# "Should COVID-19 Quantitative Antibody Titers be Implemented to Guide COVID-19 Booster Vaccinations Regardless of HIV status, Immunosuppression, or Age?"

# Study Protocol
# Version 2.5

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# 1. Synopsis

Little real-world data are available on the antibody response after COVID-19 vaccination in HIV-negative and HIV-positive individuals, the potential usage of quantitative antibody testing to determine those at greatest risk for infection while helping guide additional vaccination timing, and the antibody response of vaccine boosting in individuals with no response or low response to initial vaccinations. At the moment, clinicians must rely on general category recommendations and clinical judgement when advising their patients on the utility of vaccine boosting, as well as their level of protection from COVID vaccination. Real-world evidence is needed to better inform such decisions. The aim of this study is to assess levels of COVID-19 vaccine response through measuring surrogate Ig spike antibody measurements, to determine the rates of antibody level decay after vaccination, and to measure the efficacy of utilizing these antibody measurements to help guide the timing of booster doses among HIV-negative and HIV-positive patients.

The study population will include adults who were fully vaccinated against SARS-CoV-2 virus (i.e., two doses of Pfizer or Moderna vaccines or one dose of the J&J vaccine), and have received a Roche SARS-CoV-2 Semi-Quant Spike Ig Ab test at least 3 weeks after full vaccination as part of their usual clinical care at AHF Midtown Manhattan Healthcare Center.

Incidence rates of COVID vaccine response levels (i.e., adequate, low, non-response) will be estimated using univariate Poisson regression, overall and by vaccine type. Among individuals with at least two antibody measurements, rates of antibody levels decay will be estimated using univariate linear regression, overall and stratified by HIV status, vaccine type and baseline CD4 cell count. In the sub-population of individuals who received a COVID vaccine booster, vaccination and antibody response will be characterized at least 3 weeks after the booster is received. Univariate linear regression will be used to estimate rates of antibody levels decay, among individuals with at least two antibody measurements, including one after the booster dose. Rates of response decay will be produced overall, and stratified by HIV status, booster type and baseline CD4 cell count.

# 2. Introduction

## BACKGROUND

Currently, there is little guidance as to when to give a COVID-19 booster vaccine, particularly for those under the age of 65, the non-immunosuppressed, and with those with different types of immune modifying conditions. Clinicians have thus been asked to use clinical judgement and patient discussion to determine if such a booster vaccine is appropriate, leading to great variability in practices. In addition, there is limited real-world evidence of vaccination response both amongst vaccination type and amongst differing patient populations. Hence, individuals who have been vaccinated, may assume they are protected, but in actuality have not developed, or sustained a protective antibody response. Conversely, some people may fall into a category for which vaccinations may be given, but there are limited data to support giving an additional dose of vaccine, especially if they lie outside the guidance established for the age over 65 and immunosuppressed patient populations. However, the potential need to proactively give additional vaccinations in this population are exemplified in studies in Israeli healthcare workers as well as in the general population which show that post vaccination waning antibody levels are highly correlated with risk of re-infection, severe disease, and hospitalization and booster vaccination is correlated with decreased incidence rates.[i,ii] In contrast, those patients with sufficient antibody titers, who otherwise would have received an additional vaccine through general age and timeline guided recommendations, would no longer need to receive the additional vaccination, thus potentially conserving resources for those in greatest need such as for countries deficient in primary vaccinations. Although the totality of an individual's immune response from a primary vaccine series may mostly control severe COVID-19 illness leading to hospitalizations, in states where there are inadequate primary vaccination rates, even mildly symptomatic vaccinated carriers of the virus may serve as sources for the continued propagation of SARS-CoV-2 infection and further inhibition of pandemic control. Super-spreader congregations of even mostly vaccinated populations, like in the outbreak reported by the MMWR in Massachusetts, further exemplify the continued propagation of the virus to both vaccinated and unvaccinated individuals.[iii]

Additional vaccine doses may be particularly important for healthcare providers who are often in direct contact or close proximity to SARS-CoV-2 infected individuals, where resurgences of SARS-CoV-2 infection have been reported across the U.S., especially in the era of the SARS-CoV-2 Delta strain.[iv,v] In addition, the odds of long COVID-19 symptomology were estimated in one study to be 50% less in the vaccinated versus the insufficiently immunized population.[vi] In contrast, those healthcare workers who have sufficient immunogenicity against prevalent SARS-CoV-2 strains, may not fit the compartmentalization into time-based vaccination strategies, but rather individualized immunologic responses to vaccinations. Furthermore, due to the

interpersonal variability of immunologic response, differences in the attenuation of individual antibody levels, and the complexity added by the availability of different vaccines, dosing regimens, and decay rates, a better methodology for determining when a specific individual requires re-vaccination should be determined. With no current correlations of protection, especially in populations in which preventing infection is the goal, the higher the antibody titer the better. Studies have demonstrated that those who were vaccinated for SARS-CoV-2 are generally in favor for receiving additional booster doses. Furthermore, an increase in significant adverse events, other than lymphadenopathy, have not been reported in recipients of additional SARS-CoV-2 vaccine doses beyond the primary series.[vii] The effectiveness of additional booster vaccination over the primary vaccination series in preventing re-infection with SARS-CoV-2 for currently available vaccine types have been demonstrated in a number of studies[viii,ix], only the timing of when and to whom to give booster dosing remains in debate. Lastly, multiple studies illustrate that the maximizing of timing between vaccination doses, regardless of mRNA or adenovirus vaccination type, results in improved immunologic responses both in initial degree, but also in the persistence of response.[x,xi,xii,xiii]

Neutralizing antibody levels are predictive of immune protection from symptomatic SARS-CoV-2 infection and are correlated with commercially available measurements with semi-quantitative spike Ig antibodies[xiv,xv]. Although antiviral T and B cell memory cells can confirm additional degree of protection, current rapidly proliferating COVID-19 strains like the Delta strain may have shorter incubation periods that may not allow time for primed B and T memory cells to be activated, so protection would be more dependent on sufficient circulating antibodies. Furthermore, the high R correlation of neutralizing antibodies and spike Ig antibody responses have been strongly associated with viral neutralization and inhibition of viral-cell fusion.[xvi,xvii] A 50% protective neutralization level has been found to equate to a measured in vitro neutralization titer of between 1:10 and 1:30 is approximated at 54 IU/mL for wild-type COVID-19 Virus [95% CI: 30–96 IU/mL]),[xviii] whereas 5x that level, or approximately 250 IU/mL is the expected Spike Ig ab level correlated with in vitro neutralization of the predominant Delta strain of COVID-19.[xix]

Clinical decision-making and public health policies relating to COVID-19 have been evolving rapidly, sometimes based on a sparse body of literature. Given the high stakes of such decisions, there is an urgent need for more real-world evidence to inform clinical practice and public health guidelines.

## RATIONALE FOR THE STUDY

Limited real-world data are available on the antibody response after COVID-19 vaccination comparing HIV-negative and HIV-positive individuals. There are also limited information that would allow the potential usage of quantitative antibody testing to determine those at greatest risk for infection while could help in guiding the timing of additional vaccinations. There are also limited information on the antibody response of vaccine boosting in individuals, especially those with altered immune response that might lead to no response or low response to the primary vaccination series. At the moment, clinicians must rely on clinical judgement when advising their patients on the utility of vaccine boosting, as well as their level of protection from COVID vaccination. Additional information would be helpful in informing decisions on third doses in different populations such as HIV positive people, whose responses to COVID-19 vaccine and immune status would help define the timing and need for an additional vaccination based on current recommendations. Real-world evidence is needed to better inform such decisions.

# 3. Research Objectives

### PRIMARY OBJECTIVE(S)

Objective #1: Describe COVID-19 vaccine response including frequency of non-response, low response, and adequate response as measured by antibody test by HIV status (e.g., rates, and relationship to demographic and clinical characteristics, as well as vaccine types)

Objective #2: Describe rate of decline in antibody levels over time by HIV status, vaccine type, and baseline CD4 count after initial vaccination as well as other parameters.

### SECONDARY OBJECTIVE(S)

Objective #3: Describe response to COVID-19 boosters given (vaccine types, concordant vs. discordant boosters, duration from initial vaccine completion, antibody response, and side effects)

Objective #4: Describe rate of decline in antibody levels over time by HIV status, baseline CD4 count, by vaccine given, and after booster vaccination

Objective #5: Recording breakthrough infections after vaccinations and assessing antibody levels pre-breakthrough infection

# 4. Data Source

## AHF MIDTOWN MANHATTAN HEALTHCARE CENTER

The AHF Midtown Manhattan Healthcare Center is part of the AIDS Healthcare Foundation (AHF) network. AHF is a global nonprofit organization providing cutting-edge medicine and advocacy to over 1,500,000 people in 45 countries. Currently, the AHF Midtown Manhattan Healthcare Center provides care for 993 HIV-positive and 946 HIV-negative individuals who have had at least one clinical contact in the past 24 months.

Among HIV-positive patients active in care at AHF Midtown Manhattan Healthcare Center, the median age is 53 years (IQR: 38, 61); 95% are men, 22% are Black and 19% are Hispanic. Most HIV-positive patients have their healthcare covered by commercial insurance (52%), Medicaid (29%), Medicare (16%) and/or ADAP/Ryan White (14%). The median follow-up time at AHF Midtown Manhattan Healthcare Center is 7.3 years (IQR: 2.3, 8.6); 14% have at least 10 years of follow-up.

Among HIV-negative patients active in care at AHF Midtown Manhattan Healthcare Center, the median age is 44 years (34, 56); 91% are men, 11% are Black and 16% are Hispanic. Most have their healthcare covered by commercial insurance (70%) or Medicaid (18%). The median follow-up time at AHF Midtown Manhattan Healthcare Center is 4.9 years (IQR: 1.6, 7.9); 8% have at least 10 years of follow-up.

## DESCRIPTION OF THE DATABASE AND PREPARATION OF ANALYTICAL FILES

The OPERA® (Observational Pharmaco-Epidemiology Research & Analysis) database and research network is a multi-site observational database built from the complete patient health records managed in Electronic Health Record (EHR) systems from more than 400 participating caregivers at 142 separate locations throughout the U.S. (see coverage map, Figure 1). Through their membership in OPERA, medical practices meet the Centers for Medicare & Medicaid Services (CMS) Merit-based Incentive Payment System (MIPS) Incentive Program for Integration with a Specialized Registry. OPERA-participating physicians and ancillary healthcare providers have documented the care of nearly 1 million patients in their EHRs, including over 135,000 people living with HIV (PLWH) of which approximately 20% are women, 47% are Black, 20% are Hispanic and representing 11% of all the PWLH in the U.S. The OPERA database is refreshed from these EHR systems at each clinic on a daily basis providing up-to-date data for both clinicians and researchers. In total, there are more than 7 million documented prospective visits in the EHR systems for PLWH and 3 million prescriptions written for ART medications. The average years of follow-up (years of documenting patient visits prospectively in the EHR) for

PLWH in OPERA is 4.2 years and there are over 19,000 PLWH who have 10 years or more of follow-up.

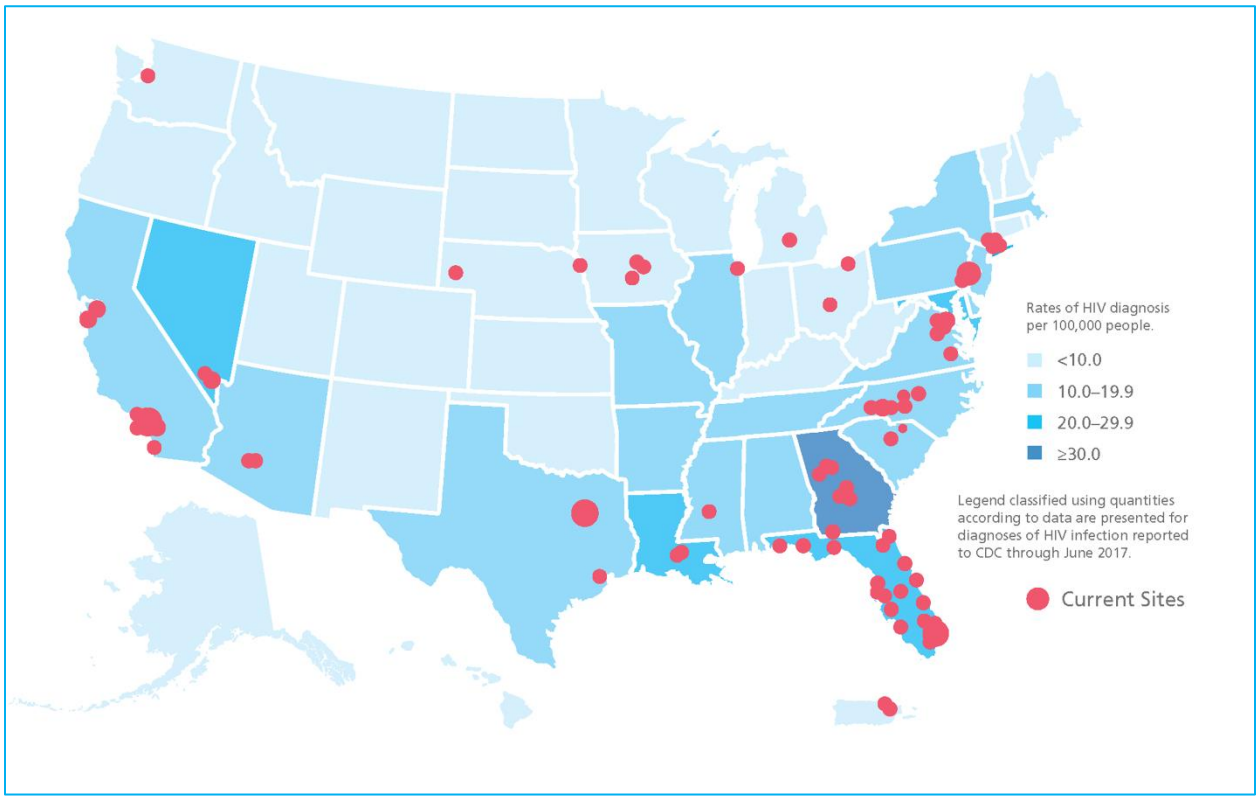


*Figure 1. U.S. Map of OPERA HIV+ Population & CDC (2010) State-by-State Estimates*

**Data Aggregation Methodology:**
Epividian provides participating clinicians with a variety of analytical reports that support the day-to-day care of patients, the management of their patient populations as well as their interventional and non-interventional research efforts. By utilizing these practice reports via the CHORUS™ portal and by pooling data in OPERA® with other clinics, clinicians can measure and compare quality-of-care anonymously as well as collaborate on research endeavors with colleagues in other geographic regions. As a result, all parties have a vested interest in maintaining the completeness and accuracy of the medical records stored in the EHR systems.

Epividian utilizes a number of proprietary algorithms to sort, classify, and aggregate the data pulled from the participating clinics' EHR systems. The process includes automated classification of clinical terms into common clinical terms with review by trained medical staff.

The standardization of the data to common terms and application of the Epividian knowledge base are key process steps in gathering data from multiple heterogeneous EHR systems and databases from many locations into a single, homogenous OPERA database for conducting research and commercial analyses. The patient health data gathered, classified and aggregated includes complete medical history & social history, visit dates, vital signs, lab orders and results, medications, problems & diagnoses, and procedures.

Epividian has developed rigorous data management processes that include both automated and manual quality checks. Data quality methods include common techniques such as:

- Detection and reporting of outliers that lead to correction, acceptance, or exclusion of observations; these can include a medical review.
- Detection of potentially missing data (e.g., a patient taking ART medications with no history of HIV infection to determine whether the use was prophylactic or treatment for infection diagnosed elsewhere).
- Data completion using multiple observations and sources (e.g., using diagnoses codes, free text, past medical history, etc. to determine if patient is naive to HIV therapy).
- Detection of observations that are known to be (or likely to be) mutually exclusive for a patient (e.g., record of medications that are typically not administered concurrently).

# 5. Study Population

Individuals presenting for care at AHF Midtown Manhattan Healthcare Center and followed through their electronic health records in the OPERA Observational Database.

### INCLUSION CRITERIA

Patients who were:

1. Cared for at AHF Midtown Manhattan Healthcare Center and followed in the OPERA observational database
2. Active in care in the last 24 months
3. Fully vaccinated against SARS-CoV-2 virus, implemented as 21 days after the second Pfizer or Moderna injections, 21 days after the one J&J injection
4. Received a Roche SARS-CoV-2 Semi-Quant Spike Ig AB test after full vaccination as usual clinical care
5. $\geq$ 18 years of age at vaccination

### EXCLUSION CRITERIA

Patients who were:

1. Unvaccinated or partially vaccinated against SARS-CoV-2 virus
2. Never tested with a SARS-CoV-2 Semi-Quant Total AB test after full vaccination

# 6. Study Design

## OVERVIEW OF STUDY DESIGN

The design for this study is an observational cohort study utilizing prospectively collected electronic medical record (EMR) data from usual clinical care at AHF Midtown Manhattan Healthcare Center, obtained from the OPERA® Observational Database.

The study population will consist of adults vaccinated against SARS-CoV-2 virus receiving the Roche SARS-CoV-2 Semi-Quant Spike Ig AB test as part of their usual clinical care. These individuals will be followed from vaccination until study end.

## EXPOSURES OF INTEREST

Initial vaccination with Pfizer, Moderna, and J&J COVID vaccines, booster vaccination with Pfizer, Moderna, and J&J vaccines, and concordant boosting versus discordant boosting

## SUBGROUPS OF INTEREST

HIV-positive versus HIV-negative patients, individuals with at least 2 measurements of antibody levels, and boosted individuals are the subgroups of interest.

## STUDY ENDPOINTS

Endpoints for both the primary and secondary objectives are non-responders and low responders and rates of decline of SARS-CoV-2 antibodies

- Non-response will be defined as: 0 to <50 U/mL
- Low response will be defined as: ≥51 to ≤250 U/mL
- Adequate response will be defined as: >251 U/mL

Roche's Elecsys semi-quantitative spike Ab Ig assay is a commercially available assay that can potentially be utilized to help guide the need for an additional vaccination dose based upon the levels of antibodies that have been previously clinically correlated with neutralizing antibodies. As part of routine care, Ab Ig assays were performed for some patients at the AHF Midtown Manhattan Healthcare Center and results were recorded in their EHR.

To normalize across different neutralization assays utilized in phase 3 studies of various COVID-19 vaccines, Khoury, et al., estimated that a 50% protective neutralization level equivalent to 20% of the mean titer in the convalescent subjects equates to a measured in vitro neutralization titer of between 1:10 and 1:30 was approximated at 54 international units IU/ml (95% CI 30–96 IU/ml) against wild-type CoV-19 infection.[xx] During the period of COVID-19 infection where the Delta virus predominated, a quantitative spike Ab's >250 IU/mL was deemed adequate, based on studies that show that an antibody titer of 4-6x wild-type SARS-CoV-2 were required to effectively neutralize Delta viral strains.[xxi,xxii, xxiii] We thus utilized a threshold level of >250 (5x wild-type ab levels) IU/mL as an adequate vaccine response against circulating Delta virus post last vaccination recommended in a series, a level of <50 IU/mL as a non-responsive post vaccination titer (inadequate for even wild-type Co-V-2 infection), and levels between (50-250 IU/mL) as a low vaccine response. Non and low-responders who had Co-V-2 Spike Ig levels that were inadequate based on the correlation of Spike Ig levels and neutralizing ab correlations relative to the predominant circulating viral strains were offered optional booster vaccinations with subsequent antibody response measurement post vaccination as standard of care. These recommendations are the current one's implemented during the Delta Co-V-2 19 outbreak by the Ministry of Solidarity and Health of France and the COVID Guidelines group in Geneva, where 260 IU/mL and 300 IU/mL, respectively, are considered gray zones of antibody protection against the Delta virus and where booster vaccinations are recommended for consideration.[xxiv, xxv]

## STUDY COVARIATES

Covariates of interest include: age, sex, race, ethnicity, HIV status, region, payer, immunosuppressive conditions, CD4 cell count, comorbid conditions, BMI. This information will be obtained from each patient's electronic health records.

# 7. Statistical Analysis

## ANALYSIS OF DEMOGRAPHICS/BASELINE CHARACTERISTICS

Demographic and clinical characteristics will be summarized in the overall population using medians with interquartile ranges (IQR) for continuous variables and frequencies with proportions for categorical variables.

## ANALYSIS OF PRIMARY OBJECTIVES

*Objective #1: COVID-19 vaccine non-response and low response as measured by antibody test by HIV status*

Records will be examined retrospectively to determine which patients, both HIV-positive and negative, were non-responders, or who developed low or adequate quantitative Ig spike antibodies using the Roche Elecsys semi-quantitative spike Ab Ig assay during usual clinical care.

Demographic and clinical characteristics will be summarized by vaccine response level using medians with interquartile ranges (IQR) for continuous variables and frequencies with proportions for categorical variables. Statistical comparisons between vaccine response level will be performed using Pearson's chi-square or Fisher exact tests for categorical variables and Wilcoxon rank-sum test for continuous variables, using an adequate response as the comparator.

Incidence rates and 95% confidence intervals of COVID vaccine adequate response, non-response and low response to COVID vaccines will be estimated using univariate Poisson regression. Incidence rates will be obtained both overall and by vaccine type. The incidence rate is defined as the number of events during follow-up divided by person-time at risk of the event. Estimating incidence rates with Poisson regression allows the use of all person-time time at risk of the outcome, even with differential lengths of follow-up between groups.

*Objective #2: Rate of decline in antibody levels over time by HIV status, vaccine type, and baseline CD4 count after initial vaccination*

Rates and 95% confidence intervals of antibody levels decay will be estimated among individuals with at least two antibody measurements. Univariate linear regression, will be employed, using the continuous antibody level as the dependent variable, and timing of tests as

the dependent variable. Robust variance estimator will be used to account for repeated measures. Rates of decay will be produced overall, and stratified by HIV status, vaccine type and baseline CD4 cell count.

## ANALYSIS OF SECONDARY OBJECTIVES

*Objective #3: COVID-19 boosters given*

In the sub-population of Individuals who received a COVID vaccine booster, the following characteristics will be described using medians with interquartile ranges (IQR) for continuous variables and frequencies with proportions for categorical variables: initial and booster vaccine types, concordant vs. discordant boosters, duration between initial vaccine completion and booster dose, antibody response after the booster, and side effects recorded. Post vaccination responses will be determined no earlier than 2 weeks post vaccination.

*Objective #4: Rate of decline in antibody levels over time by HIV status, booster type, and baseline CD4 count after booster vaccination*

Rates and 95% confidence intervals for changes in antibody levels will be estimated using linear regression, among individuals with at least two antibody measurements, including one after the booster dose. Univariate linear regression, will be employed, using the continuous antibody level as the dependent variable, and timing of tests as the dependent variable. Robust variance estimator will be used to account for repeated measures. Rates of decay will be produced overall, and stratified by HIV status, booster type and baseline CD4 cell count.

*Objective #5: Recording breakthrough infections after vaccinations and assessing antibody levels pre-breakthrough infection*

Among all individuals with full vaccination and antibody testing, the EHR will be searched for documentation of COVID infection after vaccinations. If breakthrough infections are observed, antibody levels prior to infection will be described. Note: COVID infections may not be recorded in the EHR if diagnosed outside of the clinic.

## SENSITIVITY ANALYSES

NA

## SUBGROUP ANALYSES

Patients provided COVID boosters will be evaluated by the types and combinations of vaccines they received. Further, patients given sequential antibody tests will be evaluated by vaccine type for response over time.

# 8. Study Conduct

## REGULATORY AND ETHICAL CONSIDERATIONS

OPERA® complies with all HIPAA and HITECH requirements and has received annual institutional review board (IRB) approval by Advarra IRB, including a waiver of informed consent and authorization for use of protected health information

## INFORMED CONSENT

Informed consent has been waived for this non-interventional, observational research and authorization for use of the protected health information has been approved by Advarra IRB.

## DATA PRIVACY & PERSONALLY IDENTIFIABLE INFORMATION (PII)

The data used for this research study are not identifiable by the research staff. However, all data, even when stripped of identifiers, are handled and treated, in motion and at rest, as though the data could be identified. All data are managed according to regulations including HIPAA and HITECH. These regulations and guidelines expand upon the ethical principles detailed in the 1964 Declaration of Helsinki. These data are not shared outside the researchers involved with the analysis.

## ADVERSE EVENT REPORTING

There is no potential to collect individual level data on serious and non-serious adverse events (AEs), pregnancy exposures, device deficiencies and device related events or incidents related to any pharmaceutical product during the conduct of this research, as the minimum criteria needed to report AEs, pregnancy exposures, device deficiencies and device related events and incidents are not collected. Specifically, the data are insufficient to establish attribution between a potential safety event and an individual using a product as the study design is to analyze deidentified, secondary data collected from individual medical records. Therefore, the obligation for reporting any and all adverse events lies with the healthcare provider at the point of care.

# 9. Administrative Matters

## QUALITY ASSURANCE

Epividian has working practices & procedures governing the use of observational data, the development of analysis specifications and plans, the development of analytical programming, the analytical quality assurance process and the scientific review of reports as well as clinical advisory charters for the clinical review of output intended for public domain.

Working practices for the development of analysis specifications include basic identifying information, background material, relevant definitions of key study variables, population definitions, baseline definitions, specific requirements for dataset creation, statistical requirements such as eligibility criteria, exposures, outcomes and model fitting. Working practices for programming include naming conventions, proper code documentation and commentary, content, appearance, efficiencies (i.e., use of macros), and organization of output, maintainability and generalizability. Working practices for programming quality assurance include self-reviews of observational counts, missing data values, many-to-many merges, variable formatting, numeric-character & character-numeric conversions, uninitialized variables, unresolved macro references, report completeness and report-to-specification correspondence, and system errors and logs.

The quality assurance team review may include small sample spot-checking, coding log reviews, complete coding review, selected observations from intermediary dataset reviews, and/or independent programming to reproduce the results. Documentation of non-public domain reports includes market, scientific, statistical, and clinical review. Documentation of scientific protocols, reports and manuscripts intended for public domain follows two sequential steps: an internal-to-Epividian epidemiological, statistical, and clinical review, followed by a clinical/epidemiological external advisory board review.

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