Active Vaccine Safety Surveillance – AVSS
An Introduction

DCVMN Pharmacovigilance Working Group

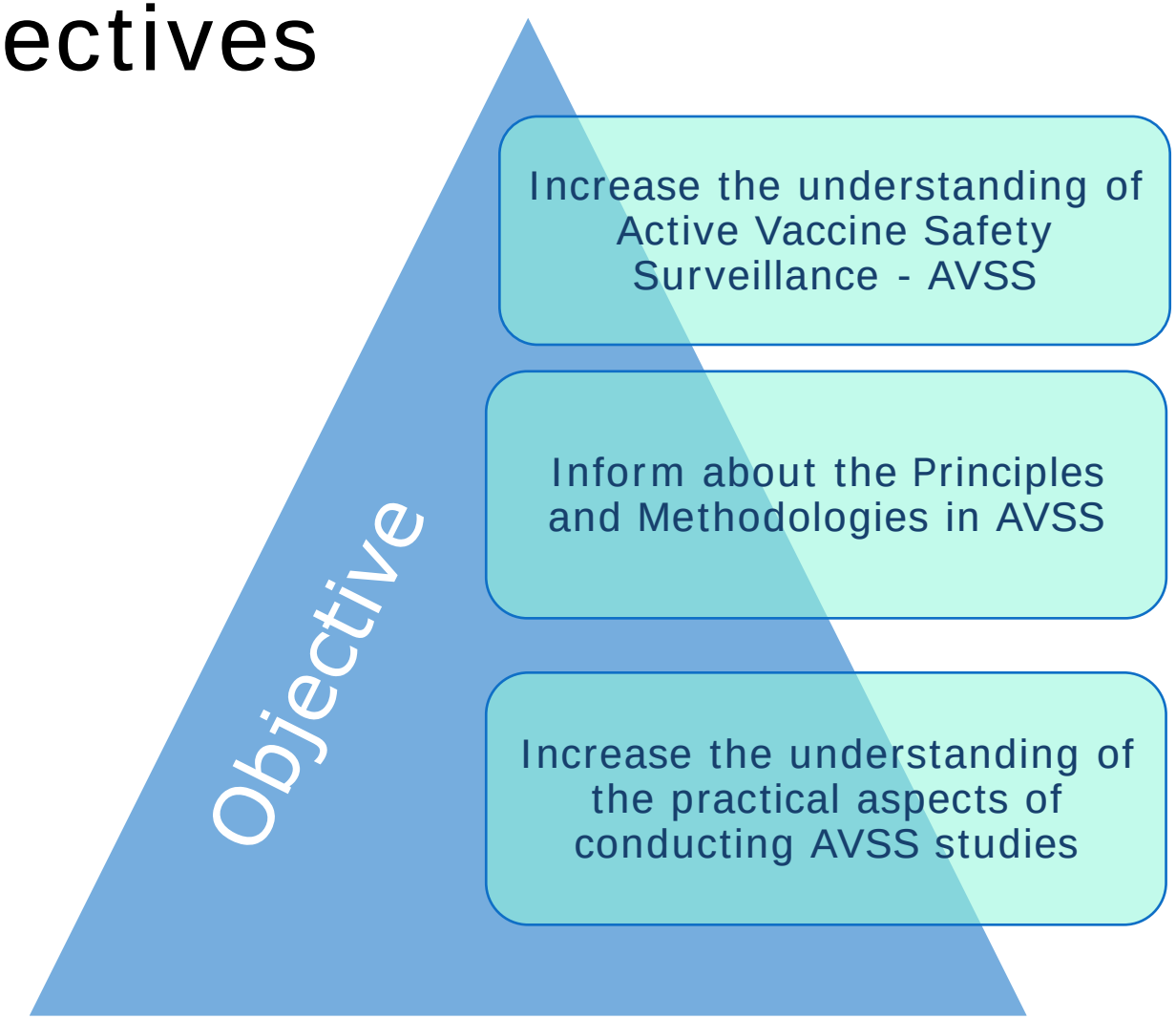
Active Vaccine Safety Surveillance Project

Workshop16-17 February 2023

- *Linda Nesbitt - DCVMN PV WG Chair*
- *Viska Indriani - DCVMN PV WG Co-Chair*
- *Katharina Hartman – Vaccine Safety Expert Consultant*

Katharina Hartmann – Vaccine Safety Expert Consultant

Course objectives



Expected outcomes

- Understand AVSS as a pharmacovigilance tool
- Understand the role and the need of AVSS
- Understand vaccine effectiveness in the frame of AVSS

- Understand the strategies applied in AVSS
- Understand the principles and methodologies applied in AVSS
- Understand how to address safety knowledge gaps

- Understand the practical aspects in conducting and managing AVSS studies
- Understand the importance and the need of multidisciplinary teams to manage AVSS studies

Module I
Introduction

- Background and definition of important terms in AVSS
- Effectiveness in the frame of AVSS
- The need for AVSS
- Approaches for performing post-authorization vaccine safety

Collection of Adverse Events Following Immunization (AEFIs) in post-authorization

Source of data

Spontaneous reporting, incl. stimulated reporting with or without using sentinel sites

Reports from the media / internet (Websites)

Passive surveillance

Literature reports

Reports from Licensor / Licensee

Active surveillance

Reports from vaccine registries / large linked databases / vaccine event monitoring

Reports from post-licensure studies (clinical and observational studies, sentinel site collection, etc.)

Vaccine Safety Surveillance in Post-Authorization

Safety surveillance is a fundamental tool in Pharmacovigilance

Passive vaccine safety surveillance

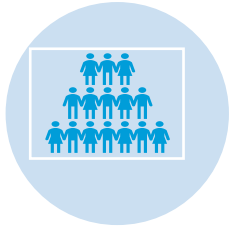
- Spontaneous reporting of AEFIs by health care providers, immunization providers, consumers, or by other sources to the appropriate level in each country depending on its national PV reporting system (NRA) or to the Marketing Authorization Holder MAH.
- Collected data does not derive from a study or any other organized data collection
- Is a relatively inexpensive strategy to cover large areas, but data quality and timeliness are difficult to control.

Active vaccine safety surveillance

- Data collection system that seeks to ascertain – as completely as possible – the number of AEFIs in a given population by a continuous organized process.
- Put in place to overcome the limitations and to complement passive systems – does not replace passive surveillance.
- Provides the most accurate and timely information, but it is an expensive strategy.

Hartmann 2023

Passive Vaccine Safety Surveillance Strengths

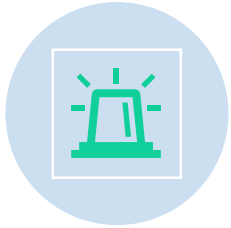


Covers all medicinal products / vaccines during their whole life cycle

Covers the whole patient population, incl. special sub-groups ("real life")

Ability to detect AEFIs that are

- rare
- unexpected
- unknown
- clinically relevant
- serious



Early signal function

Signal generation function

“the tip of the iceberg”

Inexpensive and less labor - intensive strategy to cover a large population

Passive Vaccine Safety Surveillance Limitations

DCVMN
Developing Countries Vaccine Manufacturers Network

No direct information on incidence

No information on vaccine exposure (no denominator)

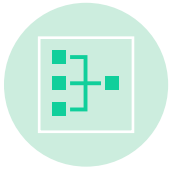
Reporting rate not stable over time (risk of over- / underreporting)

Sensitive to selective reporting

Not representative (bias)

Clinical information often too limited in terms of quality and quantity

Case evaluation / causality assessment questionable



No control group(s)

Generated signal cannot be tested

Poor case identification

Possibility to fake AEFIs

Active Vaccine Safety Surveillance
Post-Authorization Studies

DCVMN
Developing Countries Vaccine Manufacturers Network

Post-Authorization Safety Studies PASS (EMA GVP VIII)

- Any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of the risk management measures (EMA GVP Annex I).
- May be an **interventional clinical trial (Phase IV) or an observational, non-interventional study.**
- May be aimed at collecting data to enable assessment of safety of medicinal products in everyday medical practice.

Post-Authorization Efficacy Studies PAES (EMA PAES Guidance)

- Studies conducted within the authorized therapeutic indication to complement available efficacy data in the light of well-reasoned scientific uncertainties on aspects of the evidence of benefits to be / or only can be addressed post-authorization (EMA Scientific Guidance of efficacy studies 2014).
- Although the term refers to “efficacy”, PAES collect data in a setting that reflects general clinical practice rather than a randomized clinical trial.
- PAES are providing rather «effectiveness» data than «efficacy» data.

Active Vaccine Safety Surveillance
Non-Interventional study / Observational study

Features of Non-interventional / Observational Studies

- Interventions (e.g., vaccinations) are in accordance with the local clinical practice (e.g., national immunization scheme, EPI scheme)
- Investigator does not interfere with the choice of the intervention (e.g., vaccine)
- No assignment of the study participant to a pre-defined intervention (i.e., no randomization)
- No additional diagnostic or monitoring procedures applied to study participants
- Epidemiological methods used for analysis of the collected data

Sources of Observational Data (Real World Data)

- Vaccination / Immunization registries (patient registries)
- Hospital / medical chart reviews
- Data from hospital / sentinel sites
- Data from insurance claims databases
- Electronic health records
- Data from post-marketing safety studies

Post-Authorization Safety Studies PASS
EU Guidelines GVP Module VIII

DCVMN
Developing Countries Vaccine Manufacturers Network

HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 October 2017
EMA/813938/2011 Rev 3*

Guideline on good pharmacovigilance practices (GVP)
Module VIII – Post-authorisation safety studies (Rev 3)

Date for coming into effect of first version	2 July 2012
Date for coming into effect of Revision 1	25 April 2013
Date for coming into effect of Revision 2	9 August 2016
Revised draft Revision 3* finalised by the Agency in collaboration with Member States	27 September 2017
Revised draft Revision 3 agreed by the EU Network Pharmacovigilance Oversight Group (EU-POG)	4 October 2017
Revised draft Revision 3 adopted by Executive Director as final	9 October 2017
Date for coming into effect of Revision 3*	13 October 2017

HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 June 2020
EMA/395730/2012 Rev 3*

Guideline on good pharmacovigilance practices (GVP)
Module VIII Addendum I – Requirements and recommendations for the submission of information on non-interventional post-authorisation safety studies (Rev 3)

Date for coming into effect of first version	2 July 2012
Date for coming into effect of Revision 1	25 April 2013
Release for public consultation of Draft Revision 2	11 August 2015
End of consultation (deadline for comments)	9 October 2015
Revised draft Revision 2 finalised by the Agency in collaboration with Member States	14 April 2016
Revised draft Revision 2 agreed by European Risk Management Facilitation Group (ERMS FG)	15 July 2016
Revised draft Revision 2 adopted by Executive Director as final	4 August 2016
Date for coming into effect of Revision 2	9 August 2016
Draft Revision 3 finalised by the Agency in collaboration with Member States	13 May 2020
Draft Revision 3 agreed by the EU Network Pharmacovigilance Oversight Group (EU-POG)	29 May 2020
Revised draft Revision 3* adopted by Executive Director as final	15 June 2020
Date for coming into effect of Revision 3*	24 June 2020

Post-Authorization Safety Studies PASS
GVP Module VIII

HMA Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 October 2017
EMA/813938/2011 Rev 3*

Guideline on good pharmacovigilance practices (GVP)
Module VIII – Post-authorisation safety studies (Rev 3)

Non-interventional PASS concerned by this GVP Module VIII are those *initiated, managed, or financed* by a MAH voluntarily or pursuant to an obligation imposed by an EU competent authority.

Objectives:

- ✓ Quantify potential or identified risks
- ✓ Evaluate risks of use in populations with limited or missing safety information and after long-term use.
- ✓ Provide evidence about absence of a risk
- ✓ Assess patterns of drug utilization to add knowledge on product's safety (e.g., for indications, dosage, co-medication, medication errors).
- ✓ Measure effectiveness of a risk minimization activity.

Purpose of GVP Module VIII:

- ✓ Provide general guidance for the transparency, scientific and quality standards of noninterventional PASS conducted voluntarily or due to an obligation imposed by an NRA
- ✓ Describe procedures whereby an NRA may impose on a MAH an obligation to conduct a PASS
- ✓ Describe procedures applying to non-interventional PASS due to an obligation imposed by an NRA for the protocol oversight, reporting of results, and for subsequent changes to the MA.

Efficacy vs Effectiveness

- ✓ **Efficacy** is the degree to which a vaccine prevents disease, and possibly also transmission, under ideal and **controlled circumstances** – comparing a vaccinated group with a placebo group.

- ✓ When a vaccine is given to **a population various factors**, such as the medication individuals are taking, underlying chronic illnesses, age, and how the **vaccine is stored and administered** under everyday conditions, can reduce how effective the vaccine is at preventing disease.

- ✓ **Effectiveness** refers to how well the vaccine performs in **everyday practice** (real world effectiveness).

Post-Authorization Efficacy Studies PAES

DCVMN
Developing Countries Vaccine Manufacturers Network

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Vaccine effectiveness measured in terms of:

- Protection of individuals
- Disease control within the population

Situations in which vaccine PAES may be required:

- To evaluate effectiveness in different subpopulations (vaccine clinical trials typically performed in healthy individuals).
- To determine the clinical outcome following initial assessment on surrogate endpoints.
- To evaluate effectiveness of a vaccine in preventing serious infectious disease (e.g., mortality, hospitalisation).
- To determine long-term effectiveness of a vaccine (i.e., waning).
- To study effectiveness in combination with other vaccines.

Protocol_ACCESS_COVID-19 EHR Vaccine Effectiveness Protocol Template.docx (vac4eu.org)

12 October 2016
EMA/PDCO/CAT/CMDh/PRAC/CHMP/261500/2015
Paediatric Committee (PDCO)
Committee for Advanced Therapies (CAT)
Pharmacovigilance Risk Assessment Committee (PRAC)
Committee for Medicinal Products for Human Use (CHMP)
Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh)

Scientific guidance on post-authorisation efficacy studies

- For post-authorization efficacy studies (PAES), there should be a **well-reasoned scientific uncertainty** to **enhance the understanding** of therapeutic efficacy and **the benefit-risk** of a medicine with implications for better use in clinical practice.
- In addition, it should be **ethical and feasible** for a study to be designed with a **suitable methodology**, taking in account the post-authorization setting and whether the study can be conducted in a timeframe and manner that gives reliable and interpretable answers to the question at hand.
- **Agreement** should be sought as early as possible **between the regulator and sponsor** on the appropriateness of a study design.

Hartmann 2023

Terms of Key Relevance for AVSS Knowledge Gap*

Refers to the lack of available or easily accessible information on vaccines in countries needing respective information in contexts like:

- Vaccine introduction
- New safety issue
- Change in the vaccination program
- Inadequate passive surveillance system

A lack of information can be a

- Research gap
- Question not yet answered sufficiently

*Definition proposed by the CIOMS Working Group on Vaccine Safety

Why and When Active Vaccine Safety Surveillance /1?

Active Vaccine Safety Surveillance AVSS is an important tool for proactive, timely and rigorous safety surveillance to address **knowledge gaps.**

Introduction of new vaccines with limited safety data package at time of deployment (e.g., emergency use in pandemic situations)

- New vaccine against diseases endemic only to resource-limited countries with limited passive vaccine surveillance systems and no safety data from other countries available
- Introduction of an established vaccine to a new market / immunization program

AVSS and the Risk Management Plan (RMP)

- AVSS methods used to further identify, characterize, assess and minimize risks (e.g., knowledge gaps) as described in the Risk Management Plan Part III, Section 2 and in Part V .
- Evaluating safety in specific populations (missing information as defined in the RMP)
- Conducted voluntarily by the MAH or pursuant to an obligation imposed by an NRA / EU competent authority.

Knowledge gaps are ideally addressed in the RMPs

Why and When Active Vaccine Safety Surveillance /2?

DCVMN
Developing Countries Vaccine Manufacturers Network

See also the 6-step algorithm in *CIOMS Guide to Active Vaccine Safety Surveillance, 2017, p 8*

AVSS can be implemented any time through-out the post-authorization life-cycle

Reasons for considering AVSS (examples):

- Study included by the MAH in Part III of the RMP (Pharmacovigilance Plan).
- Study imposed by the NRA / NIP:
  - ✓ as a condition for authorization of a new vaccine.
  - ✓ to establish safety in the own population when introducing a new or established vaccine into their jurisdiction.
  - ✓ change in the vaccination program (e.g., new dosing, new immunization schedule, etc.).
- To study a new identified safety issue (e.g., detected through signal management activities in passive surveillance)
- To study international or local safety concerns raised e.g., in the literature, by the media, etc.
- When extending the use of the vaccine to a new population or circumstances e.g., in an outbreak situation for timely impact assessment
- To study the safety profile of a new vaccine in LMICs with limited passive surveillance capacities (e.g., when introducing a new vaccine aimed at diseases of resource-limited countries).

Each of the examples may prompt stakeholders (e.g., MAH NRA, NIP, MOH) to question whether passive surveillance is sufficient – or additional data is needed for assessment of the benefit / risk balance.

Hartmann 2023

Post-Authorization Vaccine PV Approaches

	Passive Surveillance	Active Surveillance	
		Non-interventional	Interventional
Setting	• Spontaneous reporting • Stimulated reporting / enhanced passive reporting • Sentinel sites for enhanced passive surveillance	• Active case finding (e.g., field studies) • Registries • Large linked databases • Vaccine event monitoring systems	• Interventional Phase IV study
Data Analysis	Various AEFI analyses: • Case series • Disproportionality analyses (Data mining) • Observed / Expected (O/E Analysis)		
Key design		Observational study design: • Cross-sectional • Cohort • Case-control • Case only studies	Interventional study design: • Controlled / uncontrolled • Blinded / unblinded • Randomized / non-randomized

Hartmann 2023

Module II
Principles and Methodology

Data needed in AVSS

- Type of data needed
- Data collection

Study designs in AVSS

- Basic question
- Choice of the appropriate type
  - Feasibility questions
- Types of epidemiological study designs – Toolbox

Background rates – Observed/Expected Analysis

Data Sources
Data collection strategies in AVSS

Primary Data Collection – Field Study

- Information collected specifically for the research in the «field»,
  - ✓ e.g., sentinel surveillance, prospective observational studies not using information already recorded in databases / registries.

Secondary Data Collection – Databases / Registries

- Information collected in a record system / database, collected for other reasons , not associated with the specific research study.
  - ✓E.g., automated healthcare databases / health administrative databases, population / vaccination registries, hospital or primary care clinic registries, etc.
  - ✓Record Linkage strategies
- Identification of the secondary data source if «fit for purpose», reliable and relevant to the study research question / meets the needs of the study (structured feasibility assessment of the data source).
- Data access consideration (accessibility of the data, contracting logistics. etc.).

Choosing the Study Design
Basic questions

What is the research question?

- Framing of the research question:
  - ✓ e.g., does vaccine X trigger a risk of event Y?
  - ✓ e.g., is the rate of an AEFI with vaccine X greater than would have occurred by chance (i.e., without the immunization, background rate)?
- Answering evidence gaps to enable informed decision making (i.e., knowledge gaps)?
  - ✓ Relevant to the National Regulator?
  - ✓ Relevant to the National Immunization Program?

Which research design is most appropriate to answer the research question?

- What is the most appropriate methodological approach?
- Feasibility assessments to plan and design for an appropriate study
  - ✓ Scientific feasibility
  - ✓ Operational feasibility

Choosing the Study Design
Scientific Feasibility Questions

- What is the most appropriate study design - prospective / retrospective; type of specific design?
- What is the most appropriate data collection strategy - primary (field study) or secondary (large healthcare databases)?
- What is the adequate risk period?
- Is a comparator required – if so, what is an adequate control group?
- What is the required sample size?
- What are the most appropriate statistical methods to control for bias, confounding, missing data?
- What are the inclusion / exclusion criteria?
- What are the expected limitations of the study?

Hartmann 2023

Choosing the Study Design
Operational Feasibility Questions

DCVMN
Developing Countries Vaccine Manufacturers Network

Governance

- What are the ethical requirements (Ethics / Scientific Committee submissions)?
- What are the regulatory submission requirements?
- What are the Data Protection Directives in the respective county / region?
- Is there a need for Informed Consent?
- Is there a need to collect and report serious adverse events ? If yes - how will this be performed?

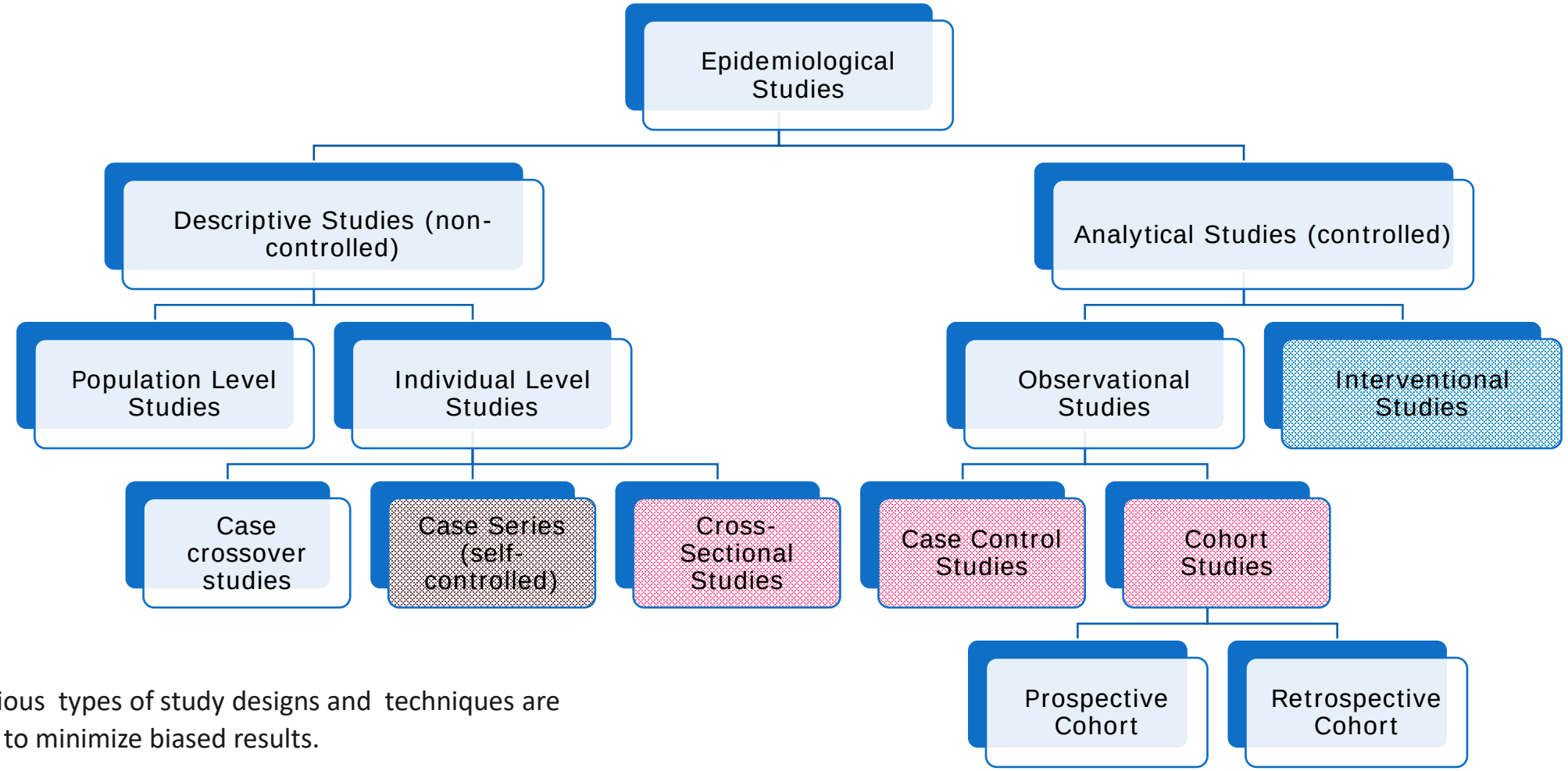
Vaccine manufacturers constraints

- What are the timelines for delivering results according to regulatory requirements / expectations?
- Are the level of resources and budget for the study acceptable?

Partnership / Collaborations

- How can the company / sponsor get access to the data?
- What kind of study to implement (e.g., industry – sponsored, collaboration, outsourced, etc.)?
- Which types of collaborations are needed?
  - ✓External collaborators (e.g., coordinators, etc.) required?
  - ✓Can the Principal Investigator be identified?
  - ✓How can the experts be identified?

Basic Epidemiological Study Designs*



Phase IV Clinical Trials (e.g., large simple safety trials)

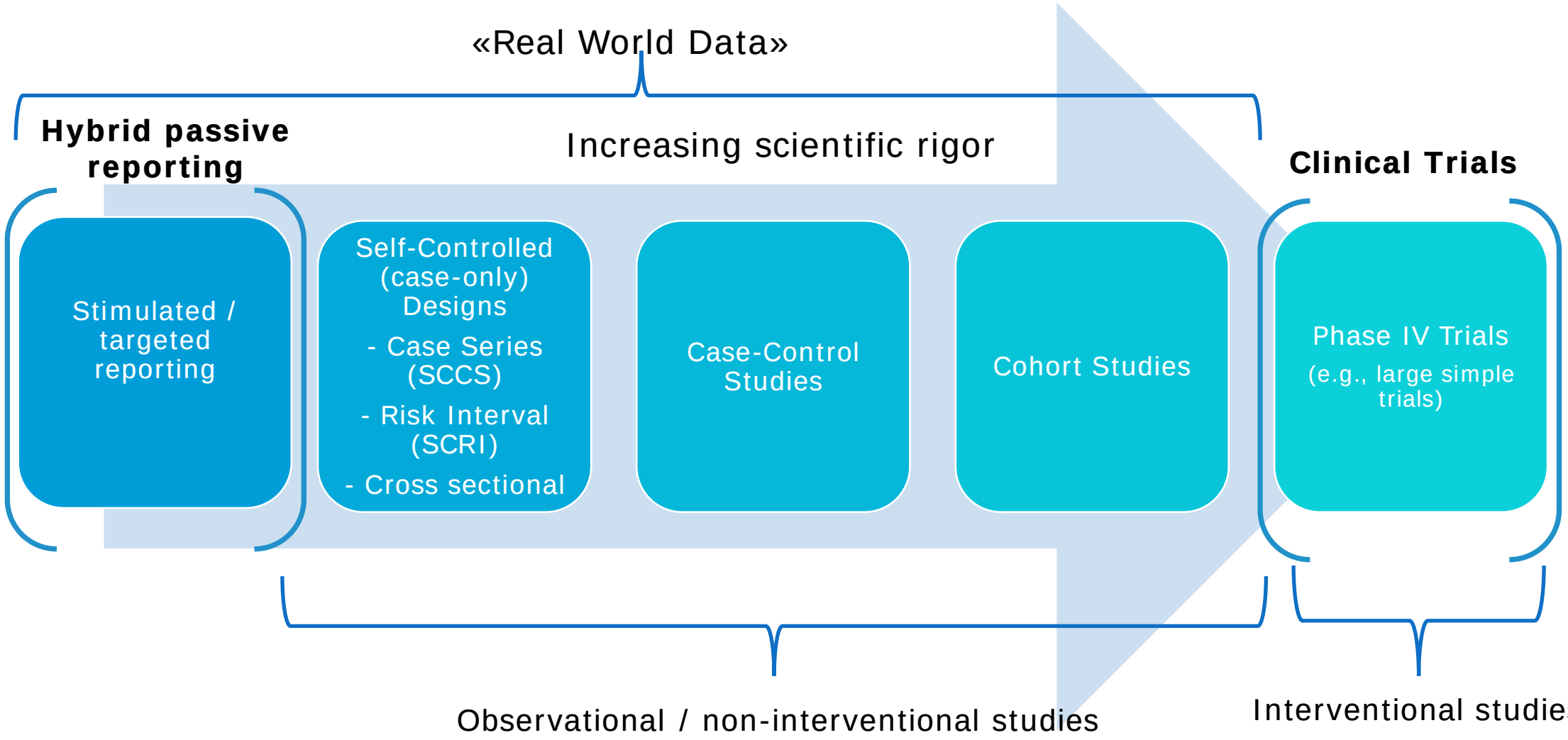
Designs preferably used in AVSS

Design preferred for vaccine AVSS

*various types of study designs and techniques are used to minimize biased results.

Hartmann 2023

Types of Common Study Designs in AVSS



Hartmann 2023

Hybrid Passive Vaccine Safety Surveillance
Stimulated / Targeted Reporting

DCVMN
Developing Countries Vaccine Manufacturers Network

Public information campaign to increase reporting during a mass vaccination

Encourage and facilitate reporting in specific situations, e.g., for new vaccines during a limited time period

Stimulation strategy focused on AEFI of special interest (AESI)

Resources and efforts more effective by limiting stimulated reporting to few sentinel sites

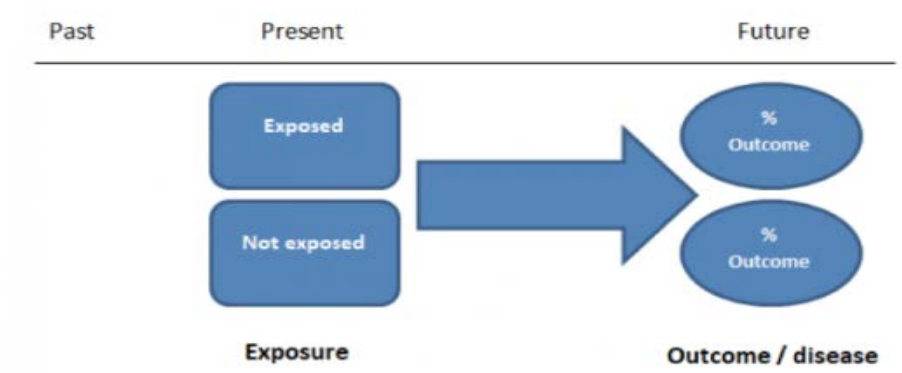
Various methods to enhance passive surveillance:

- Telephone / online reporting / Apps
- Systematic stimulation via e-mail reminders, personal visits etc.
- Additional training to healthcare providers (short-term effect to increase data quality)

Cohort Studies

Basic study design is always from exposure to outcome / disease / AEFI

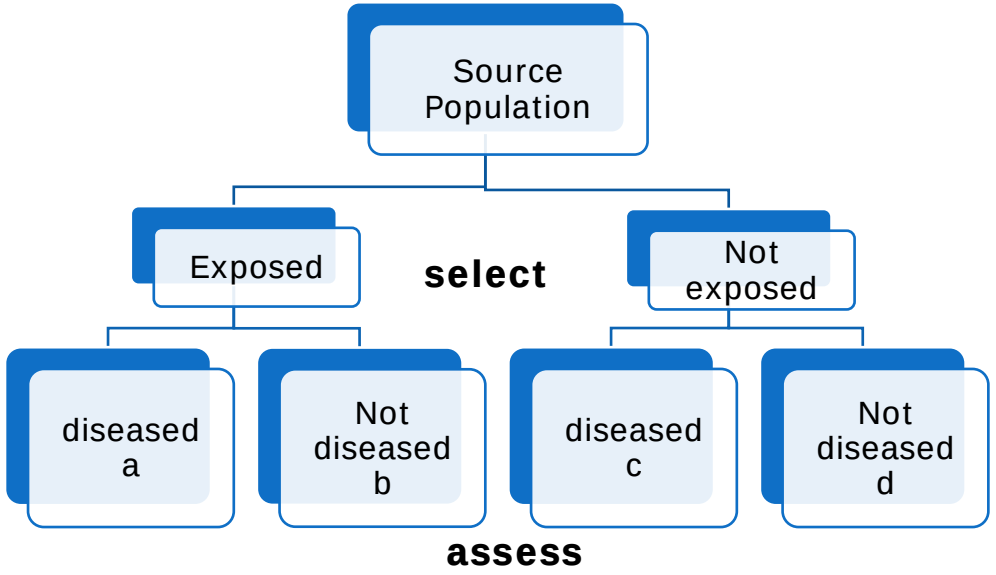
Prospective cohort study



Exposed and unexposed populations followed into future for the development of outcome (disease / AEFI).

Retrospective (historical) cohort study

Exposed and unexposed population followed retrospectively; exposure and outcome (disease / AEFI) have already occurred.



		Diseased: yes	Diseased: no
Exposed	yes	a	b
	no	c	d

Relative Risk RR:

$$\frac{a}{(a+b)} : \frac{c}{(c+d)}$$

Cohort studies

ADVANTAGES

- Measures risk: Relative risk directly computable
- Assessment of multiple outcomes possible
- Standardized observation with well-defined case definitions
- Well defined temporal sequence
- Transparent analysis

Prospective:

- Less chance of bias
- Matching / stratification to control confounders

Retrospective (historical):

- Use of datasets collected for other purposes “secondary data” (e.g., registries, healthcare databases, hospital patient cards, etc.)
- Greater statistical power to detect rare AEFI
- Earlier detection of potential safety signals

PROBLEMS

- Require well-defined comparator groups

Prospective:

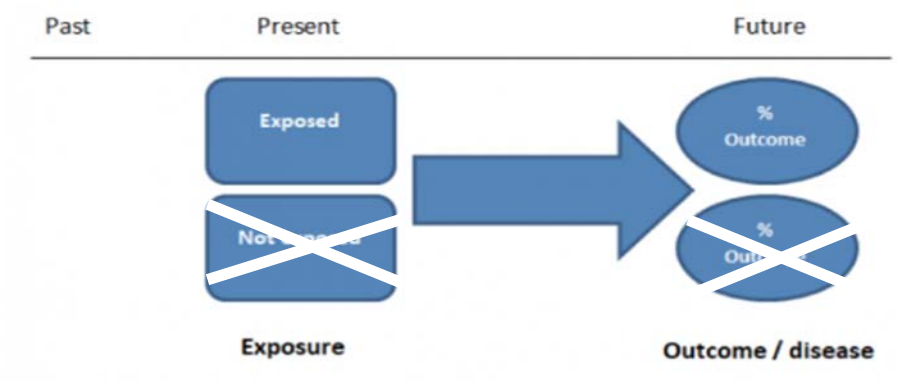
- Studies must be very large for rare AEFIs and AEFIs with long latency interval
- Time consuming
- Loss to follow-up participants
- Logistic requirements and costs (expensive)

Retrospective (historical):

- Bias
- Often poor information on exposure and outcome
- Susceptible for misclassification of exposure
- Temporal confounders
- Changing trends in AEFI detection and variation in diagnostic / coding criteria over time

Cohort Event Monitoring (CEM)

Cohort event monitoring



The **Cohort Event Monitoring** (CEM) is a new application that enables the **monitoring** of a **cohort** of patients or individuals prescribed a medicine / **exposed to a vaccine** in the hospital or in secondary care settings **for specific health outcome of interest (e.g., AEFIs, AESIs).**

- Observational monitoring of a cohort of vaccinated individuals vaccinated with vaccine of interest (uncontrolled)
- Cohort is built up of all individuals receiving the vaccine together with demographic data(incl. medical history)
- Selection of individuals, e.g.,:
  - Use of Hospital-based Sentinel Surveillance Systems (HBSS)
  - Use of Demographic Health Surveillance Site (DHS / DHSS)
  - Use of registries
- All AEFIs recorded /collected during a pre-defined time period using appropriate data collection methods (apps, telephone, questionnaires, visits, etc.)
- Can generate signals and AEFI incidence rates (hypothesis generation and testing)
- Basis for Observed- to – Expected Analyses using background rates from the same / similar setting (see O/E Analysis)

Example from research-limited setting

A cohort study utilizing health and demographic surveillance sites (HDSS) in Ethiopia.
Berhane Y et al, PLOS ONE 2014

Issue: To monitor AEFI comparing the rate of injection-site abscess following pneumococcal conjugate vaccine (PCV-10) and the pentavalent vaccine (DTP-HepB-Hib).

Location: Ethiopia

Datasources: Vaccination cards that specified type of vaccine and site of injection plus vaccine registration books maintained at vaccination centres.

Vaccine: Pneumococcal conjugate vaccine (PCV-10) and the pentavalent vaccine (DTP-HepB-Hib).

Outcomes: Household-based surveillance – at 48 hours and 7 days after vaccination by trained interviewers using uniform follow up visit form. Hospital-based surveillance – study personnel visited health care facilities weekly.

Population: House-to-house survey in all the study sites enumerated eligible study population. Photo ID with unique identification number was issued to mothers of eligible infants.

Design: Cohort study

Methods: The study was conducted in existing HDSSs in Ethiopia. Household population records are updated annually. Data on vaccines received and AEFI were collected systematically and prospectively at vaccination centres, households, and clinics/hospitals. Verbal autopsies were conducted for any deaths identified. Unique identification number allowed linkage between data sources. Informed consent was obtained.

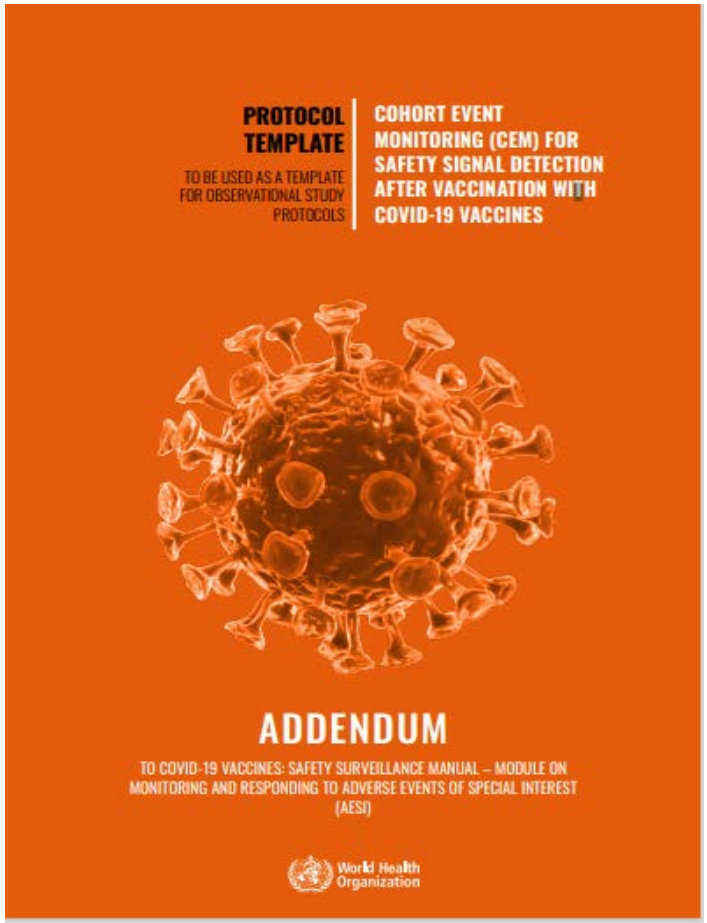
Findings: No significant differences were observed.

Lessons: The study illustrates the use of data on immunization history linked to data on health events ascertained from home visits, clinic visits, hospital admissions, and demographic observations of mortality using the common individual ID number assigned to all HDSS residents.

DCVMN
Developing Countries Vaccine Manufacturers Network

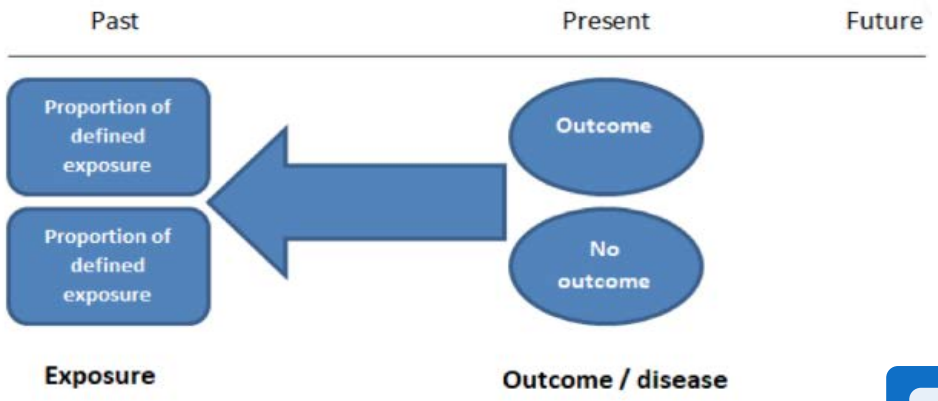
Protocol template for cohort-event monitoring of Covid-19 vaccines

Protocol template
Cohort Event Monitoring (CEM)



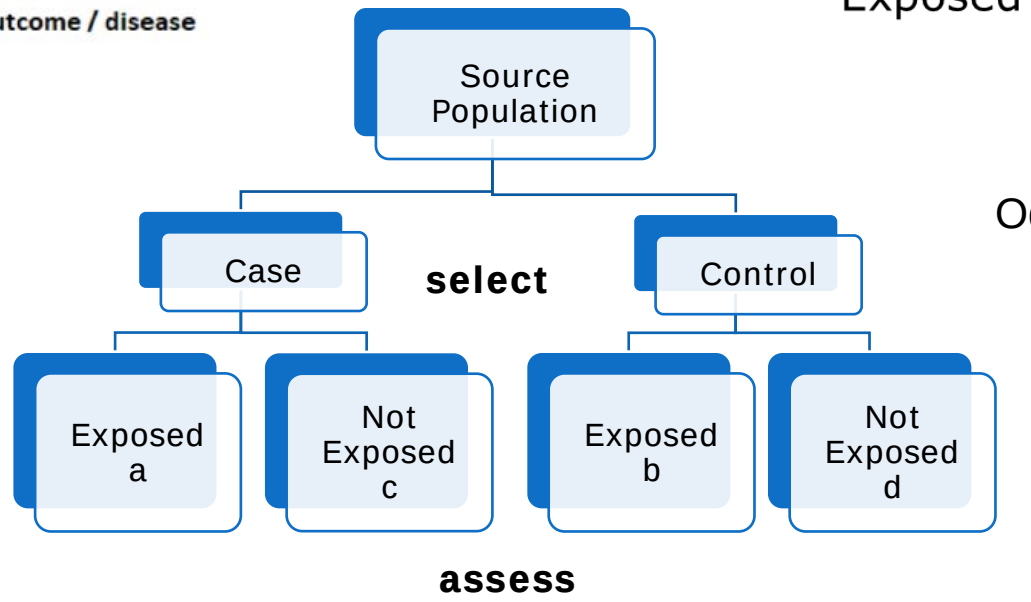
Case-control Studies

Basic study design is always from outcome / disease /AEFI to exposure



Individuals with a disease / AEFI (cases) from a source population are compared to disease /AEFI - free individuals (controls)with respect to prior exposure to a medicine / vaccine.

Cases and controls represent the same source population from the same time period.



Vaccine received yes / no (Exposed)	Diseased (case) yes	Diseased no (control)
yes	a	b
no	c	d

$$\text{Odds Ratio} = \frac{a\,d}{b\,c}$$

Odds of vaccination among cases (a/c) is compared to odds of vaccination among the controls (b/d)

Case - control Studies

ADVANTAGES

- Standard design
- Best for rare AEFIs and long latency intervals to provide evidence of an association
- Uses small data samples from entire population
- Fast and inexpensive
- Assessments of multiple risk factors possible
- Use matching to controls on variables for time-varying confounders

PROBLEMS

- Particularly prone to bias
  - selection of cases
  - selection of controls
  - exposure assessment → recall bias
- Retrospective approach
  - data quality
  - misclassification
- Inefficient in case of rare exposure
- Unvaccinated population may be a limiting factor
- Relative and attributable risk not directly computable
- Potential for failing to identify confounding variables

Example from resource limited setting

A case-control study of a rare AEFI in Mexico and Brazil
Patel MM et al, NEJM 2011

Issue: To assess the association of a newly introduced monovalent rotavirus vaccine (RV1) with intussusception.

Locations: Mexico and Brazil.

Datasources: Review of vaccination cards and provider records plus parent interviews.

Vaccine: Monovalent rotavirus vaccine.

Outcomes: Hospital-based surveillance with review of clinical records by trained study personnel.

Population: The study was conducted in 53 hospitals in 7 states in Brazil and 16 hospitals in 10 states in Mexico.

Design: Case-control study (in addition to self-control case series).

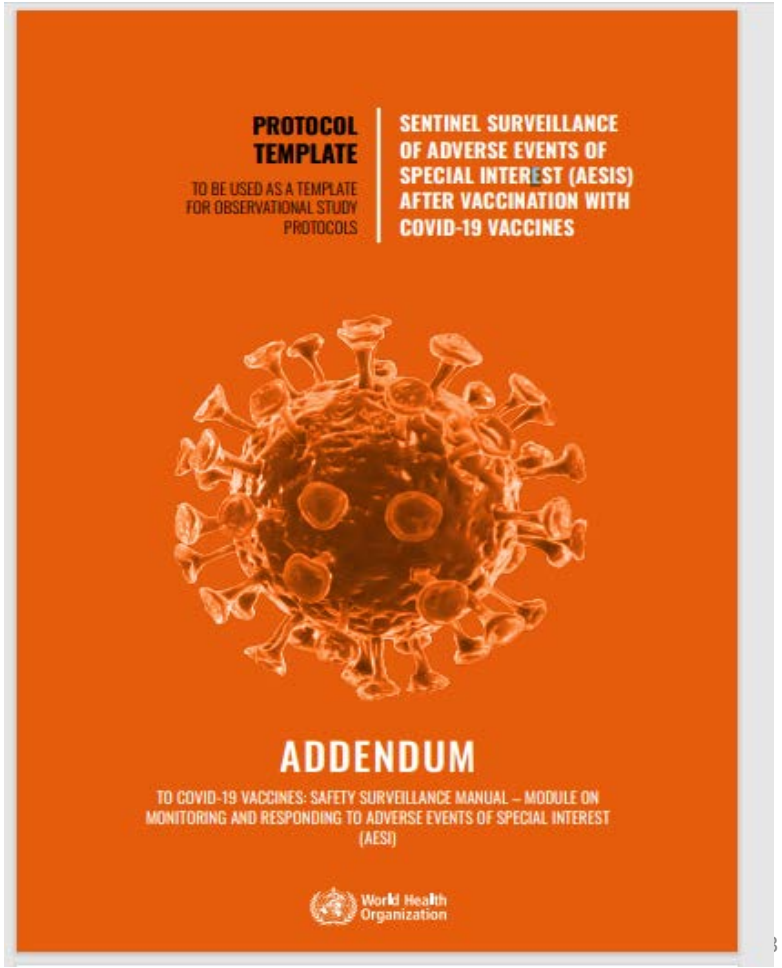
Methods: Cases of intussusception were identified independently of their vaccination status through prospective enrolment at the participating hospitals. Informed consent was obtained. Controls were identified from the same population as the cases by matching on neighbourhood of residence. In addition to the case-control analysis, a self-controlled case series analysis was also performed.

Findings: A small increased risk of intussusception was found.

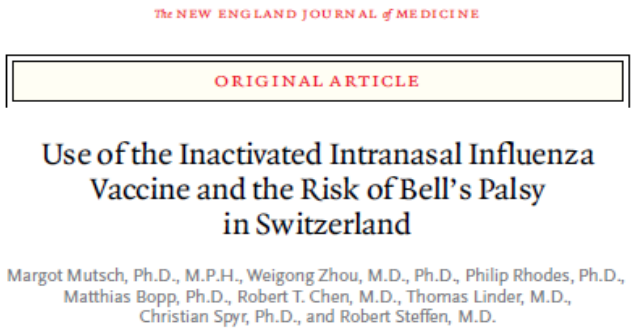
Lessons: Although not strictly from RLC settings, the study illustrates the basic principles of conducting a case-control study. Use of hospital-based surveillance would be applicable only in settings where the particular AEFI (intussusception in this case) would have come to medical attention. Matching controls to cases based on neighbourhood of residence is a useful strategy which could be applied in settings without a well-enumerated population database or register from which to select controls. This type of study could be relatively expensive as trained study personnel were employed to conduct periodic monitoring and review of records at several hospitals

DCVMN
Developing Countries Vaccine Manufacturers Network

WHO Sentinal surveillance template
Protocol template
Case – Control Study Design



Bias in case-control studies
Example


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Use of the Inactivated Intranasal Influenza Vaccine and the Risk of Bell's Palsy in Switzerland

Margot Mutsch, Ph.D., M.P.H., Weigong Zhou, M.D., Ph.D., Philip Rhodes, Ph.D., Matthias Bopp, Ph.D., Robert T. Chen, M.D., Thomas Linder, M.D., Christian Spyr, Ph.D., and Robert Steffen, M.D.

NEJM 2004; 350: 896-903

	Bell's palsy (N = 250)	Controls (N = 722)	adj. OR (95% CI)
intranasal vaccine	63 (25.2%)	7 (1.0%)	84.0 (20.1-351.9)
i.m. vaccines	10 (4.0%)	41 (5.7%)	1.1 (0.6-2.0)

Non-randomized, selection bias, problem with matching

- Case-control study overestimated the risk of Bell's palsy
- Case series analysis performed with all eligible cases (N=773):
  - Various calculations were performed to adjust for overestimation
  - Rates estimated in the defined risk period (1-91 days p.v.):
    relative risk of 19 for the 3 months period
    excess risk rate of 13 cases per 10'000 vaccinees

Open, randomized controlled multi-center clinical trial

During Flu season 2001/2002 (performed in 7 countries)

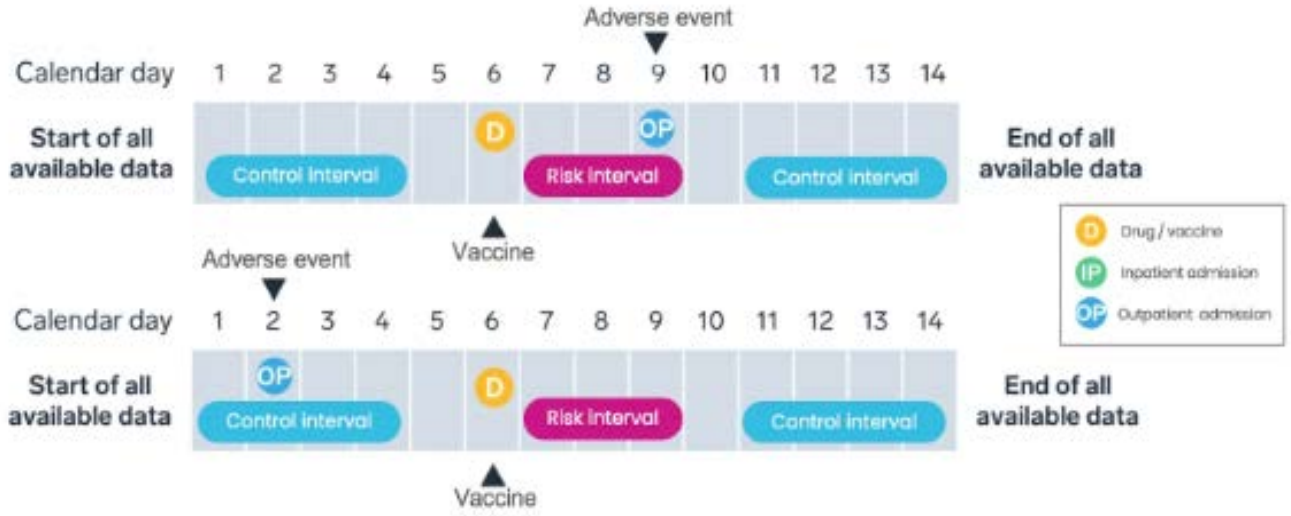
	Bell's palsy	no signs	Total
Nasalflu vaccinees	14	6'377	6'391
i.m. vaccinees	1	6'368	6'369
Total	15	12'745	12'760

Relative Risk RR (95% CI) = 13.9 (CI 1.8 – 106.1)

- intranasal vaccine: 2.19 / 1'000 vaccinated
- i.m. vaccine: 0.16 / 1'000 vaccinated
- RR 13.9 (CI 1.8-106.1)
- attributable risk: 2 / 1'000 vaccinated

Self-Controlled Case-only Design

Self-Controlled Case Series (SCCS)



Mattox / Patrick Aetion, 2023

Hypothetical patient timeline in the SCCS design

Hypothetical timelines of two vaccinated individuals. The top individual experienced an adverse event (e.g., requiring an office visit) during the risk interval. The bottom individual experienced an adverse event during the control interval. An optional wash-out period may exist between the risk interval and control interval.

Hartmann 2023

- Relatively novel strategy, originally developed to estimate the relative incidence of an acute, transient adverse event in a pre-defined post-vax risk period, compared to other times (within the control window).
- Comparison between incidence rates in pre-defined exposed time periods (i.e., risk period) vs incidence rates of self-matched unexposed time periods ((i.e., outside of the risk window) time, only using cases (each case is its own control - comparison made within, not between individuals).
- All confounding factors, known or unknown, are controlled implicitly, however, does not account for variations over time
- Can have high efficiency relative to retrospective cohort methods for investigating transient effects of accurately recorded preventive agents, i.e., vaccines.

Self-Controlled Case Series (SCCS)

ADVANTAGES

- Collections of individuals with a single exposure (vaccine) evaluating the clinical outcome (e.g., AEFIs), no control group necessary.
- Best suited for relatively acute events and transient exposures accurately recorded with defined risk periods.
- Effective control for all fixed cofounders that are stable over time (even for the unknown/unmeasured ones).
- Allows for analyses in highly vaccinated populations, for active surveillance in resource-limited settings where unvaccinated population is difficult to find.
- Allows monitoring of defined AEFIs in a timely and cost-effective manner.
- Number of subjects required for SCCS tend to be smaller, produce statistically and clinically valid results with far fewer subjects.
- Self-control designs expand epi research capabilities: many different SCCS models, and extensions of the SCCS methods used in SCCS study designs.

PROBLEMS

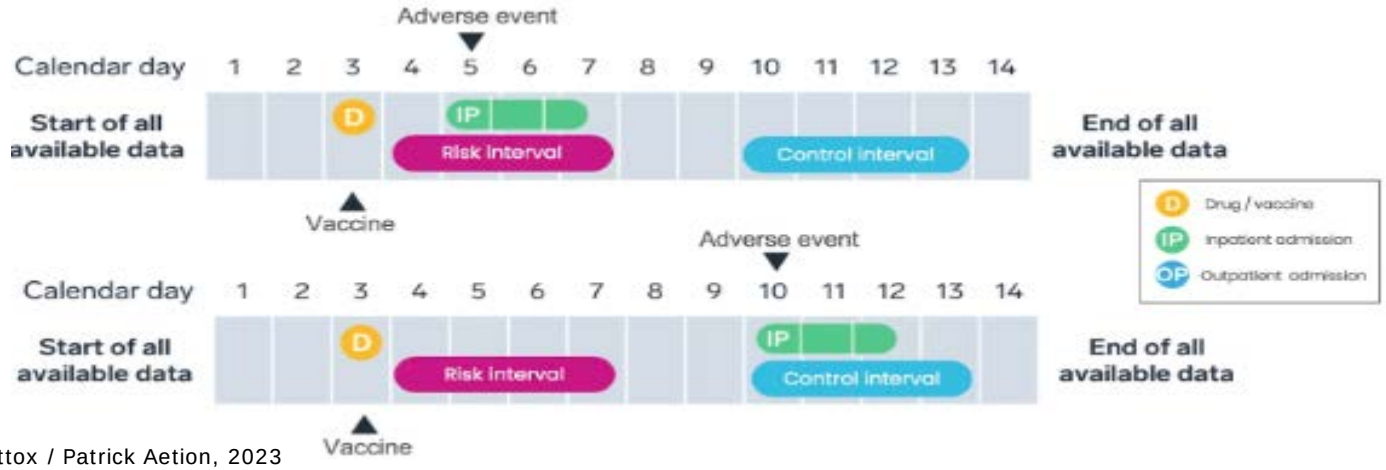
- Inclusion of pre-vaccination time periods may bias association between vaccine and event, if outcome of interest affects likelihood of future vaccination:
  - Assumption is that events do not alter the probability of subsequent exposure and events.
- Liable to selection and information bias as in any case control study.
- Referral bias in clinic-based studies, the sample may not be representative of the broader population.
- Does not account for variations over time within the same person.
- Precise timings of observation periods (i.e., risk period, control period) needed.

Hartmann 2023

Self-Controlled Case-only Design

Self-Controlled Risk Interval Study (SCRI)

Vaccinated persons, only informative cases included



Mattox / Patrick Aetion, 2023

Hypothetical patient timeline in the SCRI design.

Hypothetical patient timelines of two vaccinated individuals. The top individual experienced an adverse event (e.g., hospitalization) during the risk interval (window). The bottom individual experienced an adverse event during the control interval. An optional wash-out period may exist between the risk interval and control interval.

- The self-controlled risk interval study SCRI is a simplified / restricted version of the SCCS study design.
- Like the SCCS, SCRI estimates the relative incidence of an acute, transient adverse event in a pre-defined post-vax risk period, compared to other times within the control window.
- The SCRI includes only vaccinated individuals experiencing an adverse event (“health outcome of interest HOI”).
- Each individual contributes person-time in pre-specified risk and control window.
- Risk and control windows are fixed but need not to be equal.

Hartmann 2023

Self-Controlled Risk Interval Study Design SCRI

ADVANTAGES

- The same SCCS study design advantages apply to the SCRI study design.
- In addition:
  - Specifically suitable to assess an association between an acute / short risk exposure and an AESI.
  - Short control windows after risk windows selected instead of using all follow-up time available.
  - Less susceptible to time varying confounders due to shorter analysis period.
  - Since each individual's observation period is short, control for age and time effects often not required.
- .

PROBLEMS

- The same SCCS study design limitations apply to the SCRI study design.
- Power is reduced as compared with SCCS due to the inclusion of less unexposed time (only informative cases included), but often suffice for use with large databases where events are not very rare.
- Short risk exposure windows can be a limitation.

Example from research-limited setting

Active vaccine safety surveillance using a self-controlled analysis in Guatemala.
Asturias E. et al., Vaccine 2013

Issue: To study the safety of DTwP-HepB-Hib combination vaccine.

Location: Guatemala

Datasource: Documented at study enrolment at two paediatric clinics.

Vaccine: DTwP-HepB-Hib combination vaccine.

Outcomes: Parents reported possible AEFIs.

Routine telephone contact with parents.

Reviewed medical records of any health care encounters.

Active daily monitoring of database of paediatric emergency room and hospital.

Population: Healthy infants who received study vaccine at well-child care visits at two paediatric clinics in Guatemala City. Parents accessible by telephone.

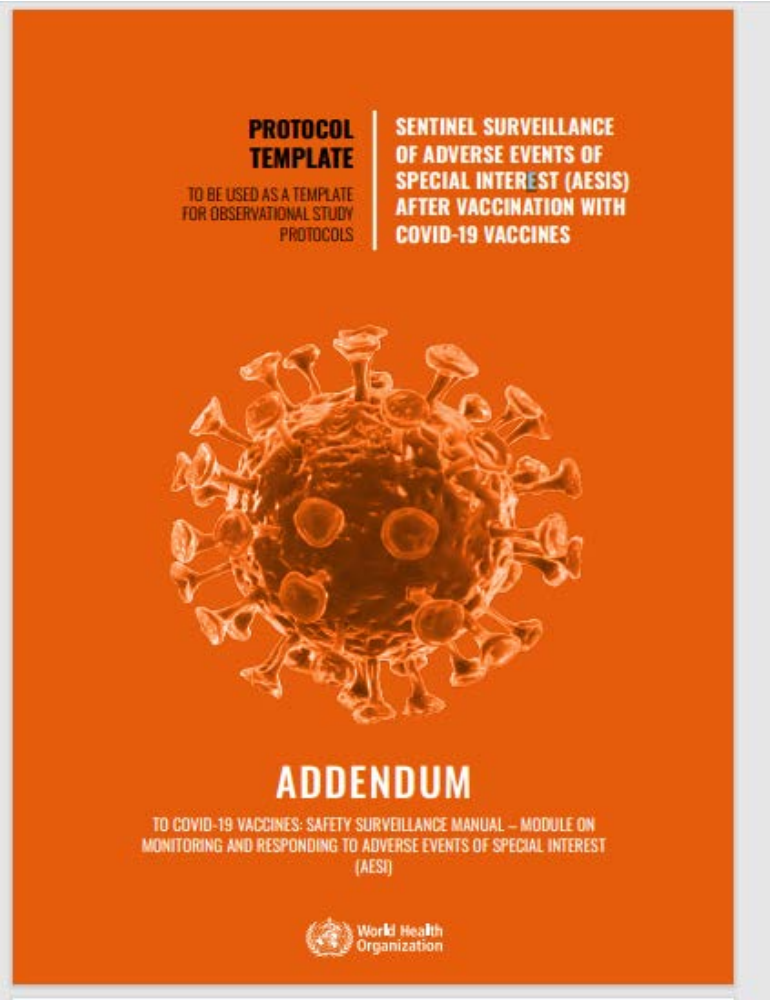
Design: Self-control case series.

Methods: Only vaccinated infants were studied to determine relative risk of AEFI occurring within 30 days of vaccination compared with days 31-60. Informed consent was obtained. Parents/guardians were asked to report any possibly serious symptoms to study physician or nurse. They were contacted by telephone at regular intervals to inquire about symptoms and health care visits. The research nurse completed AEFI form and reviewed medical records of health care visits. AEFIs were also captured through active daily monitoring at the paediatric emergency room and hospital using an electronic database (matched using unique identification number). Post-neonatal mortality rate was compared with the rate for the department of Guatemala (which is the jurisdiction in which the capital, Guatemala City is located), in 2008-2009.

Findings: The liquid pentavalent vaccine was not associated with increases in serious adverse events or hospitalizations.

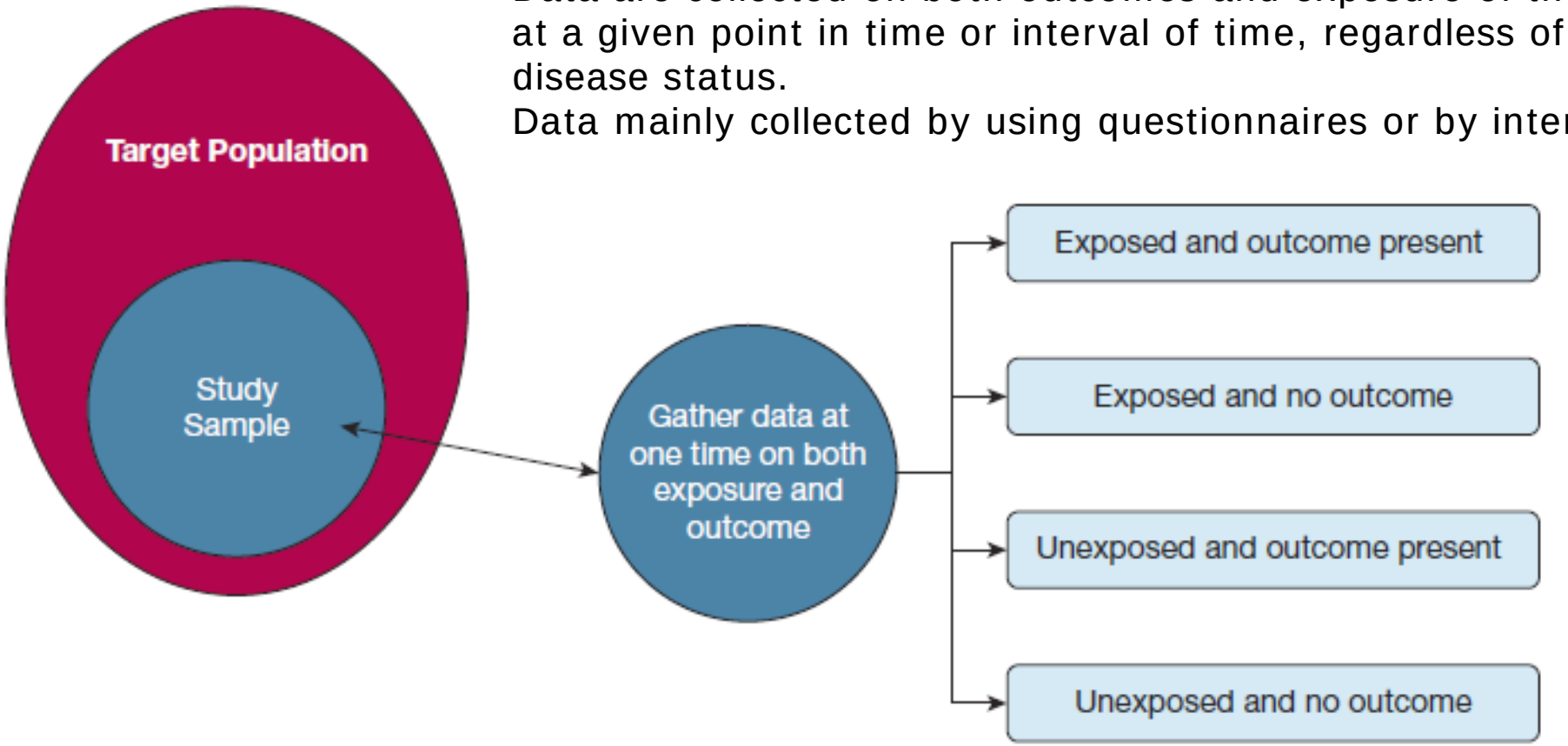
Lessons: This was a comprehensive active surveillance system in an RLC country that could serve as a model for other countries. The use of a self-control methodology meant that data was only needed on vaccinated infants and an unvaccinated comparison group was not needed. The feasibility of ascertaining all AEFI through multi-source active follow up was demonstrated. Although the study recruited only parents with access to telephones, 95% of population of Guatemala City owns a mobile phone and the methodology may be applicable in other RLC settings with relatively high mobile phone coverage.

<u>WHO Sentinel surveillance template</u>
Protocol template
Self-Controlled Risk Interval Study



Cross-sectional Studies

Data are collected on both outcomes and exposure of the individuals at a given point in time or interval of time, regardless of exposure or disease status.
Data mainly collected by using questionnaires or by interviews.



Hartmann 2023

Cross-sectional Studies

ADVANTAGES

- relatively quick and inexpensive
- no ethical difficulties
- data on all variables collected at one time only
- multiple outcomes and exposures can be studied
- easy for generating hypothesis
- findings can be used for in-depth research studies

PROBLEMS

- unable to measure incidence
- difficult to make causal inference
- associations identified might be difficult to interpret
- unable to investigate temporal relation between outcomes and risk factors
- not suitable for studying rare diseases
- susceptible to bias
  - non-response bias
  - recall bias

Cross-Sectional Study
Example

DCVMN
Developing Countries Vaccine Manufacturers Network

Short Communication

Adverse reactions following COVID-19 vaccination: An Ecuadorian experience

Emanuel Vanegas [a b], Karla Robles-Velasco [a b], María F. Osorio [a b], María José Farfán Bajaña [a b], Zouina Sarfraz [c], Azza Sarfraz [d], Juan Carlos Fernández Cadena [e], Derly Madeleiny Andrade Molina [e], Matias Panchana Lascano [b], Ivan Cherrez-Ojeda [a b]

2. Methods

We conducted an observational cross-sectional study to assess the potential adverse reactions to the Pfizer-BioNTech COVID-19 vaccine among a sample of healthcare workers (HCWs) in the city of Guayaquil, Ecuador, from March to May 2021. All individuals involved were part of the first phase of the national COVID-19 vaccination plan in our country and were contacted through a local registry established by a local private university. In the first telephone call, potential participants were explained about the purpose of the study, and only after voluntary informed consent was obtained further information was collected. Thereafter, weekly telephone calls were set up to ascertain if adverse reactions had occurred within 14 days of receiving the vaccine.

This study was conducted according to the principles established by the Declaration of Helsinki and was approved by the Expedited Ethics Committee of the Ecuadorian Health Ministry (Approval N° 024–2020). With the information recollected in the survey, personal identification was not possible; as such, anonymity, and personal data protection was guaranteed.

Adverse reactions following COVID-19 vaccination: An Ecuadorian experience. Ann Med Surg 2021

Vaccine Side Effects Following COVID-19 Vaccination Among the Residents of the UAE—An Observational Study

Subhashini Ganesan [1,2†], Latifa Mohammad Baynouna Al Ketbi [3†], Nawal Al Kaabi [3,4], Mohammed Al Mansoori [5], Noura Nasser Al Maskari [5], Mariam Saif Al Shamsi [5], Aysha Saeed Alderei [5], Hamada Nasser El Eissaee [5], Rudina Mubarak Al Ketbi [5], Noura Saeed Al Shamsi [5], Khuloud Mohammed Saleh [5], Aysha Fahad Al Blooshi [5], Flavia Martinez Cantarutti [1], Katherine Warren [1], Faheem Ahamed [1] and Walid Zaher [1,2,4,6]*

METHODS

Study Design and Study Setting

A cross-sectional study based on an online survey and telephonic interviews was conducted between 14 March 2021 and 4 September 2021 among the residents of the UAE. The survey was designed to identify the side effects reported after receiving a COVID-19 vaccination and no personal identification details were collected. An electronic consent was obtained during the online survey and only participants who agreed entered the survey. Participants in telephonic interviews also consented orally before they were presented with the survey. The study was approved by the Medical Research Department, DOH, Abu Dhabi, UAE (approval number: DOH/CVDC/2021/329).

Vaccine Side Effects Following COVID-19 Vaccination Among the Residents of the UAE—An Observational Study - PMC (nih.gov)

Rates of adverse events following immunization (AEFIs) /1

DCVMN
Developing Countries Vaccine Manufacturers Network

Observed rate

- Rate of all adverse events (AEFIs related or not related to vaccination)
- Measured in
  - pre-licensure clinical vaccine trials (randomized / placebo-controlled)
  - post-licensure vaccine studies

Background rate

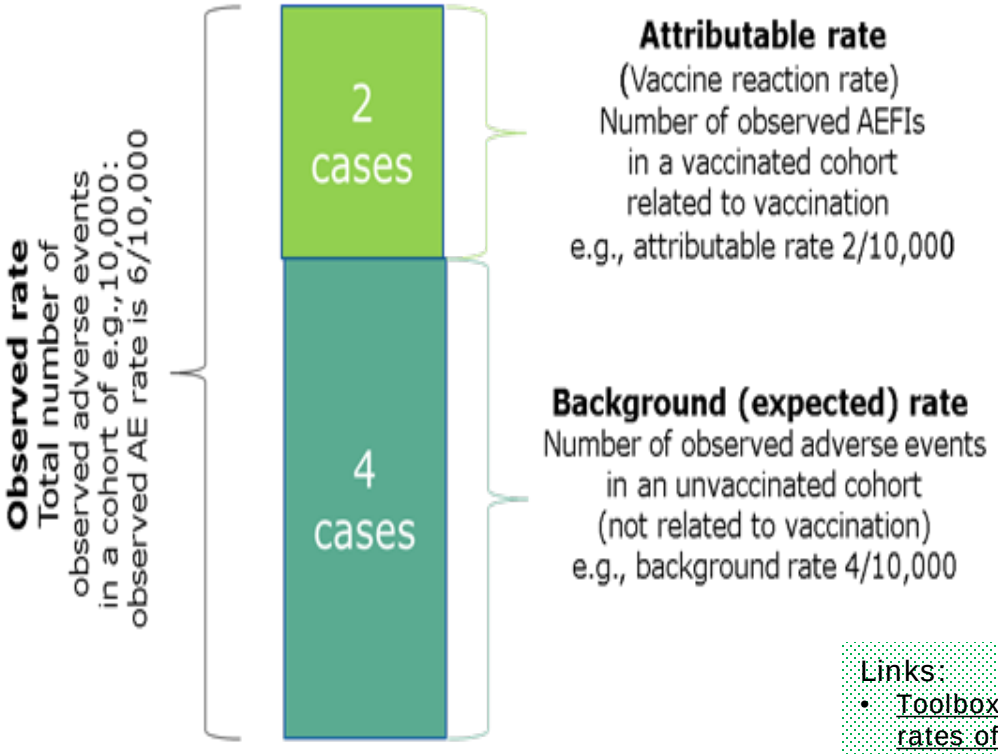
- Rate of adverse events occurring in a cohort not exposed to the vaccine, e.g., prior to the introduction of a new vaccine
- Likely to coincide in temporal relationship with the vaccination - Examples:
  - Multiple sclerosis in temporal association with hepatitis B vaccination in France

Attributable rate

- Rate of adverse vaccine reactions (AEFIs attributed to the vaccine)
- Measured / collected in
  - prelicensure clinical trials (randomized, placebo-controlled)
  - post-licensure vaccine studies
  - passive surveillance

Hartmann 2023

Rates of adverse events following immunization (AEFIs) /2



Attributable rate (Vaccine reaction rate) = **Observed rate – Background (expected) rate**

Links:
- Toolbox Background rates of AESI - VAC4EU
- Factors influencing background Incidence
- Demonstration of background rates | PLOS ONE

Challenges in assessing background rates of AEFIs /AESIs:

- Historic comparisons of AEFI rates with the expected rate within a general population is a common vaccine safety surveillance method.
- Background rate comparison methods using observational data (e.g., electronic health records, administrative claim data etc.) may generate high numbers of false positive signals:
  - Within-database background rate comparisons using observational data is sensitive (low type 2 error) but unspecific (high type 1 error) to identify safety signals.
  - Age and sex-adjusted rates and “time of risk” are crucial to minimize false-positive safety signals.
  - Caution when comparing background rates across literature and data sources, analysis methods, healthcare systems and populations.
- Availability of “locally relevant” background rates of disease incidence important for vaccine safety surveillance.

Hartmann 2023

Background Rates: Example
Vaccination and naturally occurring disease

Coincidental observation of diabetes if 1 million of young girls / women were vaccinated with a placebo

Disease	Diagnosed cases after the injection of a placebo per 1 million adolescents and young women / period of observation		
	1 Day	1 Week	6 Weeks
Asthma (ER)	27	188	813
Allergy (ER)	15	106	458
Diabetes (ER)	4	29	128
Inflammatory bowel diseases (ER)	2	10	45
Thyroiditis (H)	1	9	40
Systemic Lupus (H)	1	5	20
Multiple Sclerosis / Optical Neuritis (H)	0	2	10

Estimated risk of selected diseases in young girls/ women (9-18 years) assuming vaccination with a saline placebo according to the indicated scheme for a vaccine (0-1months) based on US rates for emergency room visits (ER) and hospitalizations (H) without vaccination

Adapted from CA Siegrist, PIDJ 2007

Observed–to–Expected (O/E) Analysis
Population-level

- O/E analyses rely on aggregate data without individual linkage
- O/E analyses compare observed rates calculated from spontaneous reporting systems or CEM with expected background incidence rates from independent sources.
- O/E analyses often used for vaccines when the AEFI is acute and short term to refine safety signals /within signal management process.

Safety concerns raised from:

- literature review data,
- medical reviews,
- disproportionate reporting,
- unexpected temporal relationship,

may trigger O/E analyses of spontaneous reports where clear knowledge on causality or magnitude of risk is lacking.

- Conclusions rely on multiple assumptions:
  - Number of administered doses administered to population known.
  - All cases presenting the AESI are spontaneously reported.
  - Background rate in the vaccinated population is the same as in the population used to calculate the expected rate
  - Population on which the background incidence was measured is not exposed to the vaccine of interest.
  - Risk period considered focuses on time period for which an excess of risk occurs in case of causal association.

Calculation of the expected number of cases for an AESI Y – Example:

- 3,000,000 doses of vaccine X sold world-wide
- Increased risk of Y within 30 days p.v., whatever dose
- Vaccination schedule: 3 doses at 2,4,6 months
- Assumptions: no dose effect and all 3 mio doses administered:
- **Person-time at risk**: 3,000,000 x 30 person-day= **2.46 / 100,000 person-years** (3,000,000 x 30/365 x 1/100,000)
- **Background incidence rate** for event Y is **4.8 cases per 100,000 person-years** (measured on unvaccinated population sharing similar demographic characteristics with the exposed population)
- **Expected number of cases of event Y:** 2.46 x 4.8 = **11.8**

Hartmann 2023

Mahaux O. et al., Pharmacoepidemiol. Drug Saf. 2016

Module III
Practical Aspects in conducting AVSS Studies

- Company functions involved in AVSS
- Basic steps to consider when deciding to conduct an AVSS Study
- Preparatory Work
  - Study protocol
  - Sample size considerations
  - Study registration
- Study Report
  - Regulatory reporting
- Toolbox

Practical Aspects when conducting AVSS Studies
Basic questions

Who will finance the study?

- MAH / Manufacturer?
- Public partner, such as Governmental Bodies (e.g., MOH, NRA, NIP, BARDA, CEPI etc.)
- Funding organizations (e.g., BMGF, GAVI, Welcome Trust, others)
- Consortia including different public and private partners
- Others

Who is responsible for the study / Who runs the study?

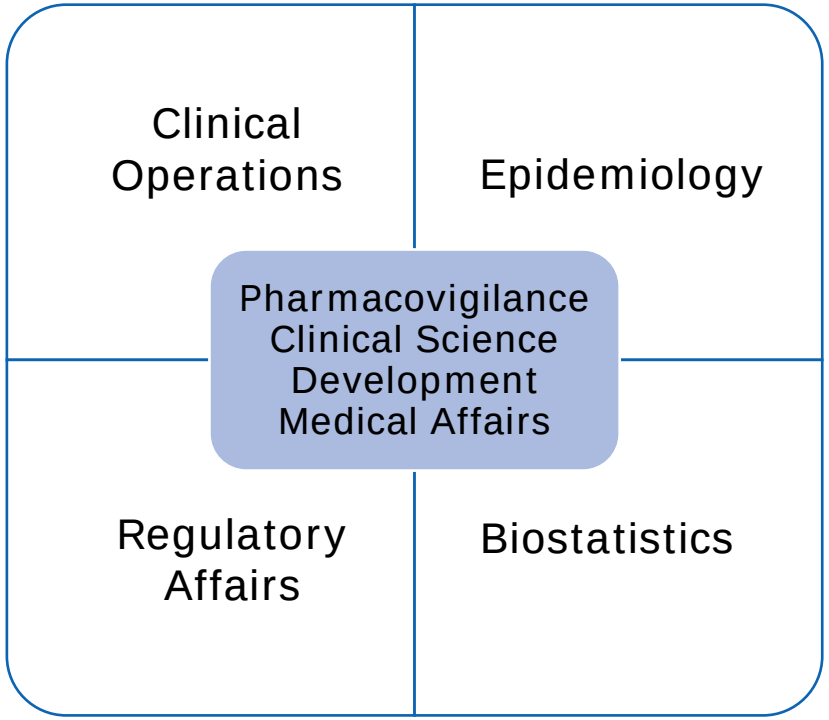
- Outsourced to CRO / academia / MAH / other?
- Private organization (e.g., MAH, CRO)?
- Public organization (e.g., governmental body)?
- Who is the Principal Investigator?
- Who is the Sponsor?
- Who oversees the study team?

What approvals are needed?

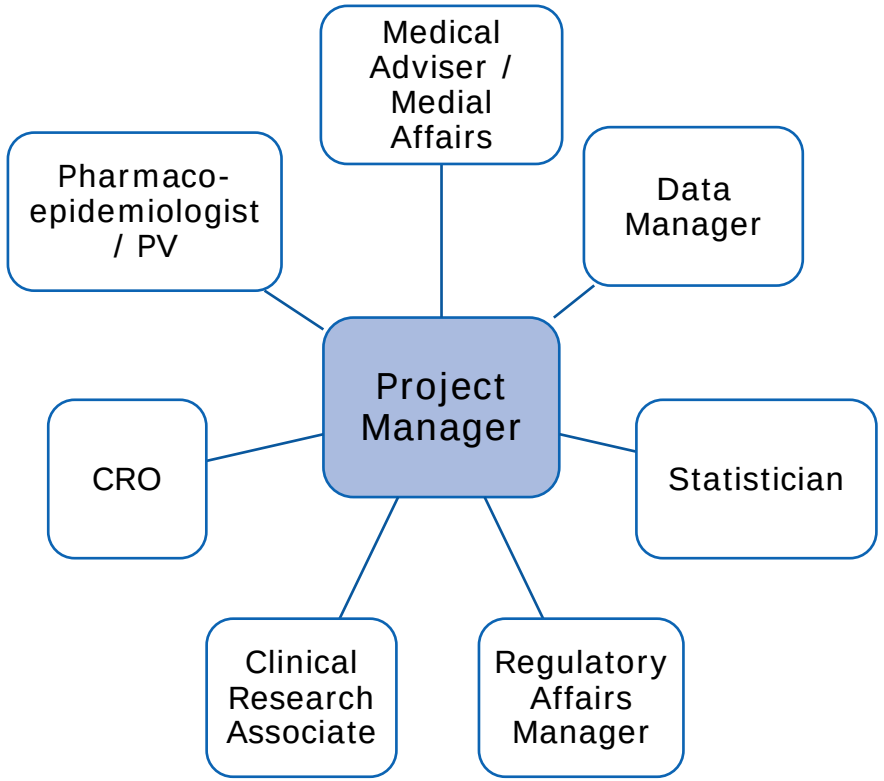
The answers to the questions determine the roles and responsibilities of each party.

Company Functions involved in AVSS
Company-sponsored study

Matrix Organization
Scientific Study Team



Matrix Organization
Operational Study Team



Project Documentation:

- ✓ Project Plan
- ✓ Who does What
  (Roles and Responsibilities)
- ✓ Tasklist
  (e.g., Gantt Chart)
- ✓ Workload Analysis
- ✓ Milestones
- ✓ Budget / Funding

Structures and Processes
Six basic steps

Planning: Objectives, study design, data collection methods / sources, ethical and data protection issues, data analysis, access to expert advice

Synopsis / Protocol writing and approval (includes defining study sites / PI / CRO / study coordinator / sample size; development of resp. forms, NRA / Ethics notification

Study preparation: Identification and training of study personnel, Statistical Analysis Plan SAP, study agreements (PI, Scientific experts etc.), set-up study site / database

Study implementation: Study registration, running the study, data collection as per protocol, data entry, stakeholder coordination as per their R and R (study oversight)

Data analysis and Report writing: Analyses as per SAP, interpretation of the data (e.g,, data robustness, limitations), writing of study report

Communication of study findings: Disclose study results in study registries, Publication, impact on B/R balance and product safety information, etc.

Hartmann 2023

Structures and Processes
Study Protocol

Format and content as per GVP Module VIII.B.3.1.

Study Title
Marketing Authorization Holder
Responsible Parties
Abstract
Amendments and updates
Milestones
Rational and Background
Research question and objectives
Research methods
Protection of human rights
Management and reporting of AEFIs
Plans for disseminating and communicating study results
References

Research Methods:
- Study design
- Setting
- Variables
- Data sources
- Study size
- Data management
- Data analysis
- Quality control
- Study limitations

Checklists for Study Protocols:

- EU / ENCePP:
  - ENCePPChecklistforStudyProtocols.doc (live.com)
  - Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies (europa.eu)
- STROBE*:
  - Checklists - STROBE (strobe-statement.org)
- NIH Observational Study toolbox:
  - nidcr-observational-protocol-template.docx (live.com)

*Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

Structures and Processes
Study registration

Check if registration of non-interventional AVSS studies is a legal requirement or recommended in the country / region the study will be performed.

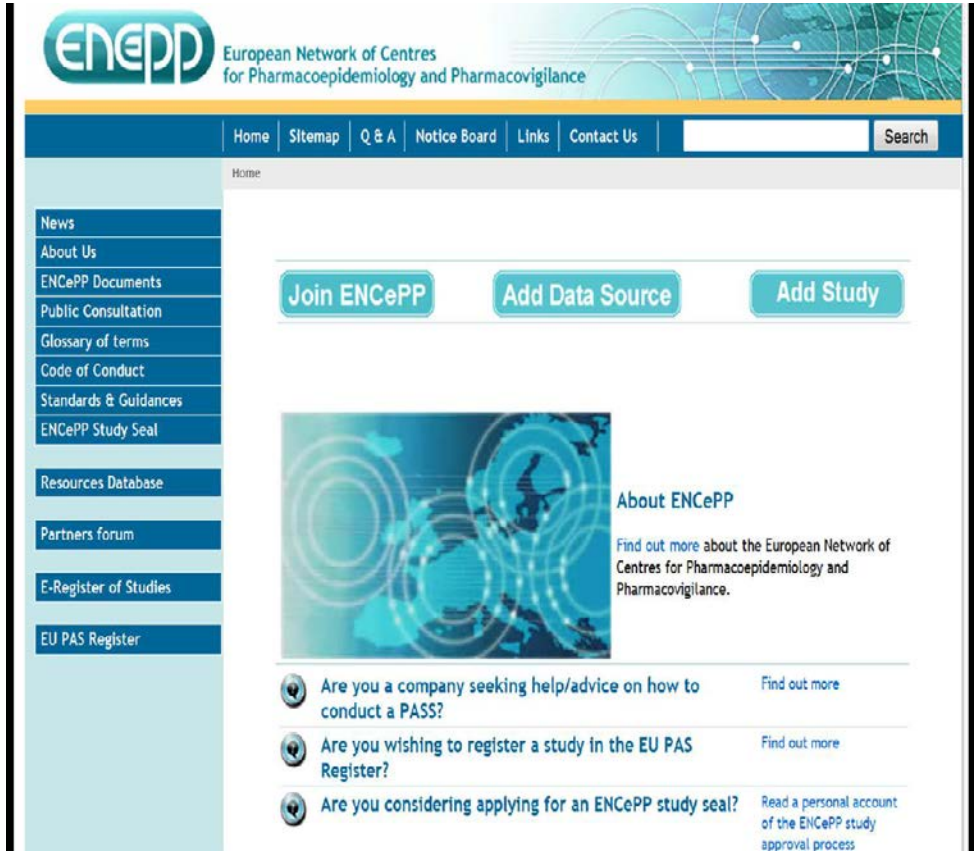
- EU: Legal requirement for imposed studies, recommended for voluntary studies(also for studies included in the RMP (for details see EMA GVP Module VIII, Addendum)
- US: Recommended (42 CFR Part 11)
- Registration condition for publication of the results as per «The International Committee of Medical Journal Editors (ICMJE)" requirements.

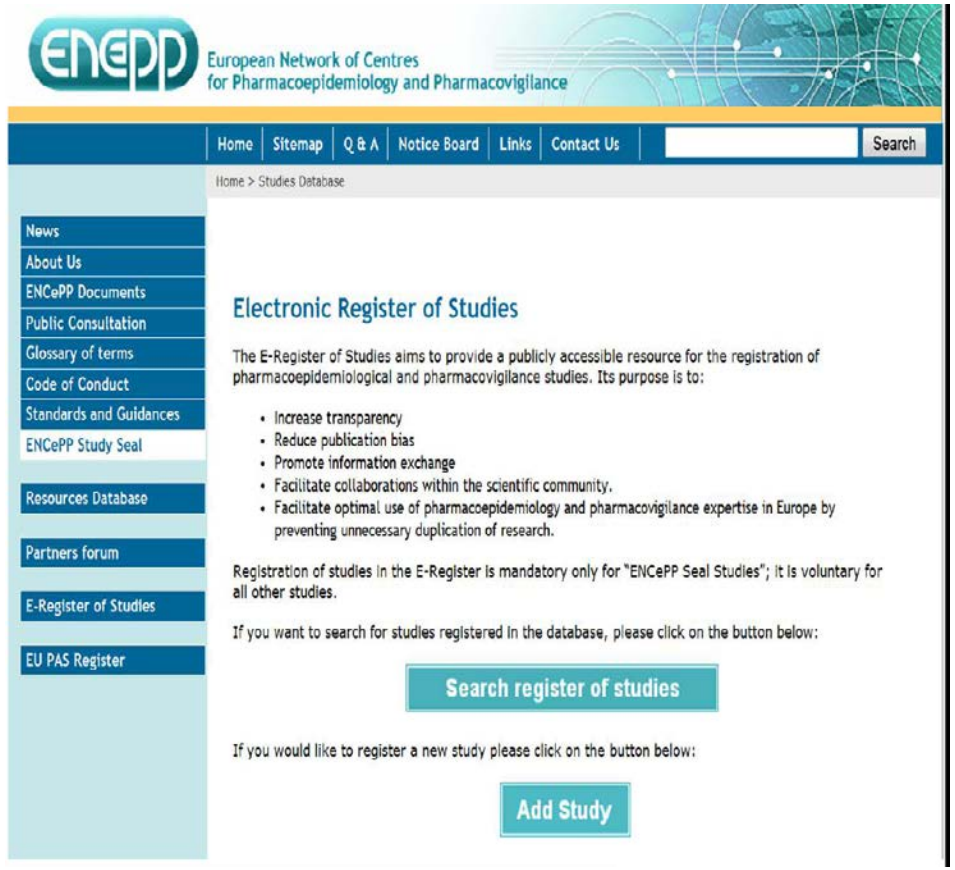
Registration of the study should be before study start or at the earliest possible date if data collection started for a study included in the RMP

Recommendation to register study also if not legally required for transparency and facilitation of information exchange – Study Registries for non-interventional studies:

- International Clinical Trials Registry Platform (ICTRP) (who.int)
- EU PAS Register (encepp.eu)
- NIH Clinicaltrials.gov (Home ClinicalTrials.gov)

The EU PAS Register





Hartmann 2023

Considerations on Sample Size Estimation /1

DCVMN
Developing Countries Vaccine Manufacturers Network

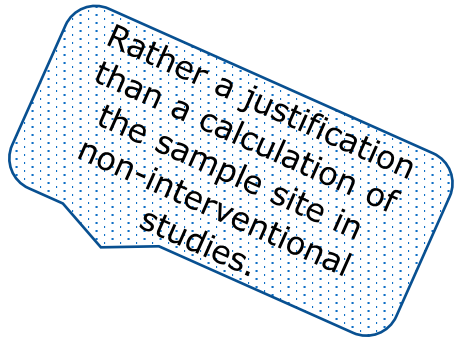
Calculation of sample size is a critical part of the study design

- Involves statistical and clinical informed judgement.
- The values placed into the formula are chosen by the sponsor and needs involvement of statisticians.
  - ✓Approaches differ depending on the type of a AVSS study design and the specific study objectives.
  - ✓Statistical methods used in the various study designs developed in AVSS are under continuous development by statisticians.
- Imperative to estimate a reasonable sample size based on best evidence available at the time to be able to give a correct answer to the research question.
- Some values are typically chosen from a standard set of possibilities, others are estimated based on literature or earlier trials.
  - ✓Researcher decides which of the several general acceptable values are best suited for the intention of the study.
  - ✓Deciding on sample size is a balancing act with several factors to be considered.

Considerations on Sample Size Estimation /2

DCVMN
Developing Countries Vaccine Manufacturers Network

Sample size determined by four factors



- *Variability of the out-come measurement (end-point) of the study:*
  - ✓Imprecise measurements are invariably encountered with clinical data.
  - ✓The higher the variability of the outcome measure (expressed as the standard deviation) the larger the sample size.
  - ✓The more precisely the endpoint can be measured / determined, the fewer subjects require.
- *Magnitude of response under investigation:*
  - ✓What is the clinically relevant and biologically plausible difference between the groups that the test is required to detect?
  - ✓The smaller the difference the larger the sample size.
- *Power to reach a true conclusion:*
  - ✓Probability to avoid type II error (β) / probability to get the right answer and avoid false-negative conclusion.
  - ✓Power (1-β) should be minimally 80%, often 90-95% to detect a particular clinical effect.
  - ✓The smaller the power, the less subjects required with the consequence of false-negative conclusions.
- *Statistical significance:*
  - ✓Probability of a type I error (α), acceptance to come to a false positive conclusion, usually 5% or 1%.
  - ✓The smaller α, the more certainty and the more subjects required.

Hartmann 2023

Considerations on Sample Size Estimation /3
Information needed in Cohort and Case-Control Studies

Type I error (α) considered tolerable and whether one- or two-sided	▪ The less willing to accept a type I error the larger the sample size.
Type II error (β) considered tolerable	▪ The larger type II error is acceptable, the smaller the required sample size, and the smaller the power (1- β).
Minimum relative risk to be detected	▪ The smaller the relative risk to be detected the larger the sample size.
Cohort study: Incidence of the disease (AESI) in the unexposed control group Case-Control study: Prevalence of exposure in the diseased control group	▪ The rarer the AEFI (cohort study) / vaccine exposure (CCS) of interest, the larger the sample size.
Cohort study: Ratio of unexposed controls to exposed study subjects Case-control study: Ratio of undiseased controls to diseased study subjects	▪ Most statistical power for a given number of study subjects if number of controls is the same as exposed subject. ▪ Increasing the number of controls for each exposed subject increases power but only with progressively smaller gains in statistical power

- Mathematical formula in the literature / textbooks to calculate sample sizes focus mainly on randomized clinical trials RCTs and need adaptions for study designs used in AVSS.
- In AVSS studies the sample calculation is troubled by a large amount of imprecision and variability of the data (e.g., adjusting for bias, confounders and missing data).
- The choice of the 4 parameters apply also for AVSS study designs: The sample size is very sensitive to
  - Variability (SD)
  - Relevant clinical difference between the study groups
  - Power (1-β)
  - Statistical evidence (α)

Sample Size Estimation /4

Simple Guide „Rule of three“

Without consideration of background incidence

Expected ADR frequency	Required number of subjects Adverse reactions		
	1	**2**	**3**
1 in 100	300	480	650
1 in 200	600	960	1'300
1 in 1'000	3'000	4'800	6'500
1 in 2'000	6'000	9'600	13'000
1 in 10'000	30'000	48'000	65'000

With consideration of background incidence

Control group	Basic ADR risk	Additional risk of an ADR		
		1 in 100	1 in 1'000	1 in 10'000
unlimited (background risk known)	1 in 10	10'000	980'000	98'000'000
	1 in 100	1'600	110'000	11'000'000
	1 in 1'000	500	16'000	1'100'000
5 x treatment group	1 in 10	12'000	1'200'000	120'000'000
	1 in 100	1'900	130'000	13'000'000
	1 in 1'000	700	19'000	1'400'000
Equal to treatment group	1 in 10	20'000	2'000'000	200'000'000
	1 in 100	3'200	220'000	22'000'000
	1 in 1'000	1'300	32'000	2'300'000

J.A. Lewis 1981

Many Tables available in Statistical Textbooks and different software programs are available to calculate the sample sizes needed; e.g., to detect different relative risks (from 0.2 -50), based on $\alpha = 0.05$ two-tailed (type I error 95%), $\beta = 0.10$ (power = 90%) and control : exposed ratio = 1:1 (up to ratios 4:1).

Structures and Processes
Final Study Report

Format and content as per GVP Module VIII.B.4.3.2.

Guidance for PASS final study report (europa.eu)

Study Title
Abstract (stand-alone summary)
Investigators
Milestones
Rationale and Background
Research question and objectives
Amendments and up-dates
Research methods
Results
Discussion: Key results; Limitations; Interpretation; Generalizability
Conclusions
References

Results:
- Main summary measures
- All statistical methods used
- Methods to examine sub-groups
- Missing data addressed
- Sensitivity analyses
- Any amendment to the SAP

Research Methods:
- Study design
- Setting
- Subjects
- Variables
- Data sources and measurement
- Bias
- Study size
- Data transformation
- Statistical methods
- Quality control

Hartmann 2023

Structures and Processes
Regulatory Reporting

Progress report and interim safety report of study results

Final Study Report

- To be submitted according to national procedures (generally within 6-12 months of the end of data collection).

Data relevant to the Benefit-Risk Balance

- Any new information affecting the B/R balance to be communicated immediately as an emerging safety issue.
- Information to be included in the Periodic Safety Update Report PSUR and in the Risk Management Plan RMP.

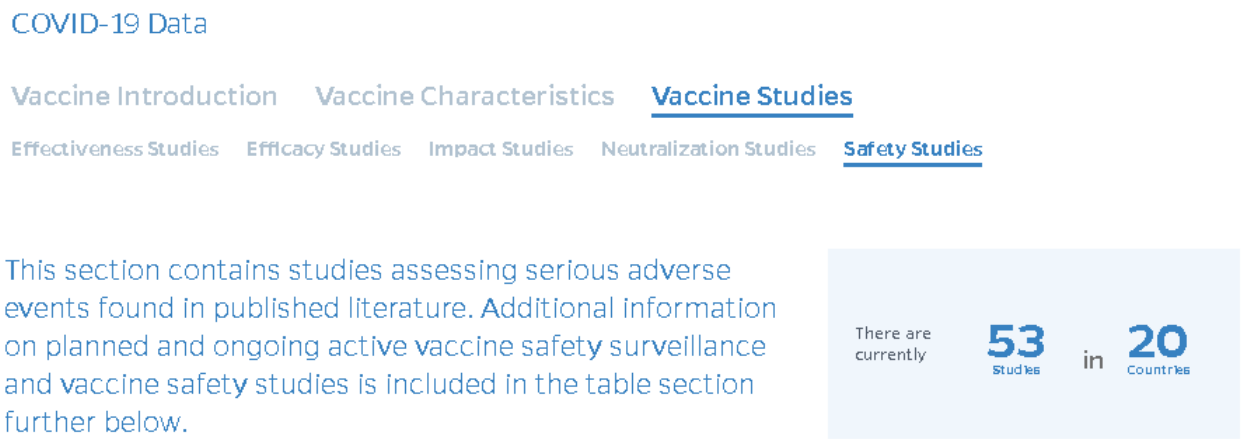
Reporting of ICSRs / AEFIs

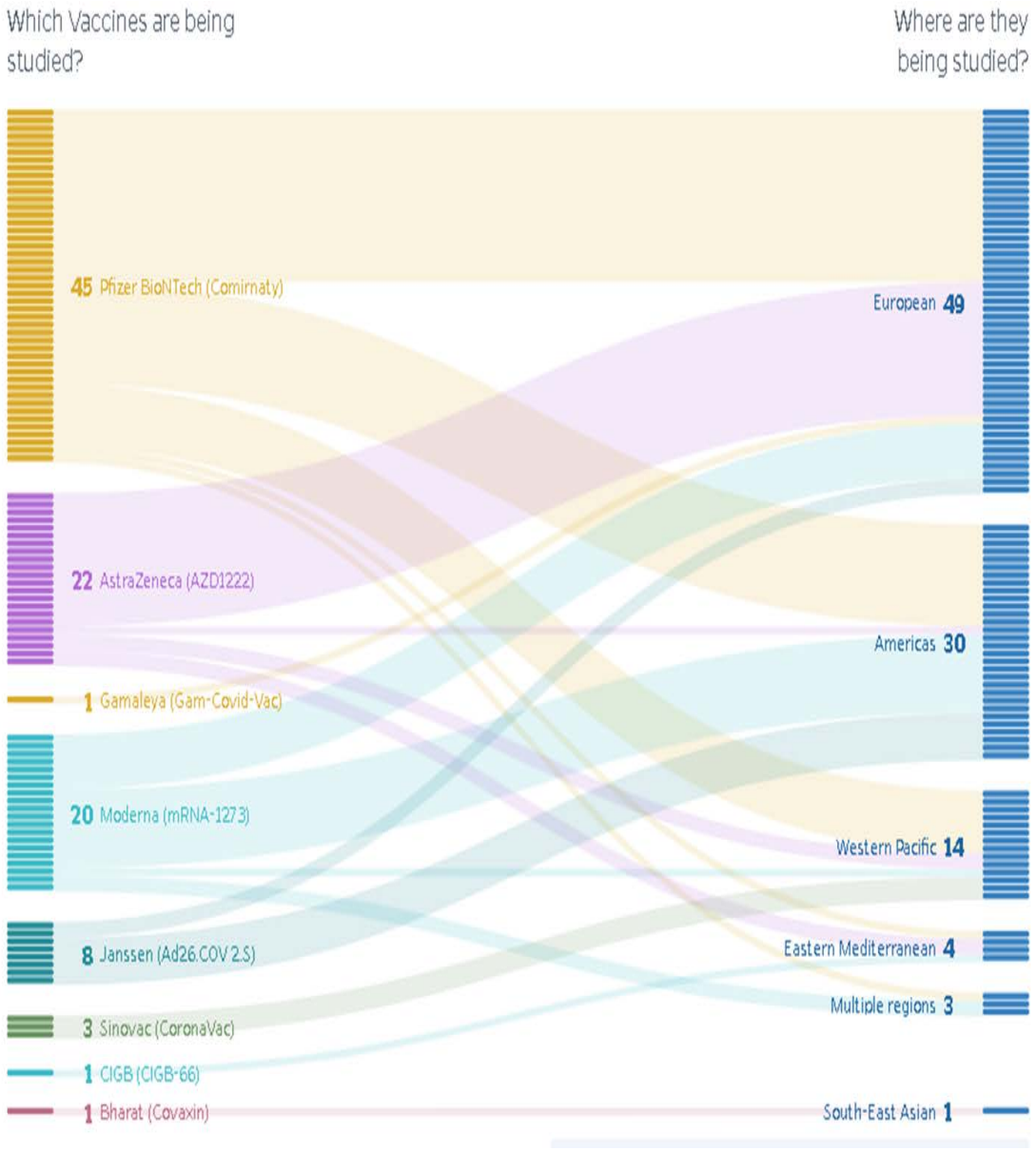
- ICSRs to be reported to NRA according to the standard / legal reporting requirements.
- AEFIs collected by primary data collection methods to be recorded and summarized in the interim safety analysis and final study report.
- AEFIs collected by secondary data collection methods to be recorded and summarized in the interim study report and in the final study report or as per study protocol.

AVSS Studies on View Hub

DCVMN
Developing Countries Vaccine Manufacturers Network

[About | ViewHub (view-hub.org)]





DCVMN
Developing Countries Vaccine Manufacturers Network

Safety Studies | ViewHub

The table below contains studies in published and preprint literature or reports, as well as planned and ongoing vaccine safety studies that have been reported via survey response (conducted March 31, 2022) focusing on Active Vaccine Safety Surveillance.

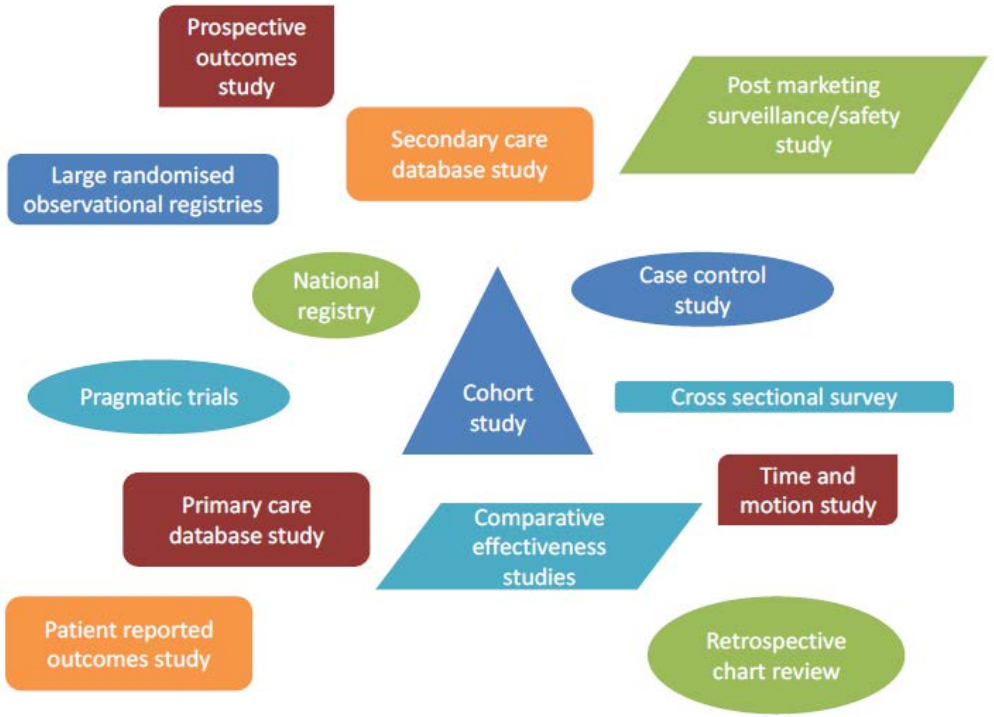
Study Name	First author and year of publication	
A Small but Significantly Greater Incidence of Inflammatory Heart Disease Identified After Vaccination for Severe Acute Respiratory Syndrome Coronavirus 2	Knowlton 2021	See Studies Details Original study link
A prospective observational study on BBV152 coronavirus vaccine use in adolescents and comparison with adults- first real-world safety analysis	Kaur 2022	See Studies Details Original study link
Acute Myocarditis Following COVID-19 mRNA Vaccination in Adults Aged 18 Years or Older	Simone 2021	See Studies Details Original study link
Adverse Effects after BNT162b2 Vaccine and SARS-CoV-2 Infection, According to Age and Sex	Dagan 2021	See Studies Details Original study link
Adverse Events following AstraZeneca COVID-19 Vaccine in Saudi Arabia: A Cross-Sectional Study among Healthcare and Nonhealthcare Workers	Alghamdi 2021	See Studies Details Original study link
Adverse events following mRNA SARS-CoV-2 vaccination among U.S. nursing home residents	Bardenheier 2021	See Studies Details Original study link

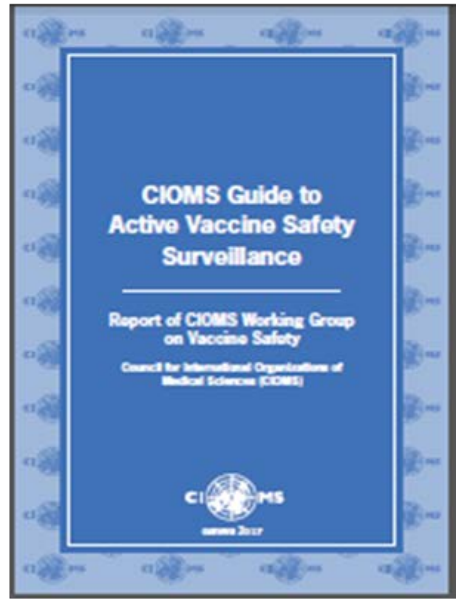
Toolbox
Supportive Forms, Checklists and Guidance

- Observational Studies - Planning & Startup (nih.gov)
- ENCePP Home Page
- CIOMS Guide to Active Vaccine Safety Surveillance – CIOMS
- Guideline on good pharmacovigilance practices (GVP) - Module VIII – Post-authorisation safety studies (Rev 3) (europa.eu)
- GVP Module VIII Addendum I Rev 3 - Final published (europa.eu)
- Protocol template to be used as template for observational study protocols: sentinel surveillance of adverse events of special interest (AESIs) after vaccination with COVID-19 vaccines (who.int)
- Protocol template to be used as template for observational study protocols: cohort event monitoring (CEM) for safety signal detection after vaccination with COVID-19 vaccines (who.int)
- Protocol_ACCESS_COVID-19 EHR Vaccine Effectiveness Protocol Template.docx (vac4eu.org)
- ENCePPChecklistforStudyProtocols.doc (live.com)
- nidcr-observational-protocol-template.docx (live.com)
- Checklists - STROBE (strobe-statement.org)
- Characterizing RWD Quality and Relevancy for Regulatory Purposes (duke.edu)
- A Framework for Regulatory Use of Real-World Evidence (duke.edu)
- Special Task force on Real World Evidence in Health Care Decision Making.pdf
- ICH M14_ConceptPaper_2022_0405 (ich.org)
- Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products | FDA
- Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry | FDA
- EMA Guideline on registry-based studies (europa.eu)
- About | ViewHub (view-hub.org)

Questions - Comments?

Confusing Real-World Studies….





Over the lifecycle, data from continuous safety monitoring strategies provide complementary insights in vaccine profile.

Hartmann 2023

1744839

motionelements.com