Data Warehouse (VDW) and pharmacy databases in addition to the California state death registry. All cardiovascular deaths and a sample of non-CV deaths will be confirmed by chart review through the efforts of an Event Adjudication Committee. A sample chart review will also be performed to confirm that antibiotic indication for use has been correctly determined by database programming.

Study size: The study will include over 2.2 million azithromycin exposures and over 7.8 million amoxicillin exposures.

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

Milestones:

- Final protocol: 31 January 2015
- Start of data collection: 30 April 2015
- End of data collection : 30 June 2016
- Final study report: 30 November 2016

## 4. AMENDMENTS AND UPDATES

None

## 5. MILESTONES

| Milestone | Planned date |
|---|---|
| Completion of feasibility assessment | 31 January 2014 |
| Final protocol | 31 January 2015 |
| Start of data collection | 30 April 2015 |
| End of data collection | 30 June 2016 |
| Registration in the EU PAS register | 30 April 2015 |
| Final study report | 30 November 2016 |

## 6. RATIONALE AND BACKGROUND

The purpose of this observational study is to examine the effects of azithromycin use on cardiovascular mortality. This observational study is 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. examined the acute effects of azithromycin use on cardiovascular death within a population receiving 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 cardiovascular 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 cardiovascular deaths per million prescriptions of azithromycin (when compared with amoxicillin), and 245 additional cardiovascular deaths among patients in the highest decile of cardiovascular risk score. The risk of cardiovascular 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. posited that the increased risk of cardiovascular death associated with azithromycin may be due to QT prolongation, resulting in ventricular arrhythmia and sudden cardiac death. Ray et al.'s study had many methodological strengths, such as adequately powered analyses and stratification of effect by baseline cardiovascular (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 cardiovascular death compared with those taking penicillin V. When the risk of cardiovascular 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 null findings. Strengths of Svanstrom et al.'s 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 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. publication was adequate power for the outcomes examined. However, Rao et al. also had several limitations, including no examination of cardiovascular 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.

While mixed, taken together, the findings from Ray et al., Svanstrom et al., and Rao et al. 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. Though no studies have reported longer-term cardiovascular effects associated with azithromycin use, there have been 2 studies which have found longer-term cardiovascular effects associated with clarithromycin, another 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).

An additional observational study, with sufficient power, adequate control of confounding, and a broadly generalizable population is required to further assess the potential cardiovascular signal. Pfizer first conducted a qualitative feasibility assessment to identify a suitable database for the conduct an observational study, which could retain the strengths of

the prior studies and permit improvement upon their limitations. The feasibility assessment, submitted to the FDA and EMA, proposed Kaiser Permanente of Northern California (KPNC) as an appropriate data source based on numerous strengths, including its electronic medical record system (EMR) and large sample size, as well as its ability to link to death certificates, directly capture 'indication of use' for a subset (approximately 1/3) of participants (allowing for algorithm validation), and allow for CV death adjudication. Kaiser's comprehensive EMR system also allows for the capture, and therefore control of, most clinical variables which may act as confounders of the association. Pfizer then further assessed the feasibility by conducting an in-depth power analysis within a combined Kaiser Permanente Northern California and Kaiser Permanente Southern California (KPNC-KPSC) database, to ensure that the database had sufficient statistical power to significantly detect effect sizes of the same, or lesser magnitude than those reported by Ray and colleagues. The feasibility analysis, which was submitted to the FDA and EMA, confirmed the power of the Kaiser Permanente database for the conduct of this study.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a Post-marketing Requirement of the FDA and EMA.

## 7. RESEARCH QUESTION AND OBJECTIVES

Primary 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

Subgroup analyses:

2. Sudden cardiac death
3. Cardiovascular 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 un-adjudicated 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.

- 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 COPD
- Among those with CAP

* Individual secondary objective analyses which merit further investigation will be adjudicated. These analyses will be submitted to regulatory authorities (FDA/PRAC), according to a later, agreed upon timeframe.

## 8. RESEARCH METHODS

### 8.1. Study design

This study will employ a retrospective cohort design to examine the effects of azithromycin on cardiovascular and sudden cardiac mortality (primary endpoints), as compared to amoxicillin, both within a general population of azithromycin users, as well as those with high baseline cardiovascular (CV) risk. The secondary endpoints will include non-cardiovascular mortality and all-cause mortality. The main measures of effects will be hazard ratios. The primary strengths of this study design for these research questions include the ability to obtain a large sample size in a timely manner (necessary given the rarity of the outcome), and the ability to estimate hazards, rather than odds, as would be available in a case-control design.

### 8.2. Setting

This study will be conducted among KPNC and KPSC enrollees.

KPNC is a group practice integrated health program with approximately 3.2 million members annually; this represents about 30% of the insured population in 14 Northern California counties encompassing the greater San Francisco Bay Area and the upper central valley of California. Members receive almost all of their care at KPNC facilities and inpatient and outpatient visits, and their corresponding diagnoses can be identified electronically. The membership's demographics closely resemble the underlying census population of Northern California.[7]

Kaiser Permanente Southern California (KPSC) is a nonprofit, integrated healthcare delivery system with a membership of over 3.4 million people in Southern California. KPSC provides integrated, comprehensive medical services through its own facilities, which includes 14 hospitals, 200 outpatient facilities and a centralized laboratory. All aspects of care and interaction with the healthcare delivery system are captured in a continuously updated research database. The KPSC membership represents an insured population that is racially and socio-economically diverse. Overall the demographic makeup of the KPSC membership

closely mirrors the Southern California and the United States population (except that compared to the United States population the KPSC membership has twice as many individuals of Asian descent and three times as many Hispanics).[8]

KPSC and KPNC are separate financial entities which share administrative practices (such as the EMR). The combined Kaiser California population possesses several advantageous qualities for pharmacoepidemiology studies. Kaiser's electronic information systems allow researchers to track patient enrollment, diagnoses, procedures, and prescriptions dispensed at Kaiser pharmacies. KPNC has a well-established research unit, the Division of Research (DOR), with approximately 500 personnel, including research scientists/investigators, programmers, data analysts, and medical record analysts; this infrastructure permits the use of KPNC's electronic resources for research. KPSC's Department of Research and Evaluation (20 research scientists and 300 personnel) provides similar services to the DOR.

The study will be conducted among Kaiser enrollees during the period of 1998 – 2012. The start date of 1998 was chosen: 1) based on availability of electronic KP medical record data, and 2) to allow for exclusion criteria "3" (see exclusion criteria, below), which requires participants to have been enrolled in KP healthcare for at least 1 year prior to the index prescription date. The end date of 2012 was chosen based on the most recent cause-of-death information available in the California State Death Registry.

### 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 prescription for azithromycin or amoxicillin between 01 Jan 1998 and 31 Dec 2012. If a patient had more than one prescription within this period, each exposure will be counted separately (thus, individuals may contribute multiple prescriptions to the analysis).

2. Consistent with the methodology of Ray and Svanstrom, only oral prescriptions will be included (not intravenous or ophthalmic) and amoxicillin-clavulanate prescriptions will also be included in the amoxicillin group.[1,2]

### 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).

3. Not enrolled at KPNC or KPSC during the 365 days prior to the index date (allowing gaps of < 60 days). This criterion ensures capture of potential confounders and effect measure modifiers.

4. Gaps in prescription coverage greater than 60 days during the 365 days prior to the index date, unless there is evidence of a filled prescription in the one year prior to the index date. This criterion ensures opportunities for capturing exposures to the medications of interest, as well as confounders and effect measure modifiers.

5. More than one type of study antibiotic prescribed on the index date, or within 10 days prior (ie, wash-out period).

6. Hospitalization within 30 days prior to the index date. This criterion considers that medication changes and medications administered during hospital stays may not be captured.

7. 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. This includes inferred nursing home stays, defined as 2 or more outpatient encounters in the year leading up the index prescription 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 within a nursing home setting may be less accurate.

## 8.3. Variables

### 8.3.1. Exposure

Outpatient prescriptions for azithromycin or amoxicillin occurring between 01 Jan 1998 and 31 Dec 2012.

### 8.3.2. Outcomes

The following outcomes will be examined in this study: 1) cardiovascular death, 2) sudden cardiac death, 3) all-cause death, 4) non-cardiovascular death, 5) cardiac death (sensitivity analysis only). All outcomes will initially be identified via database programming, through algorithms using death certificate information, ICD9/10 diagnostic and procedure codes, and other data obtained from Kaiser Permanente research databases. See Table 1 below for outcome variable database programming definitions and database sources. In many cases, the databases are queried for both ICD9 codes and ICD10 codes to maximize sensitivity. In the KP databases, death codes include both ICD9 and ICD10 results, depending on the year of death whereas non-fatal inpatient and outpatient encounters use only ICD9 codes. 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).

**Table 1. Outcome variable definitions (by database programming)**

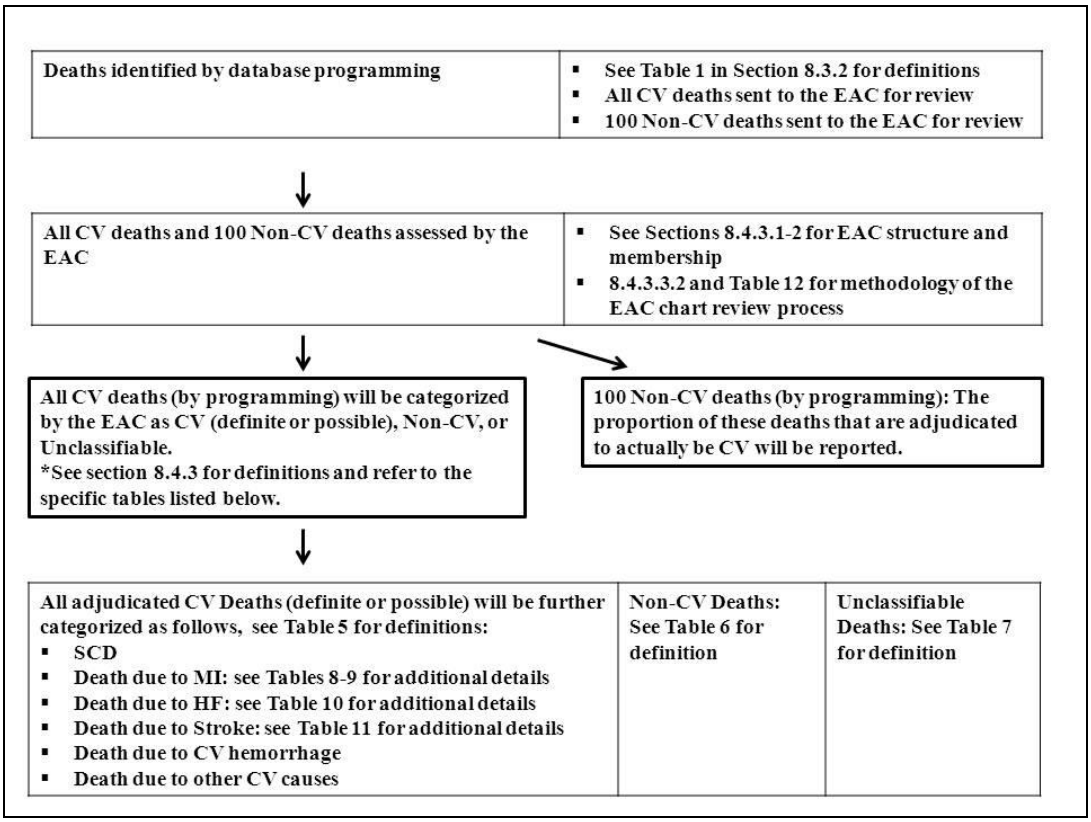
| Variable | Role | Data Source | Operational Definition |
|---|---|---|---|
| Cardiovascular death | Outcome (primary objective) | California state death registry (database accessed by the programmers) | Death certificate with underlying cause of death consistent with a cardiovascular cause, such as 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:<br>▪ ICD10 codes: I00.xx-I99.xx, R96.0x, R96.1x *or*<br>▪ ICD9 codes: : 390.xx-459.xx, 798.1x, 798.2x, 798.9x, 799.9x |
| Sudden Cardiac Death (SCD), using the methods and specific codes used by Chung and colleagues.[9] | Outcome (primary objective) | California state death registry & KPNC/KPSC databases (TRRS) [radiology]<br><br>Thrombolytic drugs from PIMS (pharmacy) database (1998-2005) and Health Connect inpatient Rx (2006-2012).<br><br>General anesthesia from ORSOS (surgical procedure) database (1998-1999) and KASIS (surgical procedure) database (2001-2012), data between 1999-2001 is | Deaths meeting the following three criteria applied in this order:<br>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 death certificate place of death indicates hospital or nursing home.<br><br>2. (inclusion): Death certificate with underlying cause of death code consistent with SCD:<br>▪ ICD9 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*<br>▪ ICD10 codes: I10.xx, I11.9x, I20.xx-25.xx, I42.9x, I42.8x, I46x, I47.0x, |

| Variable | Role | Data Source | Operational Definition |
|---|---|---|---|
| | | unreliable. | I47.2x, I49.0x, I49.8x, I49.9x, I51.6x, I51.9x, I70.9x, R96.1x, R98xx<br><br>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:<br>▪ 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 2** for the specific Radiology procedure codes used for this variable.<br>▪ Thrombolytic drugs (ED or hospital encounters): alteplase (Activase), reteplase (Retavase), tenecteplase (TNKase), anistreplase (Eminase), streptokinase (Kabikinase, Steptase), urokinase (Abbokinase)<br>▪ General Anesthesia: all records from the KP KASIS (surgery) tables associated with an indicator variable for anesthesia. This is a specific KP database |

| Variable | Role | Data Source | Operational Definition |
|---|---|---|---|
| | | | element. |
| Non-cardiovascular death | Outcome (secondary objective) | California state death registry | All deaths that are not categorized as cardiovascular 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) | California state death registry, KPNC/KPSC and social security databases | Death confirmed by registry/databases. |
| Cardiac death | Outcome (sensitivity analysis) | California state death certificates | Cardiac-specific deaths (underlying only), rather than the broader category of cardiovascular deaths<br>▪ ICD-10 codes: I11.xx, I13.xx, I20.xx-25.xx, I27.xx, I30.xx-52.xx *or*<br>▪ ICD-9 codes: : 402.xx, 404.xx, 410.xx-414.xx, 416.8x, 416.9x, 420.xx-429.xx |

Endpoints for the primary objective (ie, CV death and SCD within 5 and within 6-10 days of antibiotic dispensation will then be chart reviewed and adjudicated by the Events Adjudication Committee (see **Error! Reference source not found.**). For this study's primary objective, the primary analyses will include only deaths adjudicated to be either definitely or possibly CV in nature. All analyses of the secondary objectives will be conducted using un-adjudicated 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 cardiovascular death within 5 days, within 6-10 days, and within 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 cardiovascular death within 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 outpatient encounter with one of the diagnostic codes (

**Table 2**) within one year prior to the index antibiotic prescription ($t_0$). This will include emergency department-only encounters and non-acute institutional stay encounters but excludes telephone and email encounters. In the KP databases, inpatient and outpatient encounters use only ICD9 codes, as shown in

**Table 2** below. The KP databases include both ICD9 and CPT procedure codes, as shown in

**Table 2** below. These codes have been used and validated in previous KP publications.[7,10-22]

**Table 2. Component CVD diagnoses**

| Variable | Role | Data Source | Operational definition |
|---|---|---|---|
| Acute coronary syndrome | Component of CVD diagnosis (EMM) | KPNC/KPSC VDW (Virtual Data Warehouse) diagnosis database | ICD9 codes: 411.1x or 410.xx |
| Other ischemic heart disease | Component of CVD diagnosis (EMM) | KPNC/KPSC VDW diagnosis databases | ICD9 codes: 411.8x, 412.xx, 413.xx, 414.xx |
| Percutaneous or surgical coronary revascularization | Component of CVD diagnosis (EMM) | KPNC/KPSC VDW diagnosis databases | Percutaneous coronary intervention (PCI)<br>▪ ICD -9 procedure codes: 36.01, 36.02, 36.05, 36.06, 36.07, 36.09, 00.66<br>▪ *or* CPT 4 codes: 92980, 92981, 92982, 92984, 92995, 92996<br><br>Coronary artery bypass grafting (CABG)<br>▪ ICD-9 procedure codes: 36.03, 36.1x<br>▪ *or* CTP 4 codes: 33533, 33534, 33535, 33536, 33572, 33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33521, 33522, 33523, 33530 |
| Heart failure or | Component of | KPNC/KPSC | ICD9 codes: 428.xx, 402.01, |

| Variable | Role | Data Source | Operational definition |
|---|---|---|---|
| cardiomyopathy | CVD diagnosis (EMM) | VDW diagnosis databases | 402.11, 402.91, 425.xx |
| Valvular heart disease or heart valve surgery | Component of CVD diagnosis (EMM) | KPNC/KPSC VDW diagnosis databases | ICD-9 codes: 424.0x-3x, 424.90, 429.5x, 429.6x, 394.xx, 395.xx, 396.xx, 397.xx *or* ICD9 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) | KPNC/KPSC VDW diagnosis databases | ICD9 codes: 745.xx, 746.xx, 747.xx *or* ICD9 procedure codes: 35.34, 35.35, 35.39, 35.4x, 35.5x, 35.6x, 35.7x, 35.8x, 35.9x |
| Cerebrovascular disease | Component of CVD diagnosis (EMM) | KPNC/KPSC VDW diagnosis databases | ICD9 codes: 430.xx-438.xx (inclusive) |
| Peripheral arterial disease | Component of CVD diagnosis (EMM) | KPNC/KPSC VDW diagnosis databases | ICD9 codes: 440.xx-443.xx (inclusive) |
| Arrhythmia (all types) | Component of CVD diagnosis (EMM) | KPNC/KPSC VDW diagnosis databases | ICD9 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,[1,23-25] 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. See the Statistical Analysis Plan for the detailed CV risk score methodology. **High baseline CV risk will 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 ($t_0$); except as noted below). Only oral forms of medication were included, with the exception of nitroglycerin and insulin as described below. CV emergency room visits and current smoking status are also included. Other CV variables not shown in

**Table 2** & Table 3, such as a history of hypertension, hyperlipidemia, and diabetes mellitus are 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 |
|---|---|---|---|
| ACE inhibitor | Component of CV risk score (EMM) | PIMS (pharmacy) database (1998-2005) and Health Connect inpatient Rx (VDW, 2006-2012) | Drug names: Quinipril, peridopril, ramipril, Benazepril, Captopril, Enalapril, Enalaprilat, fosinopril, lisinopril ,perindoprli, quinapril, Trandolapril |
| ARB | Component of CV risk score (EMM) | PIMS (pharmacy) database (1998-2005) and Health Connect inpatient Rx (VDW, 2006-2012) | Drug names: Candesartan, irbesartan, Olmesartan, Losartan, Valsartan, azilsartan, telmisartan, eprosartan |
| Antiarrhythmic | Component of CV risk score (EMM) | PIMS (pharmacy) database (1998-2005) and Health Connect inpatient Rx (VDW, 2006-2012) | Drug names: quinidine, procainamide, disopyramide, mexiletine, tocainide, flecainide, propafenone, encainide, moricizine, amiodarone, sotalol, dronedarone, dofetilide |
| Anticoagulant | Component of CV risk score (EMM) | PIMS (pharmacy) database (1998-2005) and Health Connect inpatient Rx (VDW, 2006-2012) | Drug names: warfarin, dabigatran, rivaroxaban, apixaban, heparin, enoxaparin |

| Variable | Role | Data Source | Operational definition |
|---|---|---|---|
| Beta-Blocker | Component of CV risk score (EMM) | PIMS (pharmacy) database (1998-2005) and Health Connect inpatient Rx (VDW, 2006-2012) | Drug names: acebutolol, atenolol, betaxolol, bisoprolol, nebivolol, carvedilol, Nadolol, Propranolol, penbutolol, metoprolol succinate, Metoprolol tartrate, pindolol Requires: oral dosing only (not ophthalmic) |
| Calcium channel blocker | Component of CV risk score (EMM) | PIMS (pharmacy) database (1998-2005) and Health Connect inpatient Rx (VDW, 2006-2012) | Drug names: verapamil, gallopamil, fendiline, diltiazem, amlodipine, felodipine, nicardipine, nisoldipine, nifedipine, isradapine, nimodipine, Clevidipine |
| Digoxin | Component of CV risk score (EMM) | PIMS (pharmacy) database (1998-2005) and Health Connect inpatient Rx (VDW, 2006-2012) | Drug names: digoxin |
| Diabetes medication | Component of CV risk score (EMM) | PIMS (pharmacy) database (1998-2005) and Health Connect inpatient Rx (VDW, 2006-2012) | Drug names: insulin, metformin, exenatide, glimepiride, sitagliptin, saxagliptin, pramlintide, linagliptin, liraglutide, colesevelam, pioglitazone, rosiglitazone, glipizide, glimepiride, glyburide, repaglinide, nateglinide, acarbose, miglitol, acetohexamide, chlorpropamide, exenatide, tolazamide, tolbutamide, troglitazone*NOTE: injection forms of insulin are accepted. |

| Variable | Role | Data Source | Operational definition |
|---|---|---|---|
| Cholesterol-modifying medication | Component of CV risk score (EMM) | PIMS (pharmacy) database (1998-2005) and Health Connect inpatient Rx (VDW, 2006-2012) | Drug names: simvastatin, Zocor, atorvastatin, Lipitor, lovastatin, mevacor, rosuvastatin, Crestor, pravastatin, pravachol, fluvastatin, Lescol, pitavastatin, Livalo, Advicor, Simcor, Vytorin, niacin, Niaspan, Slo-niacin, nicotinic acid, Niacor, Nicolar, Nicobid, Endur-acin, ezetemibe, Zetia, fenofibrate, TriCor, gemfibrozil, Lopid, clofibrate, Atromid, ciprofibrate, Modalim, bezafibrate, Bezalip, fenofibric acid, Fibricor, TriLipix, cholestyramine, colestipol, colesevelam. |
| Loop diuretic | Component of CV risk score (EMM) | PIMS (pharmacy) database (1998-2005) and Health Connect inpatient Rx (VDW, 2006-2012) | Drug names: furosemide, torsemide, bumetanide, ethacrynic acid |
| Nitroglycerin | Component of CV risk score (EMM) | PIMS (pharmacy) database (1998-2005) and Health Connect inpatient Rx (VDW, 2006-2012) | Drug names: nitroglycerin, Nitrostat, Nitroquick, Nitrolingual, Nitro-Dur, Minitran, Nitro-Bid, isosorbide mononitrate, isosorbide dinitrate<br><br>*NOTE: topical forms are accepted in this drug class (in addition to oral forms) |
| Platelet inhibitor | Component of CV risk score (EMM) | PIMS (pharmacy) database (1998-2005) and Health Connect inpatient Rx (VDW, | Drug names: clopidogrel, prasugrel, ticlopidine |

| Variable | Role | Data Source | Operational definition |
|---|---|---|---|
| | | 2006-2012) | |
| Thiazide diuretic | Component of CV risk score (EMM) | PIMS (pharmacy) database (1998-2005) and Health Connect inpatient Rx (VDW, 2006-2012) | Drug names: hydrochlorothiazide, chlorothiazide, indapamide, metolazone, chlorthalidone, polythiazide, quinethazone |
| CV emergency room visit | Component of CV risk score (EMM) | KPNC/KPSC VDW diagnosis databases | Requires: an emergency room visit with an associated ICD9 code for one of the types of cardiovascular disease defined above: 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) | KPNC/KPSC VDW diagnosis databases | Requires: An inpatient or outpatient encounter with one of the codes (below) within one year prior to the index antibiotic prescription ($t_0$)<br>ICD9 codes: 305.1x or V15.82<br><br>OR (using VDW social history table)<br>Smoking quit date occurs within year prior to $t_0$<br>OR<br>Tobacco User = Y (Yes/ Current) |

#### 8.3.3.3. Individuals with COPD and CAP

| Variable | Role | Data Source | Operational definition |
|---|---|---|---|
| COPD | EMM | KPNC/KPSC VDW (Virtual Data Warehouse) diagnosis database | ICD9 codes: 491.xx 496.xx |
| CAP | EMM | KPNC/KPSC VDW diagnosis databases | ICD9 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, the models will include indication of use (see Section 8.4.2), demographic factors (eg, age, gender, race/ethnicity), 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 date will be included in the Statistical Analysis Plan (SAP). The use of comorbidity index scores will be considered during the development of the SAP.

## 8.4. Data sources

### 8.4.1. KPNC-KPSC Databases

This retrospective cohort study will draw from several KPNC and KPSC databases, as described in the previous tables. Information is linked between databases using unique identifiers such as medical record numbers. Kaiser Permanente California studies have previously used chart review to validate database programming codes for a broad range of cardiovascular outcomes, including myocardial infarction/unstable angina, congestive heart failure, hypertension, stroke, ventricular arrhythmias, and cardiovascular death.[7,10,11,14,18,20,21,26] Other Kaiser California studies have explored associations between medication exposures and adverse CV outcomes, including myocardial infarction and sudden cardiac death.[12,19,24,25,27] The study PI has recently completed a study with Pfizer quantifying rates of CV events in the KPNC cancer population. That study included chart review validation of over 1000 CV events, and provided validation estimates for acute coronary syndrome (87% Positive Predictive Value [PPV]), congestive heart failure (PPV 91%), and cardiac arrest/ventricular arrhythmia (PPV 70%).[28]

### 8.4.2. Antibiotic Indication Assessments

One important limitation of the prior research related to this research question is partial or fully missing data on indications for antibiotic use, possibly resulting in residual confounding.[1-4] During the proposed study period (1998-2012) at Kaiser, clinical providers were required to provide a list of diagnostic codes applicable for a given patient encounter. Since 2008, however, providers prescribing medications within the Kaiser EMR are required to directly link a single diagnosis code to a medication prescription, allowing for direct capture of indication of use. For the EMR prior to 2008, diagnostic codes are available in the Kaiser EMR databases and will be linked to the antibiotic prescriptions (obtained from the pharmacy databases) by medical record numbers and date ranges (see below), thus allowing for an indirect capture of indication of use (as was used by Ray et al. 2012).[1] Antibiotic prescriptions with a directly-linked or temporally-associated infection diagnosis will be categorized as having that specific type of infection as the indication of use. Prophylactic antibiotic prescriptions (eg, dental/procedural prophylaxis or traveler's diarrhea prophylaxis) will be considered as a separate category. If there is no infection or prophylaxis code associated with the prescription, the indication of use will be categorized as "missing."

The ICD-9 codes listed in **Table 4** below (adapted from Ray et al. 2012)[1] will be considered infection indications for an antibiotic prescription. Ray's manuscript provides the specific types of infection shown in **Table 4** but does not provide the codes, which were instead taken from the Chrisendres coding manual (icd9.chrisendres.com). The Kaiser investigators have already reviewed numerous charts of members prescribed azithromycin or amoxicillin and have found additional appropriate infection codes which have been added to **Table 4**. During the processes of database programming and chart review, 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 4** below, duplicates Ray's methodology.[1]

**Table 4. ICD codes used to define infections for antibiotic indications of use**

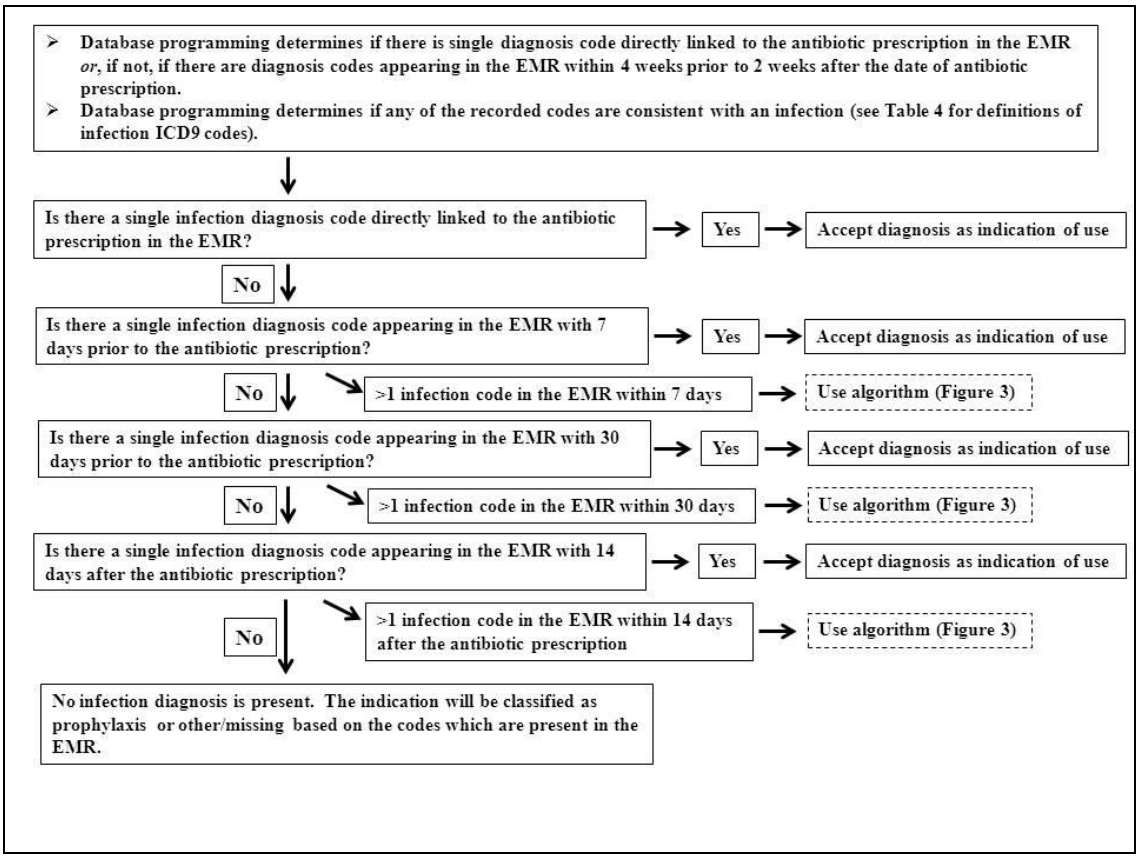
| Infectious Disease Indication | ICD-9 Coding Plan | Infection Severity Priority |
|---|---|---|
| Pneumonia | 480.xx-488.xx, 500.xx -508.xx, 510.xx -511.xx, 513.xx, 515.xx, 010.xx -012.xx, 073.xx, 517.1x | High |
| COPD | 491.xx -496.xx | High |
| Pyrexia unknown origin | 780.60 | High |
| Other serious 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, | High |

| Infectious Disease Indication | ICD-9 Coding Plan | Infection Severity Priority |
|---|---|---|
| | 449.xx, 634.5x, 635.5x, 636.5x, 637.5x, 638.5x, 639.5x | |
| ➢ 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 |
| Wounds | 870.xx -897.xx | Low |

| Infectious Disease Indication | ICD-9 Coding Plan | Infection Severity Priority |
|---|---|---|
| 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 |

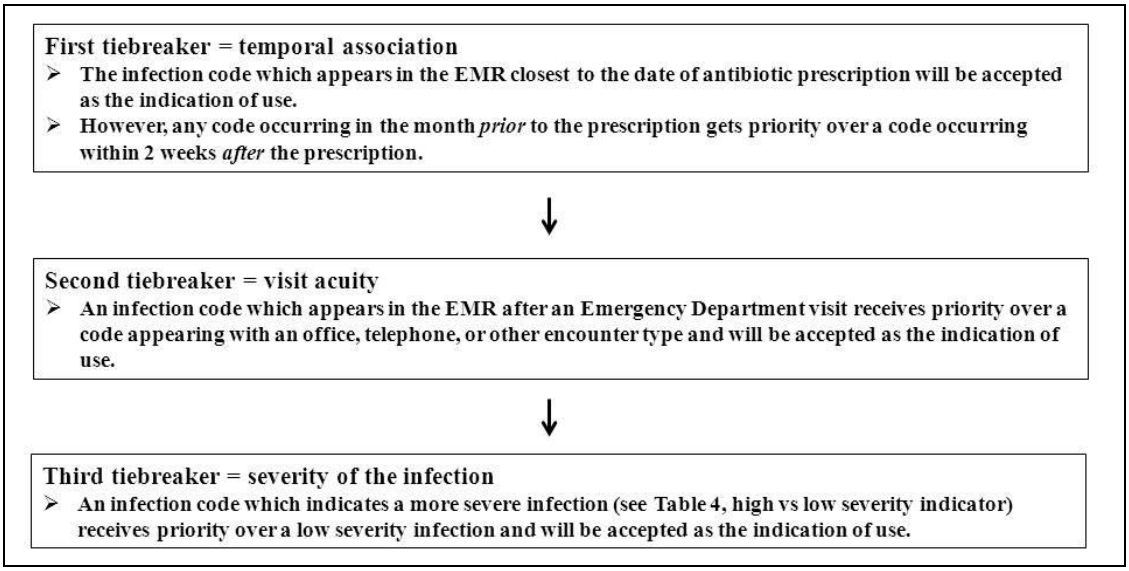
The process of determining antibiotic indication of use is summarized in the two figures below and further detailed in the text that follows. Figure 2 describes the general process and Figure 3 describes the algorithm to be employed to resolve "ties" among competing infection diagnosis codes, thus selecting only one infection diagnosis as the indication of use in all cases.

**Figure 2. Flow diagram describing antibiotic indication of use determination**




In the case of "ties" – more than one competing diagnosis for indication of use within a given time frame, the algorithm below (Figure 3) will be used to provide a single diagnosis.

**Figure 3. Algorithm to determine antibiotic indication 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 emergency department visits (without hospitalization), office visits, telephone encounters, and email encounters. Both primary and secondary codes will be accepted. The key point of methodological emphasis is that when there is a single infection ICD-9 code specifically linked to the antibiotic prescription (expected in the EMR after 2008) that diagnosis will always be accepted as the indication of use. If no such directly linked diagnosis code is present in the EMR, the methodology described in Figure 2 & Figure 3 will be used to indirectly link a prescription with an indication.

The antibiotic indications of use programmatically determined in the process described above will be validated by chart review of a random sample of 300 antibiotic prescription encounters from both KPNC and KPSC (150 at each site). In addition, antibiotic indication of use will be confirmed during the chart review process for all CV deaths. The proportion of missing indication of use after chart review will be reported for this sample of 300 antibiotic prescriptions. If the proportion of missing indication of use is less than 10% of 300, then additional prescriptions with missing indications will be randomly sampled in order to obtain a sample of 30 prescriptions with programmatically "missing" indications for chart review. This process will help identify any systematic errors (eg, errors with programming vs. true lack of data within the EMR system) leading to missing indications for the cohort in general, and according to antibiotic type. Based on the entire chart review process, the database programming plan for indication of use and the algorithm above will be modified as necessary after agreement by the investigators.

The proportion of antibiotic prescriptions with a prophylaxis 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 prescriptions 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 Cardiovascular Event Adjudication Committee Charter (**Error! Reference source not found.**).

## 8.5. Study size

A comprehensive feasibility analysis conducted within the KPNC-KPSC databases, submitted to both the PRAC and the FDA revealed a projected sample size of nearly 1.4 million azithromycin exposures and over >5.4 million amoxicillin exposures among those aged 30-75 between the years of 2008-2011, after application of the study's planned exclusion criteria. The feasibility analysis also estimated the incidence of CV death to be 25 per million amoxicillin prescriptions and the incidence of sudden cardiac death to be 14 per million amoxicillin prescriptions. The minimum hazard ratios detectable with 90% power for CV death and SCD were estimated to be 1.74 and 2.04, respectively; hazard ratios lower than those reported by Ray et al. (2012).[1]

Ninety percent power estimates were chosen for the feasibility analysis to allow for attrition that will likely occur during the death adjudication process in this study. Based on the literature, we expect to lose approximately 20-50% of the cardiovascular deaths due to the adjudication process (either cardiovascular deaths adjudicated to be non-cardiovascular deaths, or CV deaths with insufficient information to adjudicate)[29,30] However, based on the power analyses for KPNC (reported in the feasibility analsysis), and that KPNC will likely provide approximately half of the total CV deaths, assuming a 50% attrition rate, the minimum effect sizes detailed above will still be detectable with at least 80% power. Slightly higher effect estimates than reported here (although still lower effect estimates than reported by Ray et al.), should be detectable with 90% power.

## 8.6. Data management

Detailed methods for data collection are described in Sections 8.3 and 8.4. Data for this study will be extracted from KPNC and KPSC databases (previously described) that contain information about patient enrollment, dispensed prescriptions, procedures, and diagnoses. Study data will be stored and maintained by the KPNC Division of Research. Additional data will be collected during the endpoints adjudication process (for primary outcomes) by MRAs using a standardized form. The adjudication data, including the adjudicated outcome, will be entered into an Excel or Access database at DOR. All analyses will be conducted using SAS software.

## 8.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be 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 will be 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). Candidate models include a fully parametric piecewise exponential survival model and the semi-parametric 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. Possible approaches to the use of the propensity score include matching, stratification and inclusion of the propensity score as a model covariate. Decisions on propensity score model covariate inclusion and on use of the score in confounder control will be partially based on observed data. Such exploratory analyses will never involve linkage between exposures and study outcomes of interest (eg, only between potential confounders, propensity scores, and exposures of interest, or between potential confounders and study outcomes). Further details will be described in the SAP.

### 8.7.3. CV Risk Score development

The summary cardiovascular risk score will be generated for both the azithromycin and amoxicillin cohorts using methodology similar to that used by Ray and colleagues.[1,23] Some risk score elements were not explicitly defined using ICD codes by Ray et al., and therefore as a result, the ICD codes implemented may differ slightly in the present study.

The CV risk score will be developed from a logistic regression analysis of the effects of each contributing variable on the probability of cardiovascular death. The sequential steps involved in the generation of the CV risk score are summarized below and full details will be 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
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
6. Apply the CV risk score variable coefficients
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 (cardiovascular death within 5 days and 6-10 days) using an alternative propensity score method. For example, if propensity score matching is utilized for the main method, the sensitivity analysis may use propensity score stratification or inverse probability weighting).

2. 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.

3. Conduct primary analysis (cardiovascular 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

4. Conduct primary analysis (cardiovascular 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.

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

6. Conduct primary analysis with an alternative CV death definition, to include all deaths meeting CV death criteria by database programming/death certificate data. Thus, this analysis will include programmatic CV deaths determined to be non-CV deaths by chart review/adjudication.

7. Conduct primary analysis 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 high CV risk group profile as closely as possible. Therefore, a high CV risk category will be created to reflect the CV mortality incidence of approximately 160 CV deaths per million amoxicillin prescriptions, as reported by Ray et al.

8. Conduct primary analysis restricted to antibiotic prescriptions within the time period of 2008 – 2012. The most recent version of the Kaiser Permanente EMR system (Health Connect) was initiated in 2008 and offers improved antibiotic indication of use data (see Section 8.4.2 above) via direct capture of indication of use.

9. Conduct primary analysis restricted to antibiotic prescriptions which have an infection indication of use and thus excluding prescriptions given for prophylaxis or missing/other indications (see Section 8.4.2 above).

## 8.8. Quality control

Data for the study will be extracted from electronic databases maintained by Kaiser Permanente and by the Division of Research. The DOR Strategic Programming Group performs comprehensive QA of KP electronic databases, including the Virtual Data Warehouse (VDW) files. Each data content area in the VDW 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 prescriptions, 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.

In addition to these measures, the database programming code and output will be compared between the two sites (KPNC & KPSC) on a regular basis, legacy copies of the programming files will be saved on the DOR servers as the programming evolves over time, and legacy copies of the descriptive and statistical analysis data tables will be also be saved on the server. The QA process for the CV death adjudications is detailed in **Error! Reference source not found.**.

Data Abstraction

All abstractions will be conducted by trained KPNC DOR and KPSC data abstractors. Staff members have a minimum of one year of medical record coding/abstracting experience, but the department average is eight years, and some have 30 years of experience. Abstractors are trained by the principal investigator, with review/re-abstraction of reports for the initial training to confirm accuracy. The Medical Record Analysts (MRAs) have expertise in health record content, health information management practices, ICD-9 coding, medical terminology, disease processes, drugs, abbreviations, and medical-record abstracting. See **Error! Reference source not found.** for the detailed methodology of the Events Adjudication Committee.

### 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), a large sample size with adequate power to detect small effect sizes, and a population-based sample which will be highly generalizable to the US, and reasonably generalizable to many EU populations. 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, and a rigorous attempt at accurately capturing indication of antibiotic use, a likely confounding factor which may have limited prior studies. The studies chart review algorithms will be refined based on the extensive medical chart review process.

A possible limitation of the study includes some missing indication of use information given the indirect method of capture for prescriptions written prior to 2008. There may also be some degree of missing data for some of the CV risk indicator variables. However, given the chart review and subsequent algorithm refinement, the degree of missing information should be limited. In addition, the Kaiser pharmacy databases indicate when a prescription has been 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. The KPNC IRB has approved 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 investigator 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 was approved by the Institutional Review Board of the Kaiser Foundation Research Institute on May 14th, 2014 and this approval applies to both the Northern and Southern California Kaiser sites.

### 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 will be provided to all research staff members prior to study start. 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 and the EMA according to the timetable outlined in Section 5 and posted on EU PAS register.

## 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

Attached separately

## ANNEX 3. ADDITIONAL INFORMATION

Not applicable

## Appendix 1. Marketing authorization numbers for azithromycin within the European Union

| Country | Address | Oral Presentations Registered | MA numbers for oral presentations registered |
|---|---|---|---|
| Austria | Pfizer Corporation Austria Ges.m.b.H., Wien Austria | 200 mg/5mL powder for oral suspension<br>500 mg film-coated tablet<br>2 g prolonged release granules for oral suspension | 1-20313<br>1-21939<br>1-26873 |
| Belgium | Pfizer S.A<br>17 bld de la Plaine,<br>1050 Brussels,<br>Belgium | 250 mg film-coated tablet<br>500 mg film-coated tablet<br>600 mg film-coated tablet<br>200 mg/5 mL powder for oral suspension | 250 mg: BE193261<br>500 mg: BE193243<br>600 mg: BE193252<br>200 mg/5 mL: BE165961 |
| Bulgaria | Pfizer Europe MA EEIG<br>Ramsgate Road<br>Sandwich<br>Kent, CT13 9NJ<br>United Kingdom | 2 g prolonged-release granules for oral suspension | 20060293 |
| Croatia | Pfizer croatia d.o.o.,<br>Slavosnka avenija 6,<br>10000 Zagreb, Croatia | 2 g prolonged release granules for oral suspension | UP/I-530-09/09-01/101 |
| Cyprus | PFIZER HELLAS A.E.,<br>243 Messoghion Ave.,<br>154 51 N.Psychiko,<br>Athens<br>Greece | 200 mg/5 mL powder for oral suspension<br>250 mg film-coated tablet<br>2 g prolonged release granules for oral suspension | 19592<br><br>S00706<br>20602 |
| Czech Republic | Pfizer, spol. s r.o.<br>Czech Republic | 2 g prolonged release granules for oral suspension | 15/342/09-C |

| Country | Address | Oral Presentations Registered | MA numbers for oral presentations registered |
|---|---|---|---|
| Denmark | Pfizer ApS<br>Lautrupvang 8<br>750 Ballerup<br>Denmark | 250 mg film-coated tablets<br>500 mg film-coated tablets<br>600 mg film-coated tablets<br>40 mg/ mL powder for oral suspension | 19117<br>19118<br>18479<br>14083 |
| Estonia | Pfizer Europe MA EEIG, Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom | 2 g prolonged release granules for oral suspension | 625809 |
| Finland | Pfizer Oy<br>Tietokuja 4 00330<br>Helsinki<br>Finland | 250 mg film-coated tablet<br>500 mg film-coated tablet<br>40 mg/mL powder for oral suspension | 12016<br>12017<br>11615 |
| France | Pfizer Holding France<br>23-25 avenue du Docteur Lannelongue<br>75014 Paris<br>France | 250 mg film-coated tablet<br><br>250 mg film-coated tablet (monodose)<br>40 mg/mL powder for oral suspension<br>40 mg/ml (paeds) powder for oral suspension<br><br>600 mg film-coated tablet | 351 773 – 2 or 34009 351 773 2 2 and 351 774 – 9 or 34009 351 9 0<br>351 775-5 or 34009 351 775 5 1 and 351 776-1 or 34009 351 776 1 2<br>351 777-8 or 34009 351 777 8 0 and 351 778-4 or 34009 351 778 4 1<br>356 561-3 or 34009 356 561 3 1, 356 563-6 or 34009 356 563 6 0, 56 564-2 or 34009 356 564 2 1, 356 565-9 or 34009 356 565 9 9<br>356 566-5 or 34009 356 566 5 0, 56 567-1 or |

| Country | Address | Oral Presentations Registered | MA numbers for oral presentations registered |
|---|---|---|---|
| | | | 34009 356 567 1 1, 356 568-8 or 34009 356 568 8 9 , 356 569-4 ou 34009 356 569 4 0 343 336-6 or 34009 343 336 6 8, 43 337-2 or 34009 343 337 3 9, 343 338-9 or 34009 343 338 9 7, 343 361-0 or 34009 343 361 0 2, 343 362-7or 34009 343 362 7 0, 343 363-3 or 34009 343 363 3 1 |
| Germany | PFIZER PHARMA GmbH<br>Linkstrasse 10<br>10785 Berlin<br>Germany | 250 mg film-coated tablet (monodose)<br>500 mg film-coated tablet<br>600 mg film-coated tablet<br>40 mg/mL powder for oral suspension | 37174.00.00<br>37174.01.00<br>37344.00.00<br>25156.00.01 |
| Greece | PFIZER HELLAS A.E.,<br>243 Messoghion Ave.,<br>154 51 N.Psychiko, Athens<br>Greece | 200 mg/5 mL powder for oral suspension<br>250 mg film-coated tablet<br>2 g prolonged release granules for oral suspension | 44411/5-11-2009<br><br>44407/5-11-2009<br>21471/03-04-2008 |
| Hungary | Pfizer Kft.<br>1123 Budapest<br>Alkotás u. 53.<br>Hungary | 2 g prolonged-release granules for oral suspension | OGYI-T-20770/01 |
| Iceland | Pfizer ApS<br>Lautrupvang 8<br>750 Ballerup<br>Denmark | 250 mg film-coated tablet<br>500 mg film-coated tablet<br>40 mg/mL powder | 970281 (IS)<br>970282 (IS)<br>920013 (IS)<br>IS/1/05/134/01 |

| Country | Address | Oral Presentations Registered | MA numbers for oral presentations registered |
|---|---|---|---|
| | | for oral suspension<br>2 g<br>Prolonged-release granules for oral suspension | |
| Ireland | Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT 13, 9 NJ, United Kingdom | 250 mg film-coated tablet<br>250 mg hard capsule<br>500 mg film-coated tablet<br>600 mg film-coated tablet<br>200 mg/5 ml powder for oral suspension | PA 19/47/8<br>PA 19/47/1 and PA 19/93/1<br>PA 19/47/9<br>PA 19/47/10<br>PA0019/093/002 |
| Italy | Pfizer Italia S.r.l. Via Isonzo, 71 – 04100 Latina, Italt | 200 mg/ 5 mL powder for suspension<br>100 mg powder for oral suspension<br>150 mg powder for oral suspension<br>200 mg powder for oral suspension<br>300 mg powder for oral suspension<br>400 mg powder for oral suspension<br>600 mg powder for oral suspension<br>250 mg hard capsule<br>500 mg film-coated tablet<br>600 mg film-coated tablet | 027897055 and 027897026<br>027897065<br>027897077<br>027897089<br>027897091<br>027897103<br>027897053<br>027897014<br>027897040<br>027897115 |
| Latvia | Pfizer Europe MA EEIG Sandwich, Kent CT13 9NJ United Kingdom | 2 g prolonged-release granules for oral suspension | 09-0080 |
| Lithuania | Pfizer Europe MA EEIG<br>Ramsgate Road<br>Sandwich, Kent | 2 g Prolonged Release granules for oral suspension | LT/1/09/1520/001 |

| Country | Address | Oral Presentations Registered | MA numbers for oral presentations registered |
|---|---|---|---|
| | CT13 9NJ, UK | | |
| Luxembourg | Pfizer S.A<br>17 bld de la Plaine,<br>1050 Brussels,<br>Belgium | 250 mg film-coated tablet<br>500 mg film-coated tablet<br>600 mg film coated tablet | 0194/98/08/0024 /<br>0194/11111333<br>0194/11111334 |
| Malta | Pfizer Hellas S.A.<br>243, Messoghion Ave., Neo Psychiko<br>154 51 Greece | 250 mg hard capsule<br>200 mg/5 mL powder for oral suspension | MA505/03902<br>MA505/03901 |
| Netherlands | Pfizer B.V Rivium Westlaan 142,<br>2909 LD Capelle aan den IJssel | 200 mg/5 mL powder for oral suspension<br>250 mg film-coated tablet<br>500 mg film-coated tablet | RVG 14999<br>RVG 19433<br>RVG19432 |
| Norway | Pfizer AS, Lysaker, Norge | 40 mg/ml powder for oral suspension<br>500 mg film-coated tablet | 8025<br>95-245 |
| Poland | Pfizer Europe MA EEIG<br>Ramsgate Road,<br>Sandwich, Kent,<br>CT13 9NJ<br>United Kingdom | 2 g prolonged release granules for oral suspension | 15609 |
| Portugal | LABORATÓRIOS PFIZER, Lda. Lagoas Park<br>Edifício 10<br>2740-271 Porto Salvo | 40 mg/ml powder for oral suspension<br>500 mg film-coated tablet<br>2 g Granules, Prolonged Release, For Suspension | 2248284, 2248383,<br>4576286, 3969581<br>4576385, 2248383<br>5017827 |
| Romania | Pfizer Europe MA EEIG<br>Ramsgate Road,<br>Sandwich, Kent,<br>CT13 9NJ<br>United Kingdom | 2 g prolonged release granules for oral suspension | 6635/2006/01 |

| Country | Address | Oral Presentations Registered | MA numbers for oral presentations registered |
|---|---|---|---|
| Slovakia | Pfizer Europe MA EEIG<br>Ramsgate Road,<br>Sandwich, Kent,<br>CT13 9NJ<br>United Kingdom | 2 g Prolonged Release granules for oral suspension | **15/0162/09-S** |
| Slovenia | Pfizer Luxembourg SARL<br>51, Avenue J. F. Kennedy<br>L-1855 Luxembourg<br>Luksemburg | 2 g prolonged-release granules for oral suspension | 5363-I-343/14 |
| Spain | Pfizer S.L.<br>Avda Europa 20 B.<br>Parque Empresarial La Moraleja<br>28108, Alcobendas.<br>Madrid<br><br>Pharmacia Grupo Pfizer S.L.<br>Avda Europa 20 B.<br>Parque Empresarial La Moraleja<br>28108, Alcobendas.<br>Madrid | 250 mg hard capsule<br>500 mg film-coated tablet<br>250 mg powder for oral suspension<br>500 mg powder for oral suspension<br>1000 mg powder for oral suspension<br>200 mg/5 mL powder for oral suspension<br><br>500 mg film-coated tablet | 59.616<br>61.272<br>59.620<br>60.066<br>60.065<br>59.615<br><br>61.484 |
| Sweden | Pfizer AB,<br>191 90 Sollentuna | 40 mg/ml powder for oral suspension<br>2 g prolonged release granules for oral suspension | 11609<br>23285 |
| United Kingdom | Pfizer Limited,<br>Ramsgate Road,<br>Sandwich, Kent, CT 13, 9 NJ, United Kingdom | 250 mg hard capsule<br>200 mg/5 mL powder for suspension | PL 00057/0335<br>PL 00057/0336 |

**Appendix 2. 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 |
| CARD MR IMAG FUNCT W/WO MORPHOLOGY; CMPL STUDY | 75554 |
| CARD MR IMAG FUNCTION W/WO MORPHOLOGY; LTD STUDY | 75555 |
| CARD MR IMAGING MORPHOLOGY; W/CONTRST MATERIAL | 75553 |
| CARD MR IMAGING MORPHOLOGY; W/O CONTRST MATERIAL | 75552 |
| CARDIAC MR IMAGING FOR VELOCITY FLOW MAPPING | 75556 |
| CARDIAC MRI FOR VELOCITY FLOW MAPPING | 75565 |

| | |
|---|---|
| CARDIAC MRI MORPHOLOGY & FUNCTION W/O CONTRAST | 75557 |
| CARDIAC MRI W FLOW/VELOCITY QUANT | 75558 |
| CARDIAC MRI W FLOW/VELOCITY QUANT & STRESS | 75560 |
| CARDIAC MRI W/O CONTRAST W STRESS IMAGING | 75559 |
| CARDIAC MRI W/W/O CONTRAST W FLO VELOC & STRESS | 75564 |
| CARDIAC MRI W/W/O CONTRAST W FLOW VELOCITY QUANT | 75562 |
| CARDIAC MRI W/W/O CONTRAST W STRESS | 75563 |
| CARDIAC MRI W/WO CONTRAST & FURTHER SEQ | 75561 |
| 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 |
| CEREBROSPINAL FLUID FLOW W/O MATL SHUNT EVALTJ | 78645 |
| CEREBROSPINAL FLUID FLOW W/O MATL TOMOG SPECT | 78647 |
| CEREBROSPINAL FLUID FLOW W/O MATL VENTRICLGRAPHY | 78635 |
| CEREBROSPINAL FLUID LEAK DETECTION&LOCALIZATIO | 78650 |
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| 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 |
| PT INFORMATION ENTERED INTO RECALL SYSTEM | 7010F |
| 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 |
| PULM VI GASEOUS RBRTHING&WSHOT 1 PRJCJ | 78593 |
| 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 |
| QUANT DIFF PULM PRFUSION & VENTLAJ W/WO IMAGIN | 78598 |

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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 |

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| 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 |

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| 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 |

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| 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 |

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| 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 |

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| 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 |

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| 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 |

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| 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 3: 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 subset (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).[31] 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 both CV death adjudication, as well as indication of use information) and redact those documents so as to blind the adjudicators to the study antibiotic exposure. The EAC will consist of at least 4 qualified adjudicators (KPNC Cardiologists). Jonathan Zaroff, MD, a Principle Investigator of this study, will serve as one of the adjudicators but will be blinded to antibiotic exposure and all identifying information as part of the processes outlined below. The other adjudicators will be cardiologists independent of the study.

## 2. Personnel

Data abstractors

The KPNC DOR Medical Record Analyst Department will provide staff members to perform the data abstraction for this project. Staff members are required to have a minimum of one year of medical record coding/abstracting experience (supporting DOR research projects), but the department average is eight years, and some have 30 years' experience. The staff members, also known as Medical Record Analysts (MRAs), have expertise in health record content, health information management practices, ICD-9 coding, medical terminology, disease processes, drugs, abbreviations, and medical-record abstracting. KPSC's Department of Research and Evaluation employs data abstractors with similar qualifications.

Adjudicators (Committee Members)

Jonathan Zaroff, MD, is a cardiologist at KPNC with 19 years of experience performing clinical cardiovascular research. Dr. Zaroff has extensive experience performing chart review CV event adjudication, including the Pfizer-sponsored study of CV outcomes in cancer patients (see Section 8.4.1 in the study protocol), the CARDIA study,[32] studies designed and led by Dr. Zaroff at KPNC,[22,33] and studies performed by Dr. Zaroff prior to joining KPNC in 2006.[34-36] Dr. Zaroff will train at least three other adjudicators prior to study initiation and lead monthly committee meetings (see QA section 3.4 below). The other adjudicators will be KPNC Cardiologists recruited and trained by Dr. Zaroff. The

requirements for participation will include at least 3 years of experience in clinical cardiology and previous research experience. All adjudicators will be full partners of The Permanente Medical Group. Full partnership requires at least 3 years of clinical experience as a staff Cardiologist with skills and characters deemed to be excellent in quality by their peers. All adjudicators must be free of any conflict of interest related to this project.

## 3. EAC Methods

The specific methodology for the cause of death categorization (by chart review adjudication) is based on the definitions published by Leupker and Apple (2003)[31], 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),[37] and those utilized by the CARDIA (Coronary Artery Risk Development in Young Adults) observational study.[32,38] 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, through algorithms using death certificate information, ICD9/10 diagnostic and procedure codes, and other data obtained from Kaiser Permanente research databases. In many cases, the databases are queried for both ICD9 codes and ICD10 codes to maximize sensitivity. In the KP databases, death codes include both ICD9 and ICD10 results, depending on the year of death whereas non-fatal inpatient and outpatient encounters use only ICD9 codes.

### 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 5: CV Death Subtype Definitions**

| 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:<br>▪ Death witnessed and instantaneous without new or worsening symptoms<br>▪ Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest an acute MI.<br>▪ Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review).<br>▪ Death after unsuccessful resuscitation from cardiac arrest<br>▪ Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac etiology (Post-Cardiac Arrest Syndrome)<br>▪ 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).<br><br>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:<br>▪ Preceding acute MI/ischemia symptom such as chest discomfort or shortness of breath.<br>▪ EKG changes consistent with ischemia/MI (see table below)<br>▪ Fresh coronary thrombus seen at coronary angiography or autopsy<br>▪ A prior history of cardiomyopathy with chronically impaired left ventricular systolic function (ejection fraction). |
| Possible SCD | Requires:<br>▪ Evidence that death was due to presumed SCD that did not meet "definite" criteria above *and*<br>▪ A death certificate ICD9 code consistent with SCD without other underlying or immediate cause. Underlying cause of death codes c/w SCD include:<br>o ICD9 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*ICD10 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<br>*Or*<br>Autopsy evidence of a recent coronary occlusion or MI within the 30 days preceding death.<br><br>Note: Death by any cardiovascular mechanism (e.g., 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.<br><br>See section below for the definition of Definite MI (Tables 9 & 10).<br><br>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:<br>▪ No known non-atherosclerotic or non-cardiac atherosclerotic process or event that was probably lethal *and*<br>▪ Presence of one OR both of the following findings:<br>o Chest pain within 72 hours of death<br>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. |

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|---|---|
| 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:<br>▪ Evidence consistent with probable or possible MI (see table below)<br>▪ No known non-atherosclerotic or non-cardiac atherosclerotic process or event that was probably lethal *and*<br>▪ Death certificate with consistent underlying MI cause, ICD9 -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.<br>See section below for the definition of Definite MI (Tables 8 & 9 ). |
| 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.<br><br>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.<br><br>See section below and Table 10 for the definition of definite heart failure exacerbation. |
| Possible Fatal Heart Failure | Requires:<br>▪ 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*<br>▪ Death certificate code consistent with underlying HF cause, including ICD9 codes 428.xx, 402.01, 402.11, 402.91, and 425.xx *or* ICD10 codes I50.xx, I11.0x, I13.0x, I13.2x, I97.13x, and I09.81<br><br>See section below and Table 10 for the definition of possible heart failure exacerbation. |

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|---|---|
| Definite Fatal Stroke | Requires: Evidence that death was due to definite stroke (hemorrhagic, ischemic, or unknown type) with consistent imaging, surgical, or autopsy evidence.<br><br>Definition of definitive vs possible stroke: See section below and Table 11 |
| Possible Fatal Stroke | Requires:<br>▪ Evidence that death was due to presumed stroke (hemorrhagic, ischemic, or unknown type) that did not meet criteria for definite stroke *and*<br>▪ A death certificate code consistent with stroke without other underlying or immediate cause, including ICD9 codes 430.xx -438.xx. |
| Definite Fatal Cardiovascular Hemorrhage | Requires: Evidence that death was related to hemorrhage such as a non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or pericardial hemorrhage causing cardiac tamponade with consistent imaging, surgical, or autopsy evidence. |
| Possible Fatal Cardiovascular Hemorrhage | Requires:<br>▪ Evidence that death was due to presumed cardiovascular hemorrhage that did not meet "definite" criteria above *and*<br>▪ A death certificate ICD9 code consistent with CV hemorrhage without other underlying or immediate cause, including ICD9 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 (e.g. 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:<br>▪ 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*<br>▪ Death certificate consistent with CV disease without other underlying or immediate cause. |

**Table 6: Definition of non-CV death**

| Non-CV Death | Chart review definition |
|---|---|
| Fatal Non-Cardiovascular Disease | Requires: Documentation that death was due to fatal non-cardiovascular diseases and other reasons of death, including |

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|---|---|
| and Other Reasons of Death | 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 7: 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 8: History, EKG, and laboratory 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:<br>▪ 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.<br>▪ 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.<br>▪ 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. |

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|---|---|
| | ▪ 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:<br>▪ Diagnostic<br>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*<br>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*<br>o Total Creatine Kinase (CK) >2x ULN<br>o Myoglobin level >2x ULN<br>▪ Equivocal<br>o Cardiac troponin 1-2x ULN<br>o CK-MB 1-2x ULN or 5-9% of total CK or described as "mildly abnormal" (or similar language)<br>o Total CK 1-2x ULN and cardiac troponin 1-2x ULN<br>o Myoglobin level ULN<br>▪ Missing (no data available)<br>▪ Normal<br>o Cardiac troponin within normal limits (WNL)<br>o CK-MB WNL or <5% of total CK<br>o Total CK 1-2x WNL<br>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 9: 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 | *Definite* | *Possible* | *No* | *No* |

| EKG | | | | |
|---|---|---|---|---|
| | | | | |
| 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 KPNC 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 10: 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:<br>▪ 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.<br>▪ Bilateral lower extremity edema (swelling of legs, ankles, or feet). The edema should be bilateral but does not have to be symmetrical in severity.<br>▪ 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. |

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| Laboratory data | Laboratory evidence of HF acute decompensated HF requires one of the following:<br>▪ Abnormal chest imaging: 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.<br>▪ Abnormal blood level of B-type natriuretic peptide (BNP): A single BNP level >2x ULN will be considered abnormal. |

Definition of Definite Stroke

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 by the KPNC 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 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 11: 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 |

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|---|---|
| | (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:<br>▪ Altered mental status, altered level of consciousness (ALOC), coma, obtund, unresponsive, delirium, memory problems, disorientation, agitation.<br>▪ Trouble speaking: can't get the words out (Broca's aphasia), wrong words come out (Wernicke's aphasia), trouble understanding, inappropriate response.<br>▪ Visual field cut, homonymous hemianopia (HH), or diplopia (double vision)<br>▪ Difficulty swallowing, dysarthria, slurred speech, dysphonia, tongue deviation.<br>▪ Facial droop, or decrease in the nasolabial fold (NLF).<br>▪ Extremity weakness, incoordination, pronator drift (weakness of arm), hemiparesis, hemiplegia, monoparesis, monoplegia, paresis, paralysis of limb(s).<br>▪ Numbness, tingling, burning, prickly sensation, paresthesia, hemianesthesia, dysthesia, or sensation deficit anywhere on the face or an extremity.<br>▪ 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 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.<br><br>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

### 3.2.1 Death adjudication

A. The data analyst/programmer supplies the medical record numbers, name, birth date, sex, date of death, and death certificate 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 at both sites (KPNC and KPSC) 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' cardiovascular 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. The Data Abstraction Checklist (Appendix 3.1) will be completed for each study ID, by the data abstractor and will serve as the coversheet for the documentation packet that is sent to the physician adjudicator.

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

- Death certificate (including underlying and contributing causes) or, if unavailable in the chart, death certificate diagnoses/codes obtained from the databases.
- 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 cardiovascular 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-Cardiovascular 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

- Cardiovascular 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' cardiovascular status charted within 3 years prior to the date of death.

- **Other data**:
  - CODE Blue Notes (if not included in progress notes)

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.

C. All documentation will be redacted such that no personal identifying information is visible (e.g. patient names, provider names, MRNs, dates, locations) and no information is available regarding which type of antibiotic (amoxicillin or azithroymycin) 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. For paper documents (older cases, typically prior to 2008), records will be scanned and saved as pdf files and redacted as above. The study ID will be added electronically to each document included for review of cause of death or indication of use. The documentation for each study ID will be packaged into a pdf file, with the Data Abstraction Checklist as the coversheet. 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 KPNC and KPSC.

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

D. 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 KPNC-KPNC 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:
   i. Cause of death: Definite CV death, Possible CV death, Non-CV death, and Unclassifiable.
   ii. If CV death, define subtype: SCD, MI/CHD, HF, Stroke, CV hemorrhage, or other CV death type.

E. 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.

3.2.2 Validation of indication of use for antibiotic

A. The data analyst/programmer will supply the antibiotic prescription (rx) date and type (amoxicillin or azithromycin) for each study ID.

B. The data abstractors will locate the available medical chart documentation that indicates the indication for the particular antibiotic rx. The indication will first be categorized as:

- infection
- prophylactic (including dental)
- unable to tell

When the indication for use is "infection", it will be further classified into the following categories:

- Pneumonia
- COPD
- Pyrexia unkown origin
- Other serious infections
    - Cardiac infections
    - Brain/spinal infections
    - Blood infections
    - Other serious infections
- Ear-nose-throat
- Bronchitis
- Respiratory Symptoms
- Other respiratory
- Gastrointestinal
- Genitourinary
- Skin/soft tissue/joint/bone
- Wounds
- Type of infection not indicated

The data will be recorded on the Data Abstraction Checklist Form by the medical record abstractor.

C. The indication of use data will be data entered by the Project Manager and merged with the programmed indication of use for comparative analyses.

### 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, 50 drawn from each site) 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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