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| **Protocol Title:** | Post-Marketing Observational Surveillance Study to Evaluate the Occurrence of Acute Myocardial Infarction in Adults 18 Years of Age and Older Who Receive HEPLISAV-B® Compared with Another Hepatitis B Vaccine |
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## LIST OF ABBREVIATIONS

| Abbreviation or Term | Definition |
|---|---|
| ACIP | Advisory Committee on Immunization Practices |
| AMI | acute myocardial infarction |
| CAD | coronary artery disease |
| CK-MB | creatine kinase MB isoform |
| cTn | cardiac troponin |
| DMC | Data Monitoring Committee |
| ECG | electrocardiogram |
| ED | emergency department |
| FDA | Food and Drug Administration |
| HBsAg | hepatitis B surface antigen |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| HR | hazard ratio |
| ICD | International Classification of Diseases |
| ICD-10-CM | International Classification of Diseases, 10th Revision, Clinical Modification |
| IPTW | inverse probability of treatment weighting |
| KPSC | Kaiser Permanente Southern California |
| LBBB | left bundle branch block |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRV | measles, mumps, rubella and varicella vaccine |
| mV | millivolt(s) |
| NSTEMI | non-ST elevation myocardial infarction |
| PCI | percutaneous coronary intervention |
| RDW | research data warehouse |
| RIPC | Regional Immunization Practice Committee |
| Sec | seconds |
| STD | sexually transmitted disease |
| STEMI | ST elevation myocardial infarction |
| ST-T | ST-segment-T-wave |
| URL | upper reference limit |

## 1.0 STUDY SUMMARY

Hepatitis B is a vaccine-preventable viral infection causing substantial morbidity and mortality. In 2015, there were an estimated 21,900 new acute cases and up to 2.2 million people living with chronic hepatitis B disease in the U.S. [1]. Hepatitis B vaccination is recommended for adults at risk through sexual exposure, percutaneous or mucosal exposure, travelers, and those with hepatitis C infection, HIV infection, or diabetes mellitus [2, 3]. Available hepatitis B vaccines require 3 doses over 6 months, but coverage has been low (eg, <25% of persons with diabetes in 2015) [4].

HEPLISAV-B is a hepatitis B vaccine developed by Dynavax, comprised of recombinant yeast cell-derived hepatitis B surface antigen (HBsAg) and a proprietary 22-mer phosphorothioate oligodeoxynucleotide adjuvant, 1018 [5]. HEPLISAV-B vaccine is approved for prevention of hepatitis B virus infection in adults aged 18 years and older. HEPLISAV-B induced higher and earlier seroprotection than comparator vaccine Engerix-B® in Phase 3 trials, and requires only 2 doses over 1 month. In pre-licensure clinical trials, the rates of serious adverse events and events leading to study discontinuations were similar between HEPLISAV-B and Engerix-B, except for a numerical imbalance in events coded with the Medical Dictionary for Regulatory Activities (MedDRA) preferred term of *acute myocardial infarction* (AMI) in a single trial, HBV-23 (HEPLISAV-B: 0.25% [n = 14]; Engerix-B: 0.04% [n = 1]) [6]. Based on a comprehensive assessment, the observed numerical difference between treatment groups in the occurrence of events coded to the MedDRA preferred term *acute myocardial infarction* in HBV-23 is an isolated finding in the HEPLISAV-B database that appears most likely explained by random variation resulting in an unexpectedly low number of events observed in the Engerix-B group in HBV-23. This observational post-marketing surveillance study is being conducted to confirm the lack of association of HEPLISAV-B with myocardial infarction and cardiovascular outcomes.

This observational surveillance study will take place at Kaiser Permanente Southern California (KPSC), a large integrated health care organization serving approximately 4.4 million highly diverse members. KPSC has extensive experience in vaccine safety and effectiveness studies. In this non-randomized cluster design, HEPLISAV-B will be used exclusively at approximately 7 medical centers while another hepatitis B vaccine will be used exclusively at 8 other medical centers. Approximately 25,000 adult patients will receive HEPLISAV-B and approximately 25,000 adult patients will receive the comparator vaccine. Patients will be followed for occurrence of AMI through their electronic health records for 13 months.

The occurrence of AMI in patients who receive at least 1 dose of HEPLISAV-B will be compared with patients who receive at least 1 dose of the comparator hepatitis B vaccine. The number of vaccines administered and the number of suspected (unconfirmed) AMI will be

reported. Two interim comparisons of unconfirmed AMIs between vaccine groups will be conducted. The final analysis will be based on a Cox proportional hazards model employing inverse probability of treatment weighting (IPTW). Potential confounding factors with respect to cardiovascular disease risk factors in the use of the 2 vaccines will be adjusted for in data analyses. An independent data monitoring committee (DMC) will review interim and final analyses.

## 2.0 INTRODUCTION

Hepatitis B is a viral infection causing substantial morbidity and mortality. In 2015, there were an estimated 21,900 new acute cases, and an estimated 850,000 to 2.2 million people living with chronic hepatitis B disease in the U.S., with many unaware of infection [1]. The risk of developing chronic disease after infection is 90% in infants, 25% to 50% in children, and 6% to 10% in adults [7, 8]. Asian Americans and Pacific Islanders comprise more than half of Americans living with chronic hepatitis B. Approximately 1% of acute hepatitis B infections result in liver failure and death, and of those with chronic disease, 15% to 25% are at risk of death from cirrhosis or hepatocellular carcinoma [9-12].

Most new infections of hepatitis B are in adults ages 30 years and older, as the younger population has been largely protected since 1991 with universal hepatitis B vaccination of infants and catch up vaccination of adolescents [1, 13]. Hepatitis B vaccination has been recommended since 1981 for adults at higher risk of exposure, including sexual exposure (unprotected sex with an infected partner, multiple sexual partners, men who have sex with men); percutaneous or mucosal exposure (injection drug use, chronic kidney disease, healthcare workers); travelers to countries with a high prevalence of hepatitis B; and persons with chronic liver disease, hepatitis C, or human immunodeficiency virus [2]. As persons with diabetes mellitus have an increased risk of exposure if diabetes-care equipment is shared, they should be vaccinated for hepatitis B if younger than 60 years of age [3, 4].

Approved single-antigen hepatitis B vaccines for adults include Recombivax HB (Merck) and Engerix-B (GlaxoSmithKline) [14]. These are comprised of recombinant hepatitis B surface antigen (HBsAg) with an aluminum salt adjuvant and require 3 doses over 6 months. Coverage of hepatitis B vaccination has remained low in adults. In 2015, 24.6% of adults age 19 years or older were vaccinated with at least 3 doses. Among persons with diabetes ages 19-59 years of age, 24.4% were vaccinated with at least 3 doses [15, 16].

Dynavax has developed HEPLISAV-B for hepatitis B vaccination of adults. HEPLISAV-B is a hepatitis B vaccine comprised of recombinant yeast cell-derived HBsAg and a proprietary 22-mer phosphorothioate oligodeoxynucleotide adjuvant, 1018 [5]. Two doses of HEPLISAV-B are

required, with the second dose 1 month after the first; this schedule may reduce barriers and improve vaccination coverage of adults. Furthermore, HEPLISAV-B has demonstrated significantly greater and earlier seroprotection compared to Engerix-B, including in persons with diabetes.

Safety data from adults who received at least 1 dose of HEPLISAV-B in pre-licensure clinical trials have demonstrated a similar safety profile when compared to the licensed hepatitis B vaccine, Engerix-B. Adverse events were generally mild and infrequent. The rates of serious adverse events and events leading to study discontinuations were also similar between HEPLISAV-B and Engerix-B except for a numerical imbalance in events coded with the Medical Dictionary for Regulatory Activities (MedDRA) preferred term of *acute myocardial infarction* (AMI) in a single trial, HBV-23 (HEPLISAV-B: 0.25% [n = 14]; Engerix-B: 0.04% [n = 1]). The myocardial infarctions occurred in subjects in whom such events would be expected based on their high prevalence of baseline cardiovascular risk factors, occurred randomly with no temporal relationship to time of vaccine administration, occurred at lower than expected incidence rates, and were not related to a persistent inflammatory state or an autoimmune condition [6]. Based on the totality of the data, the imbalance was most likely due to random variation in the small number of events reported but did not unequivocally prove no increase in risk. However, this risk of acute myocardial infarction will be monitored in the post-marketing observational surveillance study described in this protocol.

## 3.0 OBJECTIVE

The primary objective of this post-marketing observational surveillance study is to compare the occurrence of AMI in recipients of HEPLISAV-B with recipients of another hepatitis B vaccine.

## 4.0 STUDY DESIGN

### 4.1 Study Setting

This study will be conducted by Kaiser Permanente Southern California (KPSC). KPSC is a large integrated health care organization and represents the largest Kaiser Permanente region in the U.S. KPSC spans a vast geographic area, covering a distance of over 230 miles between Bakersfield in the north and San Diego in the south. KPSC has over 7,000 physicians, 15 hospitals and 225 medical offices and serves approximately 4.4 million members with diverse ethnic and socioeconomic backgrounds largely representative of the underlying population [17]. Health plan members enroll through their employer or a family member's employer, through individual and family plans, or through state or federal programs. KPSC utilizes a comprehensive electronic health record system to track members' healthcare encounters.

The KPSC Center for Vaccine Safety and Effectiveness Research conducts research with real-world implications. In partnership with clinicians, academics, federal funders (eg, the Centers for Disease Control and Prevention, the U.S. Food and Drug Administration (FDA), and the National Institutes of Health), and industry sponsors, investigators conduct a wide range of studies, from the incidence and outcomes of vaccine-preventable disease to the safety and effectiveness of vaccines. Published studies include the post-licensure safety of measles, mumps, rubella, varicella vaccine (MMRV) [18], autoimmune conditions following quadrivalent human papillomavirus vaccine [19], safety of quadrivalent meningococcal conjugate vaccine [20], safety of zoster vaccine in the Vaccine Safety Datalink (VSD) [21], and hepatitis B testing and vaccination [22]. In addition, KPSC has used a modern advanced method, inverse probability of treatment weighted (IPTW) estimation, to adjust for potential selection bias in observational studies, including a study of the safety of testosterone replacement based on cardiovascular outcomes [23] and an evaluation of the safety of seasonal influenza vaccine among hospitalized surgical patients [24].

The KPSC Regional Immunization Practice Committee (RIPC) makes recommendations to ensure appropriate use of vaccination and implementation of new Advisory Committee on Immunization Practices (ACIP) recommendations within medical centers. KPSC has a proactive immunization program that includes: 1) alerts on the electronic health record that indicate which vaccines are due; 2) a policy of vaccinating at all visits, not just well visit or physical exam appointments; and, 3) giving recommended immunizations on a walk-in basis without appointment at no-cost nurse visits. Since all ACIP-recommended immunizations are free to members at any visit regardless of co-pay status, there is an incentive to receive immunizations within the KPSC system.

KPSC maintains comprehensive electronic health records to integrate medical information including diagnosis and procedure codes, immunizations, medications and laboratory results from outpatient, emergency department (ED), and inpatient settings within the KPSC network. All details of a patient encounter are entered into the electronic health record at the point of care. Events are coded using standard *International Classification of Diseases* (ICD) codes. Events occurring in the outpatient setting are captured directly from provider input. Those in the emergency department and inpatient settings are coded by professional coders, based on review of the health record. There is strong incentive for KPSC members to seek care within the health plan system; however, members may seek emergency medical care from outside healthcare providers. For outside facilities to be reimbursed, claims must include documentation substantiating a clinical diagnosis, which is entered into administrative data systems. In addition, KPSC is part of the Care Everywhere Network, which facilitates sharing of health records between organizations using the Epic electronic health record system. Thus, the capture of care delivered to KPSC members by electronic data is comprehensive.

## 4.2 Overview of Study Design

This is an observational surveillance study of adults aged 18 years and older who are enrolled in KPSC and receive a hepatitis B vaccination during the study period. This design will provide real world evidence on the risk of AMI in a highly diverse population vaccinated with HEPLISAV-B. Approximately 25,000 patients will receive HEPLISAV-B and approximately 25,000 patients will receive another hepatitis B vaccine according to a non-randomized cluster design. HEPLISAV-B will be used exclusively at approximately 7 medical centers in family practice and internal medicine departments, while another hepatitis B vaccine will be used exclusively at the other 8 medical centers in family practice and internal medicine departments. For each patient, the index dose is defined as the first dose of HEPLISAV-B during the study vaccination period given in family practice and internal medicine departments at medical centers assigned to the HEPLISAV-B cohort, or the first dose of hepatitis B comparator vaccine (non-dialysis formulation) during the study vaccination period given in family practice and internal medicine departments at medical centers assigned to the comparator cohort. Each individual patient will be passively followed through their electronic health records for 13 months after the index vaccine dose during the study period. The occurrence of AMI in patients who receive at least 1 dose of HEPLISAV-B at the medical centers in the HEPLISAV-B arm will be compared with patients who receive at least 1 dose of another hepatitis B comparator vaccine at medical facilities in the comparison arm. Hospitalized AMI events, based on *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM) predefined codes (Appendix 1), will be identified from electronic health records from inpatient care. The electronic health records of potential AMI events will be abstracted and redacted of hepatitis B vaccination information. Events will be independently adjudicated by two cardiologist reviewers masked to the vaccine exposure, with a third cardiologist to review cases with differing conclusions.

## 4.3 Selection of Target Medical Centers

To reduce potential selection bias resulting from physician's or patient's decisions based on a patient's risk profile, HEPLISAV-B will be provided to selected medical centers as the sole vaccine for adult use in routine clinical care in family practice and internal medicine departments. Thus, providers and patients will rarely have a choice of hepatitis B vaccines, emulating a non-randomized clustered design. HEPLISAV-B will be provided exclusively to approximately 7 medical centers for adult use in their affiliated family practice and internal medicine departments. The remaining 8 medical centers and affiliated family practice and internal medicine departments will continue to use their current hepatitis B vaccine exclusively.

Site selection for the study is based on clustering of medical centers and logistics. The electronic health record in KPSC is supported in clusters of medical centers. Each medical center consists of a hospital and associated medical office buildings. When alerts or order sets are created or modified in the electronic health record, they are usually done across all clusters. In the case of this study, changes will be made in select clusters but not others, with the order sets for adult hepatitis B vaccine for family practice and internal medicine departments changed from the current vaccine to HEPLISAV-B. Target medical centers are also selected based on their proximity to our regional research headquarters in Pasadena, since study staff will need to travel to train and monitor clinic staff in HEPLISAV-B vaccine management activities, as is standard conduct for any new vaccine. We will also select the medical centers in which our clinical investigators work so that they can serve as advocates and points of contact for clinical staff.

Prior to initiation of the study, vaccine management (eg, procurement of non-formulary vaccine) and training activities will be conducted for target medical centers including educational and operational outreach. During the study, regular vaccine uptake reports will be generated as well as monitoring of the proper usage and administration of HEPLISAV-B through standard vaccine management operations.

Overall, the rate of adult hepatitis B vaccination at the target medical centers has been similar to those in the comparator medical centers (Table 4-1). In 2015, approximately 55% overall were age 50 years or older. Recipients at target and comparator medical centers were similar in terms of age distribution, sex, history of diabetes and history of AMI. There were modest differences by race/ethnicity. The recipients in both the target and comparator medical centers had similar risk of AMI in the 12 months following the first hepatitis B vaccination. Across both cohorts, approximately 45% of persons with AMI were identified through claims submitted for care delivered outside of KPSC facilities.

## 4.4 Study Period

The study will begin with administration of the first dose of HEPLISAV-B and is contingent upon ACIP and RIPC recommendation of HEPLISAV-B. The study vaccination period will occur until 25,000 patients have received at least 1 dose of HEPLISAV-B, expected to take approximately 10.5 months based on historical vaccination trends. Each patient will be followed until the earliest of disenrollment from KPSC (not due to death and allowing for a 31-day gap in membership), death from any cause, or the end of the 13-month follow-up period after the index dose given during the vaccination period.

**Table 4-1: Adult Hepatitis B Vaccine Recipients: Active Member at First Dose Date, 2015 by Target (HEPLISAV-B) and Comparator Medical Centers**

| | 8 Comparator Medical Centers | 7 Target Medical Centers | Total |
|---|---|---|---|
| **N** | 47,964 | 45,766 | 93,730 |
| | | | |
| **Age (years)** | | | |
| **Mean (SD)** | 49.1 (10.83) | 49.0 (10.90) | 49.1 (10.86) |
| | | | |
| **Sex** | n (%) | n (%) | n (%) |
| **Female** | 23,229 (48.43) | 22,400 (48.94) | 45,629 (48.68) |
| **Male** | 24,735 (51.57) | 23,366 (51.06) | 48,101 (51.32) |
| | | | |
| **Race/Ethnicity** | n (%) | n (%) | n (%) |
| **Asian** | 4043 (8.43) | 5810 (12.7) | 9853 (10.51) |
| **Black** | 4027 (8.4) | 4742 (10.36) | 8769 (9.36) |
| **Multiple** | 242 (0.5) | 190 (0.42) | 432 (0.46) |
| **Native Am/Alaskan** | 152 (0.32) | 127 (0.28) | 279 (0.3) |
| **Others** | 340 (0.71) | 432 (0.94) | 772 (0.82) |
| **Pacific Islander** | 728 (1.52) | 691 (1.51) | 1419 (1.51) |
| **Unknown** | 1107 (2.31) | 829 (1.81) | 1936 (2.07) |
| **White** | 14,482 (30.19) | 7914 (17.29) | 22,396 (23.89) |
| **Hispanic** | 22,843 (47.63) | 25,031 (54.69) | 47,874 (51.08) |
| | | | |
| **Had type 2 diabetes history prior to the first dose** | n (%) | n (%) | n (%) |
| **No** | 9851 (20.54) | 10,094 (22.06) | 19,945 (21.28) |
| **Yes** | 38,113 (79.46) | 35,672 (77.94) | 73,785 (78.72) |
| | | | |
| **Had AMI history between 01/01/2010 to first dose date** | n (%) | n (%) | n (%) |
| **No** | 47,359 (98.74) | 45,260 (98.89) | 92,619 (98.81) |
| **Yes** | 605 (1.26) | 506 (1.11) | 1111 (1.19) |
| | | | |
| **Had hospitalized AMI in 12 months after first dose date** | n (%) | n (%) | n (%) |
| **No** | 47,891 (99.85) | 45,713 (99.88) | 93,604 (99.87) |
| **Yes** | 73 (0.15) | 53 (0.12) | 126 (0.13) |

# 5.0 STUDY POPULATION

## 5.1 Recommendations for Vaccination

The ACIP recommends hepatitis B vaccination for adults at increased risk of hepatitis B through sexual exposure, percutaneous or mucosal exposure, and travelers to countries with high or intermediate prevalence of hepatitis B [2-4]. Universal vaccination is recommended in settings in which a high proportion of persons are likely to be at risk (eg, STD/HIV testing and treatment facilities, drug abuse treatment and prevention facilities, etc). Persons with diabetes mellitus are also recommended for vaccination if age 19 to 59 years, or if age 60 years or older at the discretion of the health provider.

## 5.2 Hepatitis B Vaccination of Adults With Diabetes

In 2014, KPSC implemented an electronic alert and reminder embedded in electronic health records prompting providers to order hepatitis B vaccine for previously unvaccinated adults with diabetes [25]. This resulted in a significant increase in completion of the 3-dose series among adults with diabetes, although coverage with all 3 doses remained low (<30%). In 2015, adults with diabetes comprised approximately 79% of the 93,730 KPSC members who received a dose of hepatitis B vaccine (Table 4-1).

## 5.3 Study Inclusion and Exclusion Criteria

### 5.3.1 Inclusion Criteria

1. Received at least one dose of hepatitis B vaccine (either HEPLISAV-B in HEPLISAV-B arm, or non-dialysis formulation hepatitis B comparator vaccine in comparator arm) at KPSC during study vaccination period.
2. Enrolled as a KPSC member at time of hepatitis B vaccination during the study vaccination period.
3. Age 18 years or older at time of hepatitis B vaccination during study vaccination period.
4. Received hepatitis B vaccine at KPSC family practice or internal medicine departments, or in urgent care or nurse clinics affiliated with those departments.

### 5.3.2 Exclusion Criteria

1. Received peritoneal dialysis or chronic hemodialysis in the 3 months prior to index hepatitis B vaccination
2. Received all doses of their hepatitis B vaccine series in KPSC departments other than family practice or internal medicine or their affiliated departments as described above

## 5.4 Number of Subjects

HEPLISAV-B recipients: 25,000 patients

Other hepatitis B vaccine recipients: approximately 25,000 patients

The exact number of recipients will depend on the number of patients vaccinated with hepatitis B vaccine at the target and other medical centers during the study period.

# 6.0 STUDY METHODS

## 6.1 Exposure of Interest

The exposure of interest for this study is the index dose of hepatitis B vaccine (Section 4.2).

Hepatitis B vaccine exposure will be assigned at the cluster level. At target medical centers, providers in family practice and internal medicine departments will only be able to order HEPLISAV-B for hepatitis B vaccination of adult patients not on dialysis. Patients receiving an index dose of HEPLISAV-B in family practice or internal medicine departments will be included in the HEPLISAV-B cohort.

At non-target medical centers, providers in family practice or internal medicine departments will only be able to order a hepatitis B comparator vaccine other than HEPLISAV-B. Only patients receiving an index dose of comparator vaccine in family practice or internal medicine departments will be included in the comparator cohort. In recent years at KPSC, Engerix-B has been used for routine vaccination, while Recombivax-HB (Dialysis Formulation) has been used for dialysis patients. As dialysis patients are not included in this study, the comparator is expected to be Engerix-B.

Adults vaccinated with one or more doses of comparator hepatitis B vaccine prior to study initiation who did not complete the full 3-dose regimen may be given HEPLISAV-B if they

receive care at a HEPLISAV-B target medical center. These patients will be included in the primary analysis, while exploratory analyses will seek to identify differential outcomes between these patients and those who received their first dose of hepatitis B vaccine during the study period (Section 7.6).

While providers are advised to follow ACIP and RIPC recommendations, decisions regarding the appropriateness of administering a hepatitis B vaccination and the vaccination schedule will be determined by the healthcare providers and patients. Vaccine exposure will be identified retrospectively from the electronic health records, including vaccine, dose, manufacturer, and lot number entered at the time of vaccination. Data on vaccine exposure will be checked using quality control procedures described in Section 8.2 below.

## 6.2 Outcome of Interest

The outcome of interest is the first occurrence of AMI during the 13-month follow-up period for each patient.

### 6.2.1 Identification of Unconfirmed AMI

Hospitalizations with a diagnosis of AMI based on ICD-10-CM codes from databases of hospital discharge records and billing claims will be identified (Appendix 1). AMI cases will be extracted from any diagnosis position. The occurrence of AMI (ICD-10 I21.x) or subsequent AMI within 4 weeks of a previous AMI (ICD-10 I22.x) will be identified from inpatient encounters. ED encounters with these codes will be considered potential AMI if the patient was hospitalized or if the patient died the same or next day. The first AMI occurrence per individual within the study period will be considered a potential event. Historical AMI (ICD-10 I25.2) will not be considered a potential event.

Experienced staff members at KPSC will obtain relevant components from the electronic health record for potential AMI events. Information will be collected from 3 days prior to the potential AMI event date to 7 days following the potential AMI event date. Sections of the electronic health record to be collected if available will include:

- ED notes and orders
- Admission notes
- Transfer summary if seen at an outside facility
- Visit note associated with diagnosis date
- Consultant notes
- History and physical notes
- Laboratory results

- Cardiac procedures
- Imaging reports
- Discharge summary and final discharge note
- Death summary

### 6.2.2 Adjudication

We will adjudicate potential AMI events identified from any diagnosis position using successfully implemented methods from previous studies: Cardiovascular Research Network (CVRN) [26], Coronary Artery Risk Development in Young Adults (CARDIA) [27], Cardiovascular Health Study (CHS) [28], Atherosclerosis Risk in Communities (ARIC) [29], and Women's Health Initiative [30]. Abstracted information will be adjudicated independently by 2 trained cardiologist reviewers masked to vaccine exposure. Cases with disagreement will be reviewed by a third cardiologist. Adjudication will follow standardized criteria based on changes in troponin or other cardiac biomarker levels, cardiac signs and symptoms, clinical readings of the 12-lead ECGs, and imaging evidence, as outlined by the Third Universal Definition of Myocardial Infarction [31]. All eligible hospitalized events will be classified as either definite, probable, unable to determine, or not AMI [29, 32]. Events will be considered "probable" if the available information from the medical record strongly suggests an AMI but some criteria required for a definite AMI are missing. Detailed adjudication criteria are provided in Appendix 1.

### 6.2.3 Definition of primary AMI outcome

For the primary outcome, AMI will be defined as definite plus probable Type 1 AMI [31, 32]. A Type 1 AMI is due to a primary coronary event, such as plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe coronary artery disease (CAD) but on occasion non-obstructive or no CAD.

## 6.3 Covariates

Patient characteristics will be identified through electronic health records. Covariates to be considered will include:

1. Age, sex, race / ethnicity, socioeconomic status
2. Duration of membership prior to index dose of hepatitis B vaccine
3. Diabetes status in year prior to index dose of hepatitis B vaccine
4. Prior AMI occurrence or coded history of AMI in year prior to index dose of hepatitis B vaccine
5. Other cardiovascular disease risk factors in year prior to index dose of hepatitis B vaccine (smoking, hypertension, HbA1c levels, and serum LDL-C levels)
6. Other co-morbidities in year prior to index dose of hepatitis B vaccine (dyslipidemia, depression, obesity, coronary artery disease including revascularization, chronic kidney disease, cancer, rheumatologic conditions, liver disease)
7. Other conditions included in the Charlson co-morbidity index in year prior to index dose of hepatitis B vaccine
8. Cardiovascular disease medications in year prior to index dose of hepatitis B vaccine (oral anticoagulants, antiplatelet agents, heparin, antihypertensive meds, statins, insulin, oral hypoglycemic agents)
9. Hepatitis B vaccination in year prior to index dose of hepatitis B vaccine
10. Healthcare utilization in year prior to index dose of hepatitis B vaccine
11. Concomitant receipt of other vaccines, eg, influenza or pneumococcal
12. Vaccinations within the 13-month follow-up period after index dose of hepatitis B vaccine

As these covariates are comprised of basic characteristics, risk factors, and important co-morbidities that are usually captured during healthcare encounters, and patients have strong incentive to obtain care within KPSC, it is expected that data will be reasonably complete.

## 6.4 Data Sources and Claims

The study will be conducted using the KPSC Research Data Warehouse (RDW) which supports external and internal research projects conducted in the KPSC Department of Research and Evaluation as well as patient care management programs. The data warehouse is an integrated

and comprehensive resource of electronic health records. It contains information as far back as 1980, including records related to membership, benefits, utilization, pharmacy, vital signs, laboratory, vaccines, geocoding, mortality, and procedures. Data are linked through a unique medical record number assigned to each member of the health plan.

Care received outside of KPSC, including emergency care for patients experiencing AMI, is integrated into the RDW. If a patient is transferred to KPSC, then records for care at the outside facility, such as ECG strips and biomarker levels, are usually transferred and incorporated into the patient's health records. Patients who are not transferred often have documentation incorporated as part of the claims process or through Care Everywhere. Patients with potential AMI diagnoses who are missing records will be contacted and asked for permission to retrieve their medical records from non-KPSC facilities.

Because claims can take several months to be incorporated into electronic health records, a 3-month lag period will be used to allow for data settling. Thus, data will be reported through the date 3 months prior to the date of the data pull for the report (Section 6.5). The 3-month lag is essential to avoid bias in the number of AMI events, as there may be differences between target and comparator medical centers in the proportion of events derived from claims.

## 6.5 Data Monitoring

An independent Data Monitoring Committee (DMC) will be established, comprised of a cardiovascular disease epidemiologist, a biostatistician familiar with vaccine post-licensure safety studies, and a vaccine safety expert. The committee members will be proposed and retained by KPSC. The DMC will review quarterly reports of vaccine accrual and aggregated number of unconfirmed AMI cases, and the interim and final analyses, as specified below.

The number of patients receiving any dose of hepatitis B vaccine and the aggregate number of unconfirmed AMIs will be compiled monthly to monitor assumptions used to determine study duration (vaccine uptake and AMI event rates). The number of vaccines will be identified by cluster and age strata (<50 years and ≥50 years) and will be available beginning 3 months after the first HEPLISAV-B dose is administered. The number of AMI events will be aggregated across all medical centers and not by vaccine group, to avoid 'spending' type 1 error. As noted above, a 3-month lag period will be used to allow incorporation of claims data (Section 6.4), so the number of AMI events will first be available beginning 4 months after the first HEPLISAV-B dose (1 month of patient follow-up plus 3 months for data settling). After this 4-month period, KPSC will provide the reports to the sponsor monthly and to the DMC quarterly. These data will be used to monitor uptake and event rates that can be compared to the assumptions in the sample size calculation and help anticipate the need for extension of the study, if necessary. If HEPLISAV-B accrual is slower than anticipated or if observed AMI event rates are lower than

anticipated, the number of patients receiving HEPLISAV-B could be increased, along with an equivalent number of patients receiving comparator vaccine, by extending the study vaccination period.

# 7.0 STATISTICAL ANALYSES & CONSIDERATIONS

## 7.1 Interim Analyses

Interim analyses will be conducted comparing unconfirmed Type 1 AMI in the principal discharge diagnosis position in the HEPLISAV-B and comparator vaccine groups using adjusted multivariable Cox proportional hazards models. The first interim analysis will take place after 41 events have occurred, which is anticipated within approximately 12 months after study start. An interim report is expected to be available to the FDA by 31 August 2019. A second interim analysis will be conducted after 68 events have occurred, anticipated to occur within 18 months after study start. A second interim report is expected to be available to the FDA by 29 February 2020.

Based on review of the interim results, the DMC may recommend completion of the study as planned. Alternatively, the DMC may recommend extension of the study. If the crude estimate of the hazard ratio (HR) based on un-adjudicated events is 2.5 or greater with a lower bound of the 95% confidence interval greater than 1, Dynavax will notify the FDA immediately with written follow-up as appropriate, and a formal comparison of confirmed AMIs will be conducted and reported to the DMC. The HR threshold of 2.5 was selected based on the level of increased risk we would have the power to detect.

At each interim analysis, a conditional power analysis will be performed using AMI events to estimate the power to reject a hazard ratio of 2.0 or greater on the final analysis, conditional on the data observed up to that point. Conditional power will be computed under three scenarios for the unobserved data: 1) that the observed event rates continue; 2) that future data will fit the null hypothesis of HR=2.0; and, 3) that future data will fit the hypothesis of HR=1.0. These estimates will provide a range for the likelihood that the study will definitively rule out a hazard ratio of 2.0 should it continue to completion under its original design.

A final analysis of unconfirmed Type 1 AMI events in the principal discharge diagnosis position will be conducted after the end of the 13-month follow-up for the last subject vaccinated, and a report is expected to be available to FDA by 30 September 2020. The exact timelines will depend on vaccine uptake and AMI event rates.

## 7.2 Descriptive Analysis

A descriptive analysis of baseline characteristics will be conducted comparing HEPLISAV-B and comparator vaccine recipients. Variables described in Section 6.3 will be extracted from electronic health records. Categorical variables will be presented as absolute numbers and percentages with p-values for the $\chi^2$ test. Continuous variables such as age in years will be presented as the mean with standard deviation and interquartile ranges, with p-values for the two-sample t-test or Wilcoxon rank-sum test, as appropriate. The rates of occurrence of first AMI event during the study period among HEPLISAV-B recipients and comparator vaccine recipients will be described.

A detailed flowchart of the AMI outcomes by study cluster, including total number of cases identified through the databases, reasons for exclusion, number of cases attended outside of KPSC, number of definite / probable / unable to determine (eg, medical records not available) / not a case (eg, medical records did not substantiate a clinical diagnosis), and number of AMI by type will be provided with the final analysis report.

## 7.3 Primary Analysis

For the final analysis of the primary objective, we will use a non-inferiority framework to test the null hypothesis of increased risk of Type 1 AMI among HEPLISAV-B recipients versus comparator vaccine recipients. Based on anticipated number of confirmed events, the study will have approximately 87% power to exclude a hazard ratio of 2.0 or greater (Section 7.9), testing the hypothesis: $H_0$: HR $\geq$ 2, $H_a$: HR < 2.

The rates of occurrence of first Type 1 AMI event during the study period among HEPLISAV-B recipients and comparator vaccine recipients will be compared using a Cox proportional hazards regression model employing inverse probability of treatment weighting (IPTW) [33]. The IPTW provides an assessment of the closeness of match in the weighted analysis across all variables, providing a sense of the degree of control of imbalance between the vaccine exposure groups. Two tables will be created comparing the cohort of HEPLISAV-B recipients to the cohort of recipients of the comparator vaccine. The first table will be unweighted, showing the true distribution of recipient characteristics. The second table will be weighted by the inverse probability of treatment as estimated by a propensity score model. Standardized difference scores will be used to assess whether balance of covariates is achieved between the cohorts. These 2 tables will show the effectiveness of the weighting at reducing effective differences between the cohorts.

The primary analysis will be conducted on confirmed Type 1 AMIs. Variables to consider in the propensity model are listed in Section 6.3. The primary exposure will be vaccine group

(HEPLISAV-B vs. comparator vaccine), and the outcome will be confirmed AMI. Clustering by medical center will be considered through random effects variables representing medical center. Censoring events will include end of study, disenrollment from Kaiser Foundation Health Plan (allowing for a 31-day gap in membership), and death from causes other than AMI. A hazard ratio of AMI for HEPLISAV-B versus the comparator vaccine, adjusted for potential confounding factors, and associated 95% confidence interval will be reported.

## 7.4 Sensitivity Analyses

### 7.4.1 Sensitivity Analyses Using Alternative Statistical Methods

Sensitivity analyses will be performed using alternative approaches (besides IPTW). These will include: (1) a Cox proportional hazards model adjusted for and/or stratified by propensity score; and (2) a traditional multivariable Cox proportional hazards regression model. The use of a propensity score as a stratifying or control variable permits the control of potential confounding variables with a single summary variable, reserving degrees of freedom to test the primary association. The traditional multivariable Cox model allows examination of the effect of each potential confounder on the estimate and control for many factors simultaneously. Variables to be considered in the propensity model include those considered in the primary IPTW analysis. The traditional Cox model will be adjusted for demographics and comorbidities (Section 6.3). Adjusted hazard ratios of AMI for HEPLISAV-B versus the comparator vaccine and associated 95% confidence intervals will be reported.

### 7.4.2 Interpretation of Sensitivity Analyses

It is expected that the primary analysis and the sensitivity analyses would yield similar results. Should they be discrepant, the DMC may suggest additional analyses to better understand the reason for the differences and to determine the most likely correct analysis and interpretation.

## 7.5 Secondary Analysis

A secondary analysis will be conducted comparing the rates of occurrence of Type 1 unconfirmed AMI in the principal discharge diagnosis position in the HEPLISAV-B group to a historical group of patients from the HEPLISAV-B medical centers who received comparator vaccine in 2016. Patients ages 18 years and older will be included in the historical comparison group if they were vaccinated with non-dialysis formulation hepatitis B vaccine from 01 January 2016 to 31 December 2016 in KPSC family practice and internal medicine departments included in the HEPLISAV-B group in the post-licensure safety study and were KPSC members on the day of vaccination. Patients receiving chronic dialysis in the 3 months prior to hepatitis B vaccination will be excluded. In the unlikely event that someone receives vaccine in both time

periods, they will only be included in the HEPLISAV-B cohort. Relative risk will be estimated using a Cox proportional hazards regression model with IPTW to adjust for differences in the populations, as described in Section 6.3.

If this comparison shows a significantly elevated risk for the HEPLISAV-B group, additional analyses will be performed in order to further investigate the elevated risk. We will graphically investigate the timing of the events relative to vaccination. We will perform sensitivity analyses by first dose vs. subsequent dose of hepatitis B vaccine and by concomitant vaccination status.

### 7.6 Exploratory Analyses

In exploratory analyses, we will compare the occurrence of AMI 1) in persons receiving HEPLISAV-B as their first vaccination against hepatitis B with persons receiving the comparator vaccine as their first vaccination against hepatitis B and 2) in persons receiving a first dose of HEPLISAV-B as their second or subsequent dose of hepatitis B vaccine with persons receiving the comparator vaccine as their second or subsequent dose of hepatitis B vaccine. The models will be stratified by vaccination history (initial vs. subsequent dose of hepatitis B vaccine) and alternatively, with vaccination as a covariate and/or effect modifier.

### 7.7 Model Selection Rationale

Potential confounders to include in multivariable models are listed in Section 6.3. These covariates will be assessed for their availability and ability for adjusting crude results, including an examination of their distributions and missingness. Bivariate associations of potential confounders with the outcome (AMI), exposure, and each other will be examined. For those with suggestions of imbalance with either exposure or outcome, the association between exposure and outcome will be stratified by categories of the potential confounder to look for differences across strata (potential effect modification) and influence on summary estimates of association (confounding). The variables will ultimately be selected based on a combination of the a priori decisions and a qualitative assessment of the empirical relationships. We will assess the robustness of cut-point selections and groupings and consider tightly confounded variables and their collinearity. Note that we will NOT use an algorithmic backward, forward or stepwise process, and that the results of the multivariable model should corroborate the knowledge gained during the model-building process.

### 7.8 Clustering

We will examine clustering within medical center in our data using a random effects model [34]. In our sample data based on members vaccinated in 2015, the intra-class correlation coefficient was extremely small (<.00001), which would result in a minimal impact on power. If there is

some evidence of clustering we will adjust for it in our final model using random medical center effects.

## 7.9 Power Analyses

Approximately 50,000 patients (HEPLISAV-B: 25,000; another hepatitis B vaccine: approximately 25,000) will be included in the study and the accrual is assumed to be uniform during a period of approximately 10.5 months. Each patient will be followed for up to 13 months after their first dose of HEPLISAV-B or comparator vaccine administered during the study vaccination period. A 10% loss to follow-up during the study with a uniform loss rate is assumed. Assuming no difference in the risk of AMI between the two groups, we anticipate approximately 41 events at 12 months, 68 events at 18 months, and 78 events at the end of study if the event rate is 1.5/1000 person-years. In the first interim analysis, the study will have approximately 83% power to detect a hazard ratio $\geq 2.5$ and 60% power to detect a HR $\geq 2.0$, and in the second interim analysis the study will have 81% power to detect a HR $\geq 2.0$. In the final analysis, the study will have approximately 87% power to exclude HR $\geq 2.0$. The anticipated number of events based on other event rates and the power for a non-inferiority test based on other non-inferiority margins for the final analysis is presented in Table 7-1.

**Table 7-1: Power for a Non-inferiority Test to Reject a Hazard Ratio in a Cox Proportional Hazards Model**

| Time, Months | Event rate per 1000 person-years | # Events | Power, HR = 2.0 alpha = 0.025 | Power, HR = 2.5 alpha = 0.025 | Power, HR = 3.0 alpha = 0.025 | Power, HR = 3.5 alpha = 0.025 | Power, HR = 4.0 alpha = 0.025 |
|---|---|---|---|---|---|---|---|
| 9 | 1.0 | 16 | 0.277 | 0.44 | 0.583 | 0.696 | 0.782 |
| | 1.5 | 23 | 0.388 | 0.601 | 0.757 | 0.858 | 0.918 |
| | 2.0 | 31 | 0.490 | 0.725 | 0.866 | 0.938 | 0.972 |
| 12 | 1.0 | 27 | 0.442 | 0.669 | 0.820 | 0.906 | 0.952 |
| | 1.5 | 41 | 0.603 | 0.836 | 0.941 | 0.980 | 0.994 |
| | 2.0 | 55 | 0.728 | 0.924 | 0.982 | 0.996 | 0.999 |
| 18 | 1.0 | 45 | 0.644 | 0.869 | 0.959 | 0.988 | 0.997 |
| | 1.5 | 68 | 0.814 | 0.965 | 0.995 | 0.999 | 1.000 |
| | 2.0 | 90 | 0.909 | 0.992 | 0.999 | 1.000 | 1.000 |
| 24 | 1.0 | 52 | 0.705 | 0.911 | 0.977 | 0.995 | 0.999 |
| | 1.5 | 78 | 0.865 | 0.982 | 0.998 | 1.000 | 1.000 |
| | 2.0 | 104 | 0.942 | 0.997 | 1.000 | 1.000 | 1.000 |

**Assumptions:**

- Final HEPLISAV-B medical centers will be the same 7 as initially planned or will result in the same number of vaccine recipients in each arm
- Only doses given in family practice and internal medicine will be included (90% of all adult hepatitis B vaccine doses)
- Essentially all doses in HEPLISAV-B medical centers in family practice and internal medicine will be HEPLISAV-B
- Accrual of both HEPLISAV-B and comparator vaccine is roughly evenly distributed through the year (primarily affects number of person-years of follow up at interim analysis)
- Total doses given annually during the study period will be ~30% fewer than the number given in 2015 (~15% decline seen from 2015 to 2016, lesser decline observed subsequently)
- 10% lost to follow-up rate during 13-month follow-up, assuming a uniform loss rate, giving an average of 1.02 person-years per recipient at the final analysis

# 8.0 DATA MANAGEMENT

## 8.1 Data Processing

Electronic health record data are extracted and maintained securely in the electronic RDW database at KPSC. The database is regularly supported with appropriate backup and recovery options. Only authorized study personnel with passwords can access the database.

Data processing in this study will be performed by programmers and analysts at KPSC using SAS (version 9.3 or higher; SAS Institute, Cary, NC). No imputation for missing data will be performed. We expect there to be a very low rate of missing data in the electronic health records. Potential AMI cases missing data required for adjudication will be reported as possible/unable to determine. Any loss to follow-up due to leaving the KPSC health plan (Section 7.3) will be addressed in data analysis by the truncation of person-time in the event rate calculations.

## 8.2 Data Quality

Quality control of data will include range and consistency checks for all study variables, with additional consistency checks for hepatitis B vaccine exposure. For example, discordant records (eg, vaccine name with wrong manufacturer or invalid lot number), HEPLISAV-B administrations in non-target medical centers, and comparator vaccine administrations in target medical centers will trigger a review of the medical records. For the planned adjudication of the

AMI events, we will rely on proven methods for obtaining necessary medical records, assembling the records into a secure PDF file for review, and storage and tracking. Potential AMI events will be individually adjudicated by 2 trained cardiologist reviewers masked to vaccine exposure using a standardized form, with a third cardiologist to review cases with disagreement (Section 6.2). An online event adjudication system will be used for collection of data elements and final adjudication decisions; appropriate, automated quality checks will be employed for ensuring complete data entry, correct skip patterns, and answer range/values. Double programming will be conducted for assignment of the cohort (vaccine group) and outcome (AMI), and all source code will be reviewed by a second analyst.

## 9.0 REGULATORY AND ETHICAL CONSIDERATIONS

The protocol will be reviewed and approved by the KPSC Institutional Review Board (IRB). All study staff with access to protected health information are trained in procedures to protect the confidentiality of subject data. Informed consent is not needed for HEPLISAV-B vaccination, as the vaccine will be approved by the U.S. FDA and recommended for eligible KPSC members as part of routine clinical care. Individual written Health Insurance Portability and Accountability Act (HIPAA) authorizations will not be required prior to initiating data collection using electronic health records. Patients who are suspected to have been treated for AMI outside the KPSC system and have incomplete records at KPSC may be contacted to obtain HIPAA authorization to request a copy of their health records from outside facilities for the AMI episode. Adverse event reporting is not required, as this is a non-interventional study based on secondary use of KPSC electronic health records. Adverse events cannot be identified spontaneously under the current methodology, so there will not be individual reporting of adverse events. The study will be conducted in accordance with the protocol, applicable regulatory requirements, and good pharmacoepidemiologic practice.

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## 10.0 SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "Post-Marketing Observational Surveillance Study to Evaluate the Occurrence of Acute Myocardial Infarction," and agree to conduct the study according to the protocol and the applicable guidelines and regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

# APPENDIX 1: DEFINITIONS AND PROCEDURES FOR IDENTIFICATION AND ADJUDICATION OF ACUTE MYOCARDIAL INFARCTION

## I. INTRODUCTION

This appendix defines terms and procedures for identification and adjudication of potential acute myocardial infarction (AMI). Section II lists the *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM) predefined codes for AMI events. Section III describes criteria based on the Third Universal Definition of Myocardial Infarction [31, 35]. Section IV lists steps for outcome classification [32]. Events will be independently adjudicated by two separate cardiologist reviewers, with a third cardiologist to review cases with disagreement. Cardiologist reviewers will be masked to the exposure.

## II. ICD-10 Codes for Acute Myocardial Infarction

## Table A-1: ICD-10 Codes for Acute Myocardial Infarction

| ICD-10 Code | Description |
|---|---|
| I21.0 | ST elevation (STEMI) myocardial infarction of anterior wall |
| I21.01 | ST elevation (STEMI) myocardial infarction involving left main coronary artery |
| I21.02 | ST elevation (STEMI) myocardial infarction involving left anterior descending coronary artery |
| I21.09 | ST elevation (STEMI) myocardial infarction involving other coronary artery of anterior wall |
| I21.1 | ST elevation (STEMI) myocardial infarction of inferior wall |
| I21.11 | ST elevation (STEMI) myocardial infarction involving right coronary artery |
| I21.19 | ST elevation (STEMI) myocardial infarction involving other coronary artery of inferior wall |
| I21.2 | ST elevation (STEMI) myocardial infarction of other sites |
| I21.21 | ST elevation (STEMI) myocardial infarction involving left circumflex coronary artery |
| I21.29 | ST elevation (STEMI) myocardial infarction involving other sites |
| I21.3 | ST elevation (STEMI) myocardial infarction of unspecified site |
| I21.4 | Non-ST elevation (NSTEMI) myocardial infarction |
| I21.9 | Acute myocardial infarction, unspecified |
| I21.A | Other type of myocardial infarction |
| I21.A1 | Myocardial infarction type 2 |
| I21.A9 | Other myocardial infarction type |
| I22.0 | Subsequent ST elevation (STEMI) myocardial infarction of anterior wall |
| I22.1 | Subsequent ST elevation (STEMI) myocardial infarction of inferior wall |
| I22.2 | Subsequent non-ST elevation myocardial infarction (NSTEMI) |
| I22.8 | Subsequent ST elevation (STEMI) myocardial infarction of other sites |
| I22.9 | Subsequent ST elevation (STEMI) myocardial infarction of unspecified site |

## III. CRITERIA FOR AMI

According to standard definitions, a diagnosis of AMI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia [31, 35].

### 1. Type 1

AMI due to primary coronary event, such as plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

Detection of a rise and/or fall of [cardiac biomarker] values (preferably cTn, alternatively CK-MB) with at least 1 value above the 99th percentile URL AND at least 1 of the following:

a. Symptoms and signs of myocardial ischemia (eg, chest discomfort, upper extremity discomfort, mandibular discomfort, or epigastric discomfort, dyspnea, fatigue, nausea, diaphoresis, syncope)

b. New ischemic ECG changes (significant ST-T changes) or new LBBB:

   i. New (or presumed new) ST elevation at the J point in 2 contiguous leads with the following cut points: $\geq$0.1 mV in all leads other than leads V2 to V3 where the following cut points apply: $\geq$0.2 mV in men $\geq$40 y of age; $\geq$0.25 mV in men <40 y of age, or $\geq$0.15 mV in women; OR

   ii. New (or presumed new) horizontal or down-sloping ST-segment depression $\geq$0.05 mV in 2 contiguous leads and/or T inversion $\geq$0.1 mV in 2 contiguous leads with prominent R wave or R/S ratio >1; OR

   iii. New (or presumed new) LBBB pattern on ECG

c. Development of pathological Q waves (new or presumed new Q waves)

   i. Q wave in leads V2 to V3 $\geq$0.02 sec or QS complex in leads V2 and V3; OR

   ii. Q wave $\geq$0.03 sec and >0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4 to V6 in any 2 leads of a contiguous lead grouping (I, aVL; V1 to V6; II, III, aVF; V7 to V9); OR

   iii. R wave $\geq$0.04 sec in V1 to V2 and R/S $\geq$1 with a concordant positive T wave in the absence of a conduction defect.

d. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality (infarct/fixed perfusion defect on myocardial scintigraphy, regional wall motion abnormality on echocardiography/MRI) – this must be new as compared to prior non-invasive study

e. Identification of an intracoronary thrombus by angiography or autopsy.

**2. Type 2**

Ischemic imbalance - Spontaneous clinical syndrome where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand (eg, coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/bradyarrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH).

Detection of a rise and/or fall of [cardiac biomarker] values (preferably cTn, alternatively CK-MB) with at least 1 value above the 99th percentile URL AND at least 1 of the following (see Type 1 above for details):

a. Symptoms and signs of myocardial ischemia

b. New ischemic ECG changes (significant ST-T changes) or new LBBB

c. Development of pathological Q waves (new or presumed new Q waves)

d. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

**3. Type 3**

Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased (AMI death, no biomarkers)

**4. Type 4a**

PCI related AMI is arbitrarily defined by elevation of cTn values (>5 x $99^{th}$ percentile URL) in patients with normal baseline values ($\leq 99^{th}$ percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling AND at least 1 of the following (see Type 1 above for details):

a. Symptoms of myocardial ischemia
b. New ischemic ECG changes (significant ST-T changes) or new LBBB
c. Angiographic findings consistent with a procedural complication
d. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

**Type 4b**

AMI associated with stent thrombosis when detected by coronary angiography or autopsy in the setting of myocardial ischemia with a rise and/or fall of cardiac biomarkers with at least one value above the 99$^{th}$ percentile URL.

**Type 4c**

AMI associated with stent restenosis defined as ≥50% stenosis at coronary angiography or a complex lesion associated with a rise and/or fall of cTn values above the 99$^{th}$ percentile URL and no other significant obstructive CAD of greater severity following (a) initially successful stent deployment, or (2) dilation of a coronary artery stenosis with balloon angioplasty (<50%).

**5. Type 5**

Coronary artery bypass grafting (CABG) related AMI is arbitrarily defined by elevation of cardiac biomarker marker values (>10 x 99$^{th}$ percentile URL) in patients with normal baseline cTn (<99$^{th}$ percentile URL) AND at least 1 of the following:

a. New pathological Q waves or new LBBB
b. Angiographic findings consistent with a procedural complication
c. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

## IV. OUTCOME CLASSIFICATION

An online event adjudication system will be created for the adjudicators to independently assess each of the criteria above. First, adjudicators will be asked if the event meets the criteria above. Second, adjudicators will be asked to consider all available information in the

health record to categorize the outcome. For this question, events are considered "definite AMI" if they meet the criteria described above. Events are considered "probable AMI" if the available information from the medical record strongly suggest an AMI but some criteria required for a definite AMI are missing. Third, adjudicators will classify definite and probable AMI by type.

1. Does this event meet the criteria above?
    a. Yes
    b. No
    c. Unable to determine (specify reason)

2. Considering all available information in the health record, please categorize the outcome?
    a. Definite AMI
    b. Probable AMI (specify why not definite)
    c. Not AMI
    d. Unable to determine (if so indicate which criteria were unavailable)

3. If definite or probable AMI, indicate type.
    a. AMI Type 1
    b. AMI Type 2
    c. AMI Type 3
    d. AMI Type 4a
    e. AMI Type 4b
    f. AMI Type 4c
    g. AMI Type 5