Part A – Applicant

A.1 Applicant

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Part B – Scientific proposal

B.1 BASIC DETAILS

B.1.1 Title

Simulation study to explore the suitability of epidemiological designs for COVID-19 vaccine safety studies.

B.1.2 Abstract

During the vaccination stages of the COVID-19 pandemic, researchers used varied study designs to conduct vaccine safety studies. This highlighted the diversity in study designs used by researchersand variance in the results they found, even when their aims were similar. These experiences suggest that establishing a uniform approach in vaccine safety study designs is imperative. This uniformity is vital in providing policymakers with informed guidance regarding vaccine safety quicker and is essential for pandemic preparedness. Our objective is to assess and contrast the applicability of a cohort study versus a self-controlled study design. This comparative analysis aims to pave the way for establishing cohesive and consistent methodologies in future vaccine safety investigations.

To accomplish this aim, we propose a Monte Carlo simulation study. We will generate data for two scenarios. The first scenario reflects parameters strongly linked to the outcome of interest, while the second dataset features a randomly distributed prevalence of the outcome within the sample. We will include the parameters age, sex, follow-up time, type of vaccine, number of doses, and unmeasured confounding, to emulate real world data challenges both the study designs face. This data will be analysed in a substantive analysis for bias of the association paramters age, sex, follow-up time, type of vaccine, number of doses, and the unmeasured confounder.

The proposed research will span two years, involving tasks such as code writing, code checks, data analysis, internal peer review, and report writing. We have identified potential alternatives to address any challenges that may arise during our planning and research.

The suggested simulation study presents a feasible and valuable research avenue, the identified risks emphasize the importance of meticulous design, validation, and interpretation. Mitigation strategies such as robust validation, comprehensive sensitivity analyses, and alternative approaches could address these risks, ensuring the study's reliability and significance in advancing statistical methodologies.

B.1.3 Layman's summary

When we look back at the COVID-19 pandemic, we know that we were not well prepared. If we look at the research that has been conducted about how safe the COVID-19 vaccines were or whether a vaccine has strong side effects, we see that researcher used varying research methods these studies. Based on this experience, it is clear that we need a consistent way to study how safe vaccines are. This is important for giving leaders good advice about vaccine safety, which helps us prepare better for future pandemics. Our goal is to compare the two most commonly used and valid methods for studying the safety of a vaccine and look at which one is closest to the truth.

To establish what the 'truth' is we will make use of a controlled enviorment, like in a lab. Our lab is made up of computers and softwares. The controlled envrioment will be established by creating data for two situations. In the first one, we will use factors, such as age, sex, type of vaccine, and number of doses, that can be the cause of the side effect. In the second one, we want to mimic the real-world occurrence of side effects happening without a clear cause, they can happen at random. We will use things like age, sex, how long we follow people, the type of vaccine they got, how many doses they had, and other factors that could have an effect on the results. This will help us make the data as close to real life as possible. Then, we'll use statistical analysis to analyse the data and compare the results to the 'truth' in our controlled enviorment. With this we can then see if one, both, or none of the two methods reach the 'truth.'

B.1.4 Keywords

KEYWORD	DEFINITION
MONTE CARLO SIMULATION STUDY	A method using random sampling to simulate various scenarios for assessing models or algorithms' performance.
VACCINE SAFETY	Encompasses the assessment and evaluation of potential risks associated with vaccines, including monitoring for side effects, adverse reactions, and ensuring the overall well-being of vaccinated individuals.
BIAS	Refers to a systematic error or deviation from the true value.
SELF-CONTROLLED CASE SERIES	An epidemiological study design examining associations within individuals between exposure and outcomes over time.
COHORT STUDY	Observational research tracking a group over time to assess outcomes related to specific exposures or characteristics.

B.1.5 SCIENTIFIC PROPOSAL

B.1.6 Research topic (What)

In January 2020 the World Health Organization (WHO) declared the novel coronavirus SARS-CoV-2 (COVID-19 virus) a public health emergency, following the global spread of the COVID-19 virus they declared it a global pandemic on 11 March 2020 [1]. Over the first two years, there were over 450 million reported cases worldwide, with 100 million in the European Union (EU) alone, leading to numerous deaths and significant disruptions globally [1]. In response, the EU and its health authorities took various measures to contain the virus, protect citizens, and save lives. The European Medicines Agency (EMA) and national competent authorities played key roles in facilitating the development, evaluation, approval, and monitoring of COVID-19 vaccines and treatments. They also collaborated with global partners, addressed medicine shortages, and provided crucial information to patients, healthcare professionals, and the public. More than three years later, on 5 May 2023, the WHO declared that COVID-19 was no longer a public health emergency [2] .

The pandemic necessitated flexible regulatory approaches to swiftly adjust procedures and accelerate the creation of vaccines and treatments, all while upholding the rigorous safety, effectiveness, and quality standards set by the EU [3]. The EMA, operating via the Emergency Task Force (ETF), provided vaccine developers with prompt scientific guidance regarding optimal methodologies and study structures. This guidance aimed to facilitate the generation of strong and reliable data, expediting the process of developing COVID-19 vaccines and therapeutics. Additionally, the EMA implemented "rolling reviews," allowing for the expedited evaluation of data. This approach aimed to hasten the assessment process and enable quicker recommendations for authorization, resulting in lowering the standard from 210 to less than 150 working days [3]. This lead the development of vaccine timeline to be more compressed compared to standard vaccine approval. As of now, eight different COVID-19 vaccines are approved by the EMA for use for varying populations [4].

In general, the vaccine safety studies happen throughout the vaccine development and after authorization and market access [3]. One key challenge during the pandemic was the short time researchers faced to conduct the post-authorization safety studies (PASS). These studies are conducted after the market authorization and in normal cases have a larger time window and give access to more information to conduct safety studies. Due to the nature of the pandemic, the post-market research period was significantly shorter [3]. A PASS is conducted subsequent to a medicine's authorization to acquire additional insights into its safety or to gauge the efficacy of risk-mitigation strategies. These studies can be clinical trials or non-interventional studies and serve the purpose of appraising the safety and risk-benefit profile of a medicine, thereby aiding regulatory decision-making [5].

There is a variety of methods to conduct vaccine safety studies [6]. Naturally, we would think that the choice for the study design used to conduct a PASS can vary based on the aims of researcher. A recent systematic review on adverse effects (myocarditis specifically) after vaccination with a COVID-19 vaccine by a fellow student, B.C.P. van Hoof (2023), reported that even if the aim is similar, researchers used different study designs and had varied conclusion for vaccine safety outcomes. He also found that the most used study designs were the cohort and self-controlled study designs. These two study designs are two prominent approaches in epidemiological research, each offering unique advantages and facing distinct challenges. Cohort studies involve identifying study populations, creating exposed and unexposed groups, and observing outcomes over time. These studies allow the calculation of incidence rates directly and facilitate the investigation of various outcomes related to a specific exposure [6]. Cohort designs are especially suitable for analyzing large datasets like electronic healthcare records, enabling the assessment of drug effects over extended periods. However, cohort studies often require substantial sample sizes and extended durations, particularly when studying rare outcomes [6]. On the other hand, the self-controlled study is

specifically designed for vaccine safety studies, and it estimates relative incidence rates within defined risk and control windows after exposure [7,8]. It inherently controls for time-invariant confounders within individuals but requires management of time-varying confounders. This method relies on three critical assumptions regarding event independence, absence of event influence on follow-up, and event non-impact on exposure chance, posing potential limitations [7]. Nonetheless, this method can be adapted in specific scenarios to mitigate these assumptions' effects, especially using extended models [6].

Reflecting on the experiences gained during the COVID-19 pandemic, it becomes evident that establishing a standardized approach in vaccine safety study designs is imperative. This uniformity is vital in providing policymakers with informed guidance regarding vaccine safety, essential for proactive readiness in handling future pandemics. Our objective is to assess and contrast the applicability of a cohort study versus a self-controlled study design. This comparative analysis aims to pave the way for establishing cohesive and consistent methodologies in future vaccine safety investigations.

B.1.7 Approach (How)

To achieve our aim, we will conduct a Monte Carlo simulation study to directly compare the self-controlled case series design and cohort design. In the section below we will first give a short introduction to simulation study methods and the two designs under investigation, followed by the application in the workplan.

Introduction to simulation study design

To achieve our aim we want to conduct a Monte Carlo simulation study. Simulation studies are essential computer experiments utilizing pseudo-random sampling to create data, playing a vital role in statistical research for evaluating new methods and comparing alternatives. Simulation studies offer the opportunity to directly compare research designs within a controlled environment/scenario created by the researcher. As such, we can use them to test varied methodological studies. Simulation studies offer empirical insights into statistical methods' performance within specific scenarios, complementing general analytic results. They are especially useful when methods assume incorrect conditions or when dealing with messy data. The term "Monte Carlo simulation" refers to statistical techniques using pseudo-random sampling, integral for various statistical methods beyond simulation studies.

We will use the guidelines set up by Morris and colleagues for conducting simulation studies to evaluate methods [9]. This offers structured guidance, terminology, coding tips, performance measure considerations, and presentation suggestions [9]. Following this tutorial, a simulation study needs to contain the components Aim, Data-Generating mechanisms, Estimands, Methods, and Performance measures (ADEMP). Below we give a short explanation of these components. The Aim refers to the specific objective the simulation study wants to answer. In our case, this would be which study design gives the least biased results. The Data-Generating Mechanism specifies how the data should be created to address the objective. This involves various decisions, such as choosing between real-world data or simulated data, determining the necessary model for the data, selecting parameters, and so on. The Estimands represent what we aim to analyze, strongly influenced by the objective; in our case, this could involve examining parameter coefficients as we will analyze for bias. The Method section outlines the overall methods to be used, including the steps we will take and the data analysis method. Performance measures entail numerical values used to evaluate the effectiveness of a method, where we will be assessing bias as our performance measure.

The primary aims of simulation studies are to precisely identify specific objectives related to the data-generating mechanisms. To achieve this, a critical decision must be made regarding whether to

employ resampling techniques or to simulate data from a parametric model. In the case of simulation from a parametric model, the complexity and fidelity of the model need careful consideration, including whether it should be based on real-world data or a simplified representation. Factors that will be varied within the simulation need to be determined, including the selection of factors and their respective levels. Decisions regarding whether factors will be varied fully factorially, partially factorially, or using a one-at-a-time approach are also integral to the study's design. The estimands and/or other targets of analysis must be explicitly defined, outlining precisely what will be measured or estimated in the simulation study. It is essential to ensure that the chosen methods for evaluation align with and are appropriate for the identified estimands. In studies comparing methods, an extensive literature review is imperative to ensure the inclusion of relevant methods for evaluation. This comprehensive approach ensures a thorough assessment and comparison of the identified methods. An essential aspect of the study involves determining and justifying all performance measures that will be estimated, highlighting their relevance to the estimands or other specified targets. For lesser-used performance measures, explicit formula should be provided to avoid any ambiguity in their calculation. Furthermore, the selection of an appropriate number of simulations is critical to achieving acceptable Monte Carlo standard error for key performance measures. The determination of number of simulations should strike a balance between computational efficiency and obtaining reliable estimates for the study's objectives [9].

Introduction of the study designs to be compared

In the context of vaccine safety studies, the cohort study design (figure 1) examines vaccinated individuals compared to unvaccinated or differently vaccinated individuals over time to analyze the incidence of a specific health outcome. It identifies and classifies a specific population based on their vaccination status and observes outcomes of interest. This study design can be conducted prospectively or retrospectively and involves comparing groups based on exposure and non-exposure, utilizing person-time as a measure [10]. Advantages of cohort studies include their ability to handle rare exposures and multiple related outcomes in the same population, with which incidence rate and absolute risks can be calculated. However, challenges arise when high vaccination rates limit the availability of unvaccinated individuals for comparison or when socioeconomic, racial, health, or access disparities affect comparability between exposed and unexposed groups [10]. Analytical methods such as logistic regression, Poisson regression, or Cox regression are employed to estimate associations between vaccination and health outcomes, like relative risk or odds ratios [10]. Absolute and attributable risks can then be estimated based on these measures and information from the comparison group. In distributed databases, strategies like matching or stratification help ensure comparability between vaccinated and unvaccinated groups, reducing confounding factors. This approach minimizes the need for pooling extensive individual-level data and allows for efficient analysis within each data parameter [10].

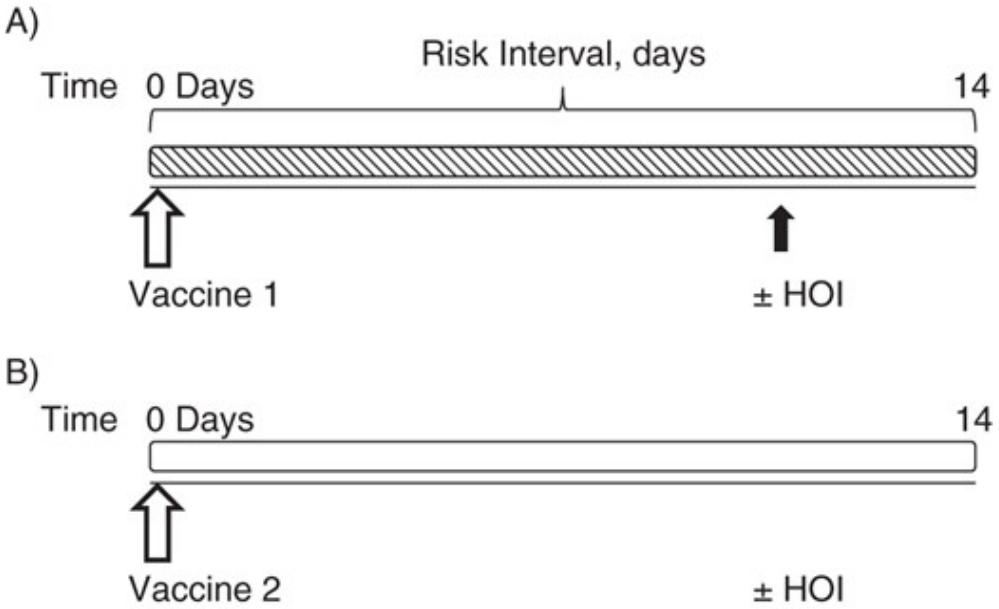

Figure 1: In a matched cohort design using an alternate vaccine as a comparator: A) People who received the specific vaccine under investigation (vaccine 1); B) People who received a different vaccine (vaccine 2). Both groups, those vaccinated with the vaccine of interest and those vaccinated with the comparator vaccine, are monitored for a specified duration. The comparison involves analyzing the occurrence of the health outcome of interest (HOI) in these two groups. The striped bar visually denotes the timeframe during which the risk for the HOI is observed after the administration of the vaccine of interest [10].

The self-controlled case series method was developed initially to investigate the potential link between MMR vaccination and aseptic meningitis in children aged 1-2 years [8]. This method was prompted by the need for quick answers about the association between MMR vaccination and aseptic meningitis because the distribution or coverage of the vaccine was not consistent or uniform across the population [8]. Compared to other methods, the self-controlled case series focuses solely on cases, estimating relative incidence while implicitly controlling time-fixed confounding factors like genetics, socioeconomic status, and sex [11]. It utilizes a likelihood approach based on cohort logic, treating event times as random and exposure times as fixed. This method shares similarities with other approaches, incorporating age control fixed confounder control and accommodating multiple events [8]. Advantages of the self-controlled case series method include its consistency in estimating relative incidence and implicit control over time-fixed confounders [8]. However, this method makes strong assumption which have to be upheld, such as: assuming exposure probability is unaffected by the outcome event, dependence on small event risks within the observation period for non-recurring events, inability to estimate absolute incidence, and requirement for variability in event timing or age [8]. Moreover, self-controlled study designs encounter challenges such as time-varying confounding, which researchers need to address. These studies primarily focus on assessing risks within the exposed group rather than the unexposed group [12].

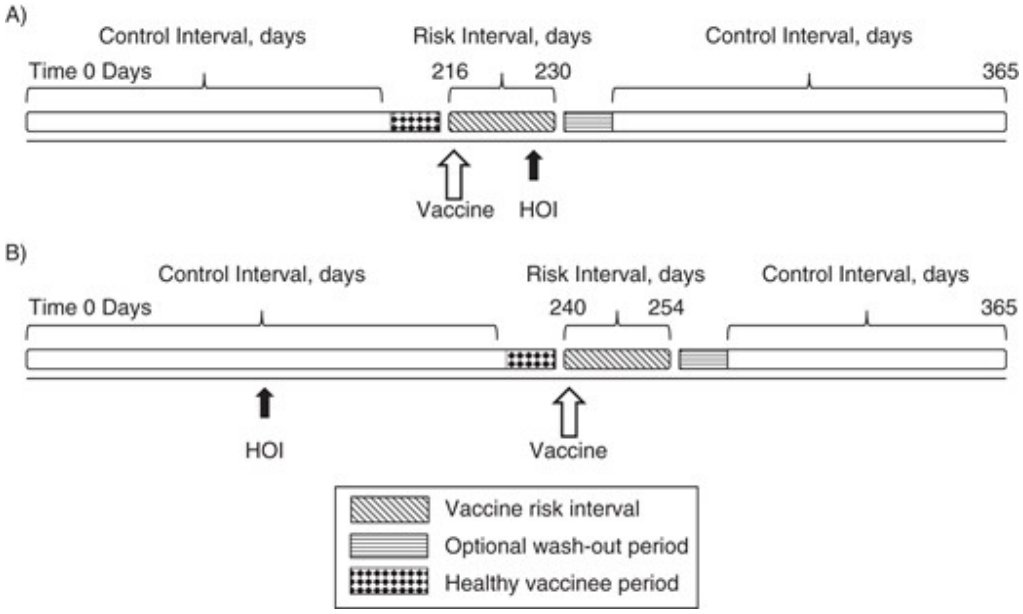

Figure 2: In a self-controlled case series design: A) Individual 1; B) Individual 2. Participants included are those who encounter at least one health outcome of interest (HOI) within a predetermined study duration. Vaccinated individuals contribute both exposed and unexposed periods based on the timing of vaccination and the specified risk timeframe. Unexposed control time might occur either before or after vaccination and tends to be longer compared to the self-controlled risk period in the study. For instance, in the first example, the vaccinated person experiences an HOI within the risk interval, while in the second example, the vaccinated person encounters an HOI during the unexposed interval [10].

The self-controlled case series method and cohort study design hold significance in vaccine safety research [13–16]. The self-controlled study concentrates on analyzing individual-level data to track changes in risk before and after exposure, implicitly addressing time-fixed confounding factors. Conversely, the cohort study compares different groups of individuals, exposed and unexposed, over time, providing a broader perspective and explicit control for assessing causal relationships and absolute risks. Our comparative analysis aims to elucidate the strengths and limitations of each methodology. The self-controlled approach, while effective in estimating relative incidence and implicitly controlling for certain factors, assumes stable exposure probabilities after an event and requires variability in event timing. It is utilized to derive an incidence rate ratio for the occurrence of an outcome between defined "risk periods" and "baseline periods". In contrast, cohort studies offer a broader scope for assessing risks and causal relationships but necessitate larger sample sizes, longer follow-up periods, and meticulous consideration of potential confounders.

Importantly, cohort studies and self-controlled case series have distinct estimands due to their differing study designs, more about this under ‘Estimands’ below. Both study designs offer valuable insights, but their methodologies and estimands are distinct, catering to different aspects of understanding the relationship between treatment exposure and outcomes in pharmacoepidemiology.

Workplan, following the ADEMP structure

Aim

This study aims to assess and contrast the bias of a cohort study versus a self-controlled study design for post-market access vaccine safety studies in a substantive analysis. We further aim to investigate which of the methods yields unbiased results when the data contains a random distribution of an outcome and an outcome with strong association with covariates.

Data-generating mechanism

Conducting simulation studies to assess the effectiveness of statistical methods necessitates a precisely defined data-generating mechanism (DGM). The term DGM is used to clarify that random numbers are used to generate a dataset [9]. Detailed specifications of the DGM are of utmost importance for interpreting outcomes accurately and drawing valid conclusions. Therefore, the DGM is defined based on the aim of the study. Since we are conducting a simulation study which compares two methods for vaccine safety studies, we made the choice of using a DGM which mimics real world data closely. The exploratory parameters will be defined based on literature, where we will use papers on the adverse effects myocarditis and pericarditis after COVID-19 vaccine treatment as our starting point [17].

For our research we want to involve two distinct scenarios for the DGM. The first scenario will reflect parameters strongly linked to the outcome of interest, while the second dataset will feature a randomly distributed prevalence of the outcome within the sample. Through these scenarios, our objective is twofold: (1) for the first scenario we want to construct a dataset where there is a strong association of the outcome with certain specified parameters and (2) second scenario we aim to create a dataset showcasing random outcome occurrences, to mimic outcome of a disease being random and not strongly associated with the specified paramters. With these two scenario's we aim to mimic two possible settings in which the outcome (adverse effect) in a vaccine safety study is (1) strongly associatied with certain parameters (e.g. vaccine, dose, sex) and (2) where the outcome is random and has no real association with the parameters. These two scenarios will help us research the two study designs and their capacity to yield correct results and conclusions, e.g. finding random distribution or the associations of the parameters. We will consider crucial parameters outlined in previous work, including age, sex, follow-up time, type of vaccine, and number of doses [17]. In addition to these parameters, we will also include a parameter for unmeasured confounding effects, to emulate real world challenges both the study designs face [18]. Unmeasured confounding effect, indicating effects of unmeasured parameters (e.g. mental health, life style, etc.), will create the base for our undefined association and mimic the unmeasured confounding problem in vaccine safety studies.

It is of utmost importance that there is congeniality between the DGM and the statistical model for the analysis [9]. If we build a DGM that follows a certain model, analyzing the data generated with a different model may lead to biased conclusions in the research. For consistency, we will employ the conditional Poisson regression model in both our DGM and data analysis. This regression model is best suited and widely used in vaccine safety studies. The conditional Poisson regression model serves as a crucial tool in analyzing self-controlled study designs [19]. It is utilized to derive an incidence rate ratio for the occurrence of an outcome between defined "risk periods" and "baseline periods". In this statistical model, it's essential to explicitly adjust for time-varying confounding factors like age and season. It is worth noting that while adjusting for time-varying confounding factors like age and season is important, the main strength of self-controlled study designs is that they can ignore confounding factors that do not change over time (e.g., sex, habitual healthy or unhealthy behaviors) [20]. Failing to account for these factors may result in the exclusion of individuals who experience the outcome but lack any exposure during the study period, as they possess only a "baseline period", effectively nullifying their contribution to the analysis. Consequently, certain studies utilizing self-controlled study design methodologies opt to include only patients who have experienced both the outcome and exposure during the study period [11,21]. Similarly, in cohort study designs the Poisson regression model can and will be used for the analysis [22].

In the first scenario, we intend to establish specific parameters as outlined below:

1. Age: This parameter will be represented as a continuous variable following a normal distribution, ensuring a range of ages across the dataset.
2. Sex: It will be categorical, following a binomial distribution, facilitating the allocation of individuals into distinct sex categories based on a probabilistic distribution.
3. Follow-up Time: This variable will be encoded as a continuous variable, enabling the representation of a range of durations for follow-up periods.
4. Type of Vaccine: Categorical representation will be employed, ensuring an even and random distribution of various vaccine types within the sample size. This randomness aims to mimic real-world scenarios where vaccine distribution can vary.
5. Number of Doses: This will be coded as an ordinal variable, distinguishing between different doses administered. Specifically, the first dose will carry less weight than the second dose, indicating a hierarchical order in dose administration.

These parameter specifications aim to create a diverse and representative dataset by incorporating various distributions and characteristics reflective of real-world scenarios. For the detailed specifications, distributions, and weight of association coefficients of the parameters, we will conducut an in-depth literature research.
In the second scenario, we want to generate the same data as mentioned above, but we want to introduce the outcome in a random prevalence among the sample.
For both scenario's we want to generate a sample size of $n_{sample} = 1000$ and the number of simulations will be set at $n_{sim} = 10000$, following the approach of most conventional simulation studies [9].

Estimands
The primary objective of most simulation studies is to evaluate or compare methodologies employed in estimating specific population parameters, referred to as estimands. An estimand typically signifies a parameter within a model that generates data, although it can occasionally denote alternative measures [9]. The selection of an estimand is pivotal and reliant on the objectives of the analysis, ranging from parameters in regression models to predictive metrics or outcome averages. In our study, our focus lies in examining the bias of two methods. Given that our DGM incorporates a true outcome measure, our aim is to assess the capability of the two study designs in closely approximating the true association.

To calculate the bias, we will analyse the two study designs under investigation under conditional Poisson regression. We are interested in investigating which method yields the least biased results. Conditional Poisson regression incorporates covariates or predictors that may influence the count of events. These covariates or predictors will be defined as age, sex, vaccine etc. and their association coefficient with the count event, the outcome of adverse effect. Since we defined the true association, we can then treat the data sets according to the two methods under investigation and use conditional Poisson regression to determine the accosiation coefficients of each 9arameter.

Methods
The proposed simulation study comprises two distinct scenarios, labeled as S1 and S2. In scenario S1, we will simulate a dataset where the outcome variable exhibits a strong association with certain predetermined parameters such as age, sex, vaccine type, and/or number of doses. The specific nature of this association will be informed by findings from an extensive literature research. In contrast, scenario S2 involves simulating a dataset where the outcome variable is randomly assigned with a certain prevalence. Both scenarios, S1 and S2, will share similar parameters, sample size of 1000 and will undergo 10000 simulations each.

The outcome variable in both scenarios will follow a Poisson regression model. The primary objective at this stage is to assess the DGM by analyzing the association coefficients derived from the two datasets and combining them.

Following the generation of these simulated datasets, we plan to subject the 10000 simulations to analysis techniques based on their specific methods, i.e., either self-controlled case series or cohort study designs.
This process will involve conducting analyses tailored to each scenario's characteristics and evaluating the association coefficients obtained from the simulations.

Conditional Poisson regression will be used in both self-controlled case series and retrospective cohort studies to analyze the association between an exposure (e.g., vaccine administration) and an outcome (e.g., adverse events).

In self-controlled case series studies, individuals serve as their own controls over different time periods. We plan to apply conditional Poisson regression as follows:

1. Data Structure: Each individual's data will be structured into episodes, with each episode having an exposed and unexposed period.
2. Modeling: Conditional Poisson regression will be used to model the occurrence of outcomes during exposed and unexposed periods within the same individual. The model accounts for within-person variation, adjusting for potential time-varying confounders.
3. Analysis Considerations:
    - Time-varying exposures: we will account for changes in exposure status within each individual over time.
    - Time trends: we will, if necessary, adjust for any temporal trends that might influence the outcome.
    - Control for confounders: we will identify and control for other variables that influence the outcome.

In a retrospective cohort study, individuals with a specific exposure are compared to those without the exposure to assess the occurrence of outcomes. We plan to apply conditional Poisson regression as follows:

1. Data Structure: Individuals will be categorized into exposed and unexposed groups based on their exposure status.
2. Modeling: Conditional Poisson regression models the incidence rate of the outcome in the exposed group relative to the unexposed group, where we will adjust for confounders.
3. Analysis Considerations:
    - Confounding variables: we will account for confounders that affect the relationship between exposure and outcome.
    - Follow-up time: there might be a need to consider varying the lengths of follow-up time for different individuals.

Performance measures
The term "performance measure" refers to a numerical value used to evaluate a method's effectiveness [9]. Considering our aim and the mentioned estimands, we think that the bias is the most appropriate performance measure. Bias indicates the average difference between the estimated value ($\hat{\theta}$) and the true value (θ), which can either be positive or negative. In our study, we have pre-defined the true association parameters [9]. Therefore, we can assess the performance of the methods by comparing them to these true associations. Prior to comparing the two study designs to eachother, we have to compare their performace ($\hat{\theta}$) to the true association in our DGM (θ). With this we will have calculated the bias the method results. Additionally, precision and the coverage of confidence intervals are areas of interest, typically at a confidence level of $(1-\alpha)$ [9].

Before conducting a formal analysis of the estimated dataset, preliminary exploratory analysis is prudent, often aided by plots. In simulation studies aiming to estimate an outcome, specific types of plots are valuable:

- Univariate plots illustrate the distribution of θ_i and SE(θ_i) for each data-generating mechanism, estimand, and both methods, facilitating the inspection of distributions and outlier identification.
- Bivariate plots of SE(θ_i) versus θ_i for each data-generating mechanism, estimand, and both methods aim to identify bivariate outliers.
- Bivariate plots comparing θ_i (and possibly SE(θ_i)) for one method against another, aid in observing correlations and systematic differences between methods.

Necessary tools
The primary tools employed in this research will involve computational resources, specifically relying on the programming language R and its specialized packages essential for our study, such as: the package *gnm* (which includes Poisson regressions), *survival* and *SCCS* for self-controlled case series [23–25]. Anticipating a highly demanding simulation process, conventional computers may encounter challenges handling the computational load. Hence, there arises the potential necessity for utilizing High-Performance Computing (HPC) resources. HPC systems are frequently utilized for studies requiring extensive computational time or high-power consumptions, scenarios that commonly surpass the capabilities of standard computers. This technology is available through the University Medical Center Utrecht. Applicatoon for the use might be necessary.

Duration of the proposed research

In figure 3, below, a draft of the expected duration of the research is given including the expected time spent on each task. We expect the research to have a duration of two years.

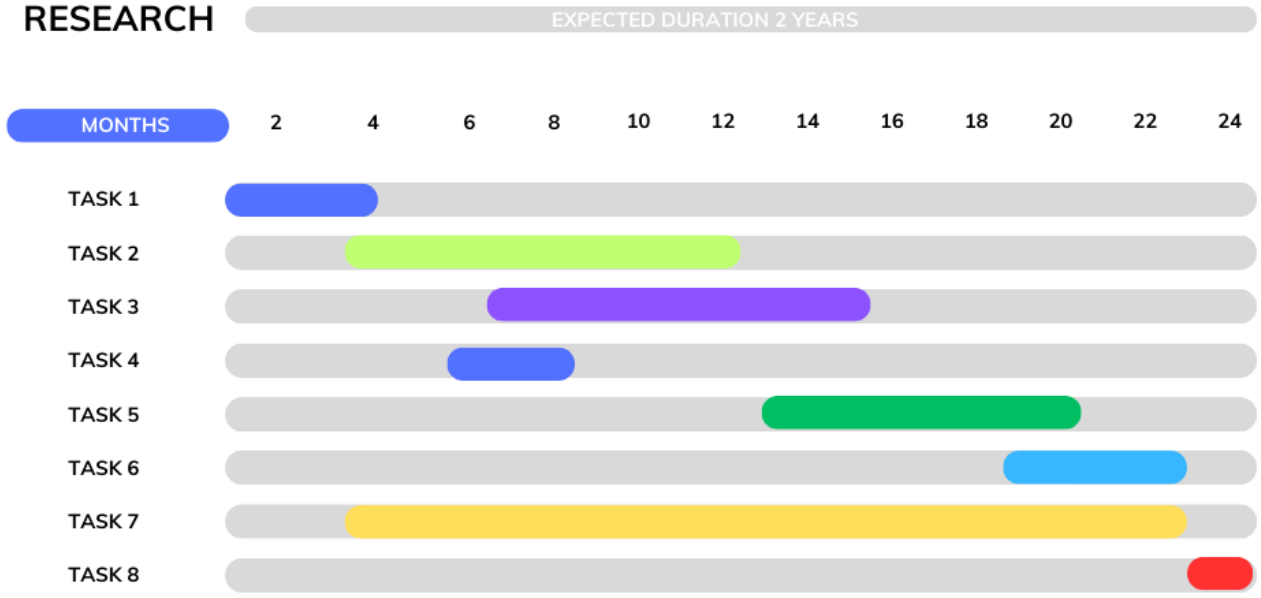

Figure 3: Duration of proposed research and time spent on each task.

These tasks outline the sequential stages and timeframes of the study, encompassing literature review, DGM development, algorithm establishment, performance assessment, testing, peer review, and report finalization for publication.

Task breakdown:

1. Literature Research (Task 1): This phase encompasses 4 months of the 24-month period. Here we will focus on finding specifications for the association variables for our DGM algorithm. We will conduct a literature research to find these association variables and possibly their values and confidence intervals. We expect to have all parameters ready at the end of this task.
2. Development of DGM (Task 2): This is typically the most intricate aspect of a simulation study, therefore, we assigned 8 months for it. The DGM entails the complete setup of the DGM alogrithm. We expect to finish our complete DGM at the end of this task.
3. Algorithm Development and Performance measures evaluation (Task 3): By the 2.5-month mark of the DGM development phase, we expect to have established a robust DGM algorithm. Here we will start performing the performance measures and evaluate our DGM further. Evaluation of the DGM's performance starts in the 7th month and spans 9 months.
4. Code verification (Task 4): An assessment of the integrity of the DGM code. Here we look at the robustness of the DGM and the data we generated. We define the robustness with the following questions: does the DGM code generate the data we wanted? If we analyse the DGM with a conditional Poisson regression with our known parameters, does it yield the correct association measures? This later is different form our aim, here we want to evaluate whether our code works and does what we intended for it. If everything works fine, task 3 can continue.
5. Implementation and Testing (Task 5): In task 5 we will perform our data analysis according to our two study designs. We will treat the data according to a self-controlled case series and a retrospective cohort study. The DGM and its corresponding performance measures are projected to conclude by the end of the first year. Testing of the two methods commences in

the 13th month, continuing for 8 months. At the end of this task we expect to have the results for our project.

6. Peer Review (Task 6): This involves a 4-month period dedicated to conducting internal peer reviews the research report. We are writing starting from task 2 onward. This necessitates the internal peer-reviewing. At the end of this task we expect to have a reviewed report.
7. Report Writing and Updates (Task 7): An ongoing process throughout the study, involving continuous writing and updating of the report. During this stage we are continuously writing our report. During each step of the research there is material to report on. We expect to yield a draft of our complete report at the end of this task.
8. Report Finalization and Submission (Task 8): The final two months are allocated to finalize the report and prepare it for publication submission. Here we will write and process any feedback for our paper and finalize it. At the end of this task we expect to have final version of our study paper and submit it for publication.

B.2.1 Feasibility / Risk assessment

The feasibility of the proposed simulation study is high, however, potential risks exist, primarily associated with the accuracy of the simulated data, methodological limitations, interpretation of results, computational technology, and time-related factors.

Risks may arise in accurately mimicking real-world data parameters during our DGM. We can fail to mimic the nature of the distribution or continue with wrong association parameters. This can be mitigated by rigorous validation of the simulated data against known statistical distributions and patterns to minimize inaccuracies. Robustness checks and sensitivity analyses could also validate the data's reliability. Careful selection and comprehensive evaluation of methodologies, alongside sensitivity analyses across various scenarios, can reduce potential biases or limitations can help mitigate this risk. To do this we can change some values to two ends of the extremes to conduct the sensitivity analysis. Incorrect interpretation or extrapolation of simulation results might lead to erroneous conclusions. This can be mitigated by detailed documentation of assumptions, transparent reporting, and thorough sensitivity analyses to enhance the reliability and clarity of interpretation. If our DGM stage fails, and we cannot mimic a real-world setting, an alternative approach could involve employing real-world datasets. However, employing real-world data leads to a different DGM. This can prolong our DGM stage further. We expect the availability of real-world data.

Further we expect possible delays due to complications during any of our tasks, figure 3. In our plan we did account for possible delays, however, there are further risks that may arise. These risks and possible alterantives are as follows:

- Literature Research: we might have difficulty in finding appropriate specifications for association variables or insufficient data on values and confidence intervals within the literature for research on myocarditis, our example adverse effect. This could delay parameter readiness. As an alternative we might consider widening looking at a different adverse effect, e.g. Cerebral Venous Thrombosis and Cerebral Venous Sinus Thrombosi; Acute transverse myelitis etc. [26].
- Development of DGM and data analysis: the risk here is the complexity in setting up the DGM, which may extend the timeline for completion. Identification of flaws in the DGM code or issues in data generation might hinder progress, potentially impacting subsequent tasks. We advise to break down the development phase into smaller milestones for better tracking and allocate additional resources if needed. For example: begin by generating each parameter separately instead of using a complex algorithm. After generating the parameters, proceed with the generation of outcomes and constructing the data matrix. Once these steps are completed, initiate the analysis. Start by conducting a comprehensive analysis using one method, including

performance measures and bias calculations. Then, move on to the subsequent method for analysis. Implemention of rigorous testing procedures, involve multiple reviewers, and allocate contingency time for addressing identified issues before proceeding to the next task.

- Peer Review: there is a possibility of delays caused by a lengthy or challenging internal peer-review process may affect subsequent stages. This could be caused by clashing schedules, last-minute priority switches and other planning related risk a fellow researcher migh face. For this we accounted a longer internal peer review periode, to allow for flexibility in timelines. If our solution does not work, it is of utmost importance that we find time in out schedule. One possiple solution can be by overlapping other ongoing tasks, or plan for contingencies if review processes take longer than expected.

Mitigating these risks involve meticulous planning, allocation of resources, flexible timelines, and contingency measures to address unexpected challenges or delays that may arise during each phase of the simulation study. We think that out workplan has accounted for these possible risks, however, unforeseen situation may arise which can delay our research.

Methodological and computational limitations may occur during the data generation model (DGM) and substantive analysis stages of our research. The primary impact on our timeline stems from computational processing power. A notable advantage of simulation studies is the cost-effective assessment of the Monte Carlo Standard Error (SE) and the ability to significantly increase the number of simulations compared to other empirical studies. However, this comes at the expense of computational time. To proceed seamlessly rather than initiate anew, it is crucial to document the final state of the DGM. Our utilization of a large sample size and a considerable number of simulations could lead to prolonged processing times on conventional computers. Initially, we will evaluate the processing speed of a conventional computer when running the data generation and analysis with our normal sample size and simulation parameters. If this results in extended processing times, it becomes imperative to employ High-Performance Computing (HPC). Moreover, it's crucial to consider that HPC resources are frequently in high demand, necessitating proactive testing well ahead of our schedule to ensure availability. Should HPC resources be unavailable, alternative measures must be explored. One possibility involves modifying the sample size and number of simulation, while another is leveraging Open Source HPC, such as OpenHPC. Adjusting the sample size and simulation count can be achieved through two methods: (1) reducing both by half, or (2) utilizing one significantly large sample size with only a single iteration of simulation. It's important to note that if this decision is made, adjustments to our data generation model will be necessary.

Overall, while the proposed simulation study presents a feasible and valuable research avenue, the identified risks emphasize the importance of meticulous design, validation, and interpretation. Mitigation strategies such as robust validation, comprehensive sensitivity analyses, and alternative approaches could address these risks, ensuring the study's reliability and significance in advancing statistical methodologies.

B.2.2 Scientific (a) and societal (b) impact

Our research is anticipated to yield significant impact within the field of vaccine safety studies and extend its relevance in societal aspect of pandemic preparedness.

Scientific Impact

In the short term, the research will offer critical insights into the comparative effectiveness and limitations of two fundamental methodologies employed in vaccine safety studies. These insights can enhance the methodological understanding within the field, potentially leading to refined approaches for evaluating vaccine safety data. The study's outcomes may prompt adjustments in research practices and methodologies, influencing how future vaccine safety studies are designed and executed. The outcome of this research might narrow down the choice researcher have to make in future vaccine safety studies, which might lead to faster researches done and perhaps uniform results.

In the long term, the research findings may contribute to the advancement of uniformity of vaccine safety research. Prior to achieving this, there is a need for more studies testing different study designs, e.g. case-controle, and pharmacovigilance studies. By identifying strengths, weaknesses, and nuances between self-controlled and cohort study designs, the research can foster the development of more robust methodologies, potentially improving the accuracy and reliability of vaccine safety assessments.

Relevance to Other Scientific and Societal Areas:

The implications of this research extend beyond its immediate field of vaccine safety. Insights gained from comparing these methodologies can be extrapolated to various fields within epidemiology, public health, and medical research that rely on observational studies. Yielding a better preparation in case we encounter a new pandemic. Understanding the comparative effectiveness of study designs can influence research methodologies beyond vaccines, benefiting broader epidemiological and observational studies.

From a societal perspective, the research outcomes have the potential to impact public health policies and decision-making concerning vaccine safety. The study's findings might contribute to more informed, evidence-based policies, leading to enhanced public trust in vaccination programs and potentially improving overall vaccine uptake rates.

Possible Application Perspective:

The output of this research could lead to the development of guidelines or recommendations for selecting appropriate study designs in vaccine safety assessments. These guidelines could influence researchers, healthcare practitioners, and policymakers involved in evaluating and ensuring the safety of vaccines. Additionally, the insights gained might stimulate further investigations or trials in vaccine safety, potentially leading to innovative approaches or technologies for monitoring vaccine safety in real-world settings.

In summary, the proposed research's outcomes are expected to exert a substantial impact within its research field by refining methodologies, extending relevance to various scientific domains, and potentially influencing public health policies. Its implications could pave the way for improved methodologies in vaccine safety assessment and foster a broader understanding of observational study designs in epidemiological research.

B.2.3 Ethical considerations

The proposed Monte Carlo simulation study comparing a self-controlled study versus a cohort study in vaccine safety research presents an opportunity to advance our understanding of methodological approaches in this critical domain. This study will not use any real world data, e.g. patient registry data, hospital data etc. Due to this aspect there is are no participants and there is no need to account for the Declartion of Helsinki [27]. However, this research endeavor raises several pertinent ethical considerations that warrant meticulous attention throughout the study regarding accuracy, potential misinterpretation, and transparency of the researcher.

Accuracy and potential misinterpretation of results constitute an ethical concern. It is incumbent upon us to ensure that the simulation of the DGM, the results, and conclusions are precise, reliable, and devoid of biases. We are conducting research with aim to prepare us and other researchers for a possible new pandemic. Any misinterpretation or misrepresentation we make of our findings could significantly impact the feasibility of our research and thus decision-making processes related to vaccine safety, vaccine safety studies, and potentially influencing public health policies. Therefore, it is of utmost importance to implement ample internal reviews, and discussions session. This leads to the transparency of us and our research. Transparency is integral to ethical research conduct. We must transparently report methodologies, assumptions, limitations, and potential biases. We also have to publish our simulation algorthms besides our research for full disclosure. Full disclosure of these aspects is crucial to prevent misleading interpretations and ensure a clear understanding of the study's scope, applicability, and reproducibility of our research.
There is a responsibility to anticipate any potential harm arising from the study's outcomes. Misunderstandings or misinterpretations by the public or policymakers could erode trust in vaccines or public health initiatives, emphasizing the importance of clear and accurate communication of findings. Moreover, ethical guidelines mandate the disclosure of any conflicts of interest that might influence the research [28]. Transparency regarding funding sources or affiliations that could potentially bias the study results is essential for maintaining credibility and integrity..

In case we deviate to our secondary DGM method, where we will use real-world data, we then need to address ethical considerations, the proposed study will then adhere rigorously to ethical guidelines and regulations governing data use and confidentiality set up by the World Health Organisation [29]. We will implement robust validation techniques and sensitivity analyses to ensure the accuracy and reliability of simulated results. Full disclosure of assumptions, limitations, and biases will be part of transparent reporting, while efforts will prioritize responsible and clear dissemination of findings to avoid misconceptions or misrepresentations.

In summary, the proposed simulation study in vaccine safety research recognizes the critical importance of ethical standards in scientific inquiry. By upholding these ethical principles throughout the research process, the study aims to contribute responsibly to the understanding of methodological approaches in vaccine safety studies.

B.2.4 Literature/references

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