SCDM GLOBAL CONFERENCE

SCDM Live
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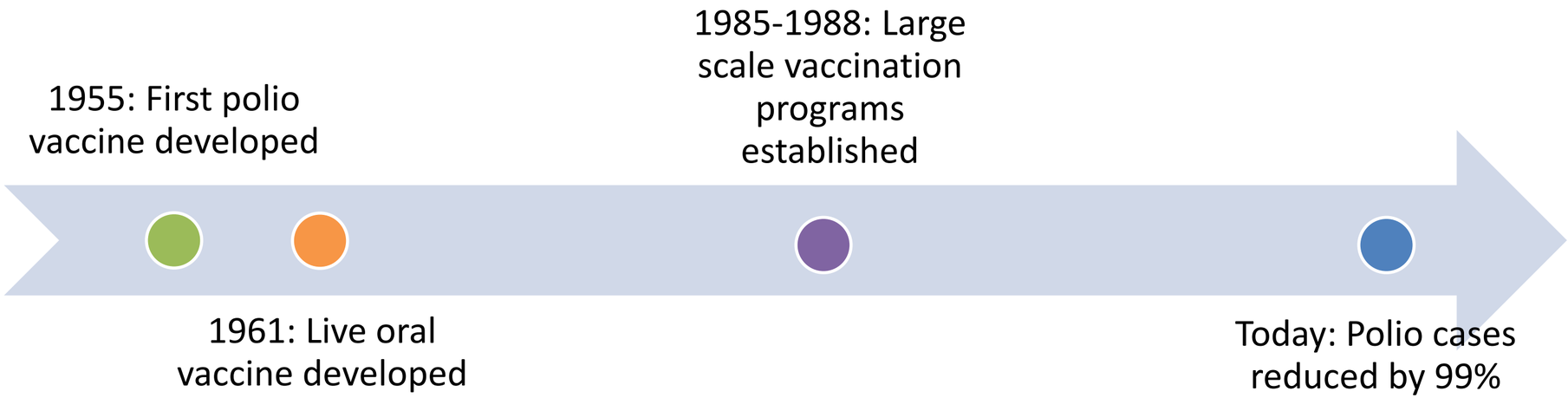
Introduction

Vaccines protect us by preparing our immune systems to recognize serious, and sometimes deadly diseases (e.g., influenza, human papilloma virus, measles, mumps, pneumococcal disease, varicella, Ebola)

Vaccine development is not a thing of the past – critical development work is ongoing today

Vaccine and drug programs have key differences in design, collection, review, and reporting of clinical study data

Success Story - Polio



When the Global Polio Eradication Initiative (GPEI) launched in 1988, more than 1000 children were paralyzed by polio every day.

Today only two countries see wild virus circulation; polio cases have decreased by 99% globally.

Certain wild virus strains have been eradicated completely.

Source:
History of Polio – GPEI (polioeradication.org)

Types of Vaccines

Vaccines may have multiple platforms or constructs:

- Inactivated: uses a completely dead version of the virus or bacteria that causes disease (polio, rabies)
- Live attenuated virus: uses a live but weakened version of the disease (measles, chickenpox)
- Conjugate: uses part of the virus or bacteria itself (Hepatitis B, HPV, pneumococcal disease)
- Viral vector: uses a modified version of a different virus (Ebola, COVID-19)
- mRNA: makes a protein which induces an immune response (COVID-19)

Regimens (additional vaccination) may vary depending on Vaccine and not all Vaccines may be suitable for specific recipients (immunocompromised patients)

Vaccine Trial Types

Required for initial registration

- Safety and immunogenicity/immunobridging
- Efficacy
- Lot to lot consistency
- Co-administration with other vaccines

Post-Marketing

- Comparator studies
- Different vaccination schedules
- Booster doses
- Formulation or manufacturing changes
- Local registration studies

Vaccine Trials by Phase

Phase 1:

Small trials, 20-100 volunteers, shorter duration (months)

Evaluate basic safety, identify very common reactions.

Phase 2:

Larger trials involving several hundred participants, several months to two years.

Collect additional information on safety and efficacy.

Data helps determine dosing, profile of common reactions.

Phase 3:

Trials involving several hundred to several thousand volunteers. Trials typically last several years.

Vaccinated group is compared to placebo comparator.

Phase 4:

Post licensure: continued monitoring of vaccine safety and effectiveness.

Participant Populations

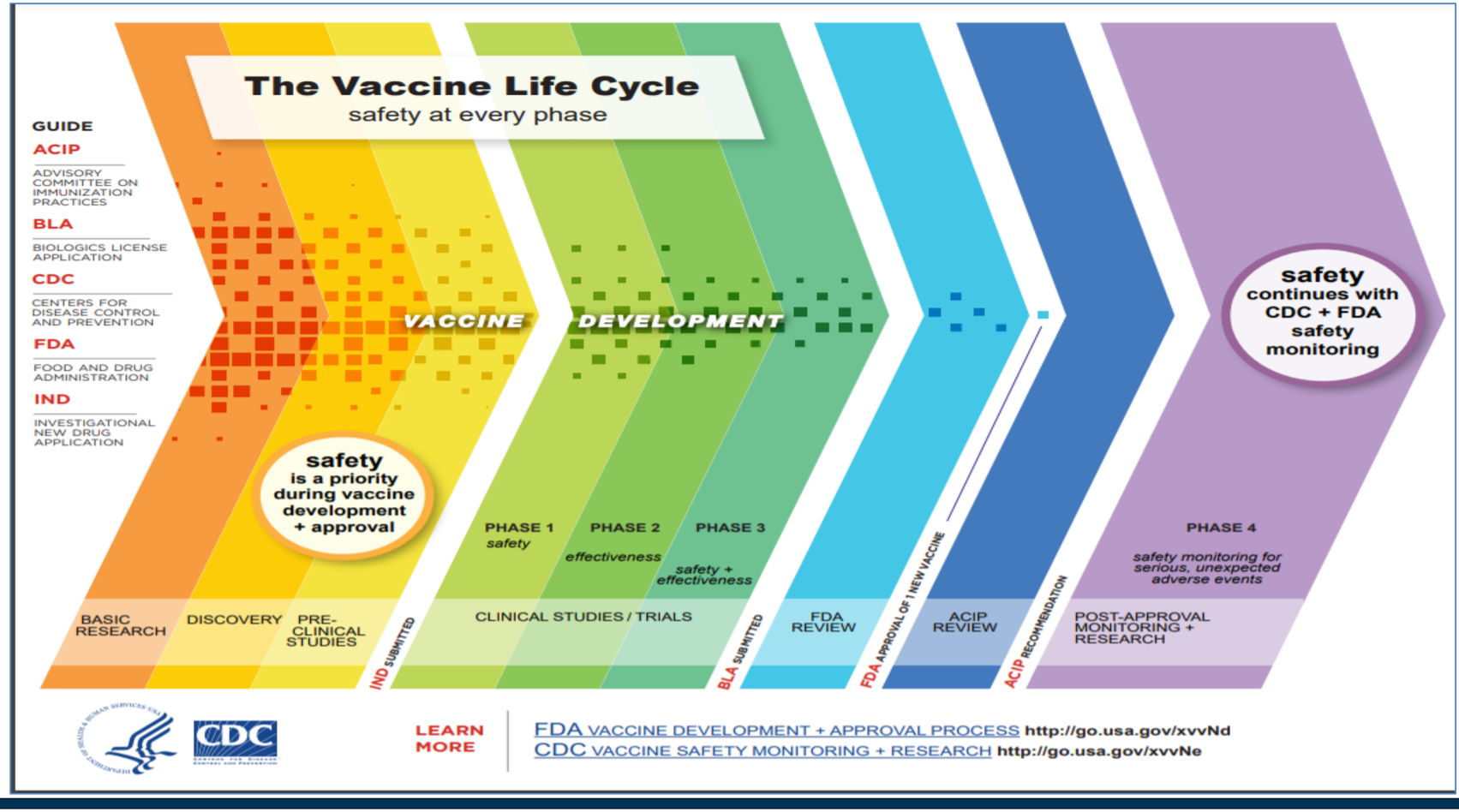
Trials generally conducted in healthy volunteers

Additional populations

- Pediatric vs. adult
- Special populations (i.e., immunocompromised, age related)

Different populations may lead to different requirements for data capture within a program

Vaccine Life Cycle - Safety at Every Phase (cdc.gov)



Protocol Development and Design

Protocol Design

Safety is key

- Vaccines intended for use in healthy populations – different risk/benefit analysis than therapies intended for patients with disease

Efficacy trials

- Large number of participants required to demonstrate efficacy – typically megatrials
- Comparator or placebo controlled

Long term follow up

- Requirement for safety monitoring
- Provides data on durability
  - Breakthrough cases
  - May identify need for boosters

Key Datapoints

Capture of specific solicited clinical events for safety reporting purposes

- Injection site events
- Systemic events

Lab tests

- Immunogenicity testing to determine if vaccine is inducing the desired result
- Additional tests may be conducted, depending on platform for vaccine or vaccine target (to characterize safety, efficacy, or immunogenicity profile)

Operational Considerations for Vaccine Programs

Trials may need to be conducted in outbreak settings (COVID, Ebola)

Involvement of external agencies or non-governmental organizations (e.g., WHO, GAVI)

Regions or timing for recruitment may be limited – vaccine for endemic disease vs. broad prevention; seasonal illness

May have multiphase trial design to speed development

Screening/randomization occurs rapidly as opposed to drug studies (no washout, waiting for labs)

Vaccines administered fewer times than drug – simpler data capture

Studies may have multiple interim analyses and associated data locks

Important to consider early in protocol development if new, unique data collection tools required for the disease target (e.g., solicited events, rash, biopsy, assay)…

Reactogenicity

What is Reactogenicity

- Reactogenicity refers to the property of a substance to produce an expected or common adverse reaction when introduced into the body. For the purpose of this guide, reactogenicity refers to **a specific expected or common reaction following vaccine administration**. In vaccine studies, a reactogenicity event(s) is typically caused by an inflammatory response to the vaccine under study and may include reactions like fever or redness at the site of administration. Reactogenicity describes immediate short-term reactions, not long-term sequelae **(Definition according to CDISC TAUG)**

  - Several factors, both intrinsic and extrinsic, can impact reactogenicity in a subject. They include host characteristics, such as age, gender, race/ethnicity, body mass, general health and pre-existing immunity, and vaccine administration and composition factors, such as route and site of administration, injection technique, type of antigen, vaccine formulation, and type of adjuvant.

- The broader term '**safety profile**' refers to all adverse events (AEs), considered related to the vaccination, that could potentially be caused/triggered or worsened at any time after vaccination, and includes AEs, such as anaphylactic reactions, diseases diagnosed after vaccination and autoimmune events

Reactogenicity - Examples

- Examples in **adults**:
  - Local solicited AEs:
    - Erythema/Redness
    - Swelling/Induration
    - Pain/Tenderness
  - Systemic solicited AEs:
    - Fatigue
    - Fever
    - Headache
    - Nausea
    - Myalgia

- Examples in **infants**:
  - Local solicited AEs:
    - Erythema/Redness
    - Swelling/Induration
    - Pain/Tenderness
  - Systemic solicited AEs:
    - Reduced activity, Sleepy, Fatigue
    - Loss of appetite
    - Vomiting
    - Diarrhea
    - Irritable, fussy, crying and screaming
    - Fever

Guidance for Industry

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

How do we collect Reactogenicity?

- **Subject data through diary**: daily recording of pre-specified symptoms
  - Specified in the protocol
  - Specific number of days post vaccination
    - The number of days can vary from program to program
  - Paper diary or ePRO
    - For paediatric studies, a parent or caregiver will complete the diary
- **Investigator assessment**:
  - Review of subject diary data → recording of investigator opinion in CRF
  - Will be used for analysis

Example paper diary

Day 1

Date: dd/MMM/yyyy

1/ Local symptoms at injection site	Diameter in millimeters
Redness of the skin	------- mm
Swelling	------- mm

	0	1	2	3
Pain/Tenderness	☐	☐	☐	☐

2/ General symptoms	0	1	2	3
Fatigue/Tiredness	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Generalized Muscle Pain (Myalgia)	☐	☐	☐	☐

3/ Body Temperature	␣␣␣.␣ ˚F	
Did you measure your body temperature using the preferred method (oral)?	☐ Yes	☐ No
If your answer is no, please indicate which method you used.	☐ Armpit ☐ Ear (tympanic)	☐ Other method

4/ Medical consultation and medication use	Yes	No
Did you take a medicine to prevent or treat any of the symptoms listed above after you received the study vaccine?	☐	☐
Did you go to a doctor or hospital for any of the local or general symptoms listed above?	☐	☐

Investigator assessment

- **Overall assessment by investigator** of reported diary information → will be used for analysis
  - Start & end date of symptoms, outcome and max. toxicity (severity)
    - Intermittent symptoms → flag in datasets
    - Continuation of symptom beyond observation period → derivation of record in AE dataset
  - Difference in investigator opinion and subject reported data:
    - Flag in datasets
    - Reason for difference to be captured as well
      - E.g. subject reports grade 3 fatigue, but investigator concludes after discussion with subject that the tox grade was only grade 2
    - Specific attention is needed for this during data cleaning/review
  - Medically attended events
  - Medication taken before/after vaccination to prevent/treat symptoms
  - Relationship to vaccination
    - Local solicited symptoms are always considered ‘related’
    - Systemic solicited symptoms → investigator needs to assign ‘related’ or ‘not related’

How do we report / Regulatory expectations

SDTM Standards

cdisc

Therapeutic Area Data Standards User Guide for Vaccines

Version 1.1 (Provisional)

Prepared by the
Vaccines Team

STUDY DATA TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

This Document is incorporated by reference into the following Guidance Document(s):

Guidance for Industry *Providing Regulatory Submissions in Electronic Format – Standardized Study Data*

Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review

Guidance for Industry

Technical Specifications Document

This guidance is for immediate implementation.

CBER Study Data Submission Specifics

1. 1. Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review; Guidance for Industry; Technical Specifications Document This document provides detailed information and specifications for the content of datasets submitted to FDA's CBER Office of Vaccines Research and Review (OVRR). These specifications reflect current CBER OVRR thinking, are built to be consistent with the FDA Study Data Technical Conformance Guide, and are generally consistent with the Therapeutic Area User Guide (TAUG) for Vaccines.
   2. For clinical studies sent to CBER, we recommend that sponsors include a Study Data Standardization Plan (SDSP). Please see CBER SDSP appendix (SDSP Example Template Vaccine) at https://www.phuse.eu/css-deliverables for detail information.
   3. CBER currently does not require SEND (Standard for Exchange of Nonclinical Data) format for nonclinical study. However, SEND formatted datasets are acceptable.

Source: https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

Multidisciplinary: vaccines Share

The European Medicines Agency's scientific guidelines on vaccines help medicine developers prepare marketing-authorisation applications for human medicines.

Source: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-vaccines

SDSP – CBER appendix

The purpose of the **Study Data Standardization Plan (SDSP)** is to establish and document a plan for describing the data standardization approach for clinical and nonclinical studies within a development program. The Study Data Standardization Plan (Standardization Plan) assists FDA in identifying potential data standardization issues early in the development program[1].

[1] Study Data Technical Conformance Guide [http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm]

CBER Appendix:

Mandatory for studies submitted to CBER, as appendix to the SDSP. The purpose of this appendix is to document additional study data information. This document should be submitted well in advance of any licensing application (ie, no later than the end of phase 2 meeting) to CBER. The CBER SDSP appendix should include tables of proposed SDTM domain/variable usage, supplemental domain usage and proposed analysis.

Example from Phuse guidance:

SDTM Version: 1.4 / SDTM IG 3.2			
STUDY ID: ABC-IS-005	**TITLE:** A Phase 2 Safety and Immunogenicity Study of High Dose of MyNewBiologic by Repeated Dosing in Immunocompromised Subjects		
DOMAIN	**Select Domains to be Submitted (X)**	**Variables to be utilized (besides required)**	**Additional Comments**
IE (Inclusion/Exclusion Criterion Not Met)	X		
IS (Immunogenicity Assessment Specimen)	X	ISCAT, ISMETHOD, ISBLFL	
LB (Laboratory Test Results)	X	LBCAT	
MB (Microbiology Specimen)	X	MBSPID	Preprinted on the CRF

Lab Data and Immunogenicity

Immunogenicity

What do we mean?

- Immunogenicity: ability of a substance to provoke an immune response
- Serology test: test which looks for antibodies to a particular disease
- Disease may have one or more serotypes or variants (pneumococcal disease, flu, HPV, COVID all have multiple variants)

Each program targets different disease (specific endpoints, efficacy)

- May require development of new assays – development risk higher for earlier vs. more established programs.
- Studies can be ready to start but dependent on very long lead time for assay development (6 months – 1 year or more)
- Later phases of development may require additional or more specific testing (endpoint; wild vs. vaccine type variant; diagnostics)
- Requires assessment on endpoints etc. to link back to data collection tools and design

Immunogenicity

Operational considerations

- Assays may be still in development while early studies are ongoing - technical changes or processing issues could pose additional risk
- Focus on specimen management – multiple labs may be used, need to consider what flow of specimens will look like
- Sample processing – staged type of assay
- Level of data management expertise varies depending on type of lab – niche/specialty labs generally less experienced than central labs
- Throughput constraints - testing labs may have capacity issues, depending on number of samples and resources to process

Immunogenicity

How do we collect?

- Generally handled as external data
- Assay data represents endpoints and is therefore masked
  - Masking especially important for placebo controlled trials to prevent treatment group inference (response to treatment is evident)
  - May require unmasked reviewers or different process for review/reconciliation
- May take significant time to process samples and get data back to support contemporaneous review and achieve database lock
  - Difficult to come back to the sites with queries later if significant lag in processing time
- Best practices:
  - Align on testing and transfer expectations as early as possible, particularly regarding timing for transfer of last sample data to support database lock
  - Ensure labs/vendors understand sensitivity of data and masking/blinding requirements
  - Engage central lab to facilitate sample management: receipt from sites and shipping to testing labs

Immunogenicity

Reporting of immunogenicity

- Alignment with CDISC structures (IMUNG, MORI, LAB)

Consistency of regulatory expectations

- Agencies may review and comment on assay process through the life of a program; may have comments on how the scientific or technical process is handled
- May need to consult agencies proactively if problems detected with assay performance

Central Monitoring/Data Validation considerations

Central Monitoring

Central Monitoring is a component of Risk Based Monitoring (RBM)

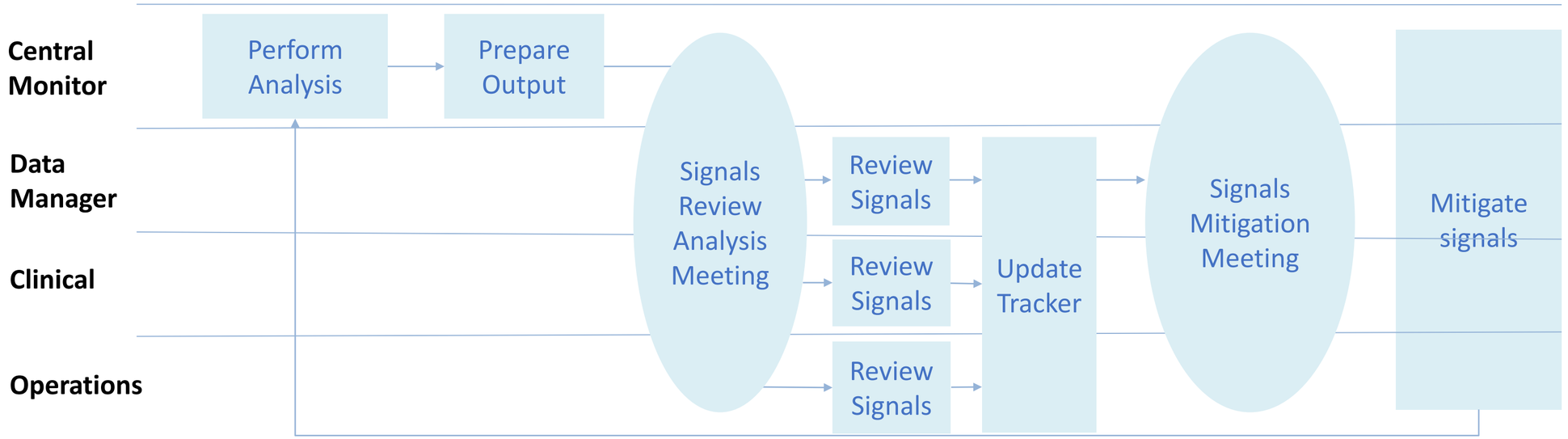
Frequency of review determined by the Central Monitor (CM) and Data Manager (DM) and is dependent on data flow.

- Can vary throughout the lifecycle of the study.

Central Monitoring Analytics include:

- Key Risk Indicators (KRI), Data Trend Analysis, Quality Tolerance Limits (QTL)

Central Monitoring Workflow



What do we look for in signals

Iterative process to identify trends, issues, risks in overall study conduct

Confirm items being flagged that are actual issues for study

- If not, ensure do not continue to flag

Confirm severity and priority of the items

- Item may be watched at a site to see if it worsens before taking an action.
- If item is critical, immediate action may be taken

Follow-up actions may include site re-training, enhancement of process/tools (e.g., new edit checks, data validations, reports)

Central Analytics powered by the Study Data Collected

Examples of KRI, QTL, Trend Analysis

- Missing data or missing visits
- AE entry issues
- High query rates
- Low/High AE rates
- Demography- diversity analysis
- Discontinuation rates related to key protocol milestone.

Examples of Follow-up Actions

- Site follow-up, retraining
- Enhancement to data cleaning, monitoring tools, e.g., entry guidelines, edit checks, reports
- Safety assessment
- Enrollment/recruitment plan adjustments
- Protocol clarifications

Vaccines specific risks and trends that can be identified

Missing Immunogenicity Sample Tracking

eDiary – subjects experiencing local reactions and systemic symptoms

Study specific illness analysis

Study Specific Missed Assessment KRIs

- Immunogenicity compliance
- ediary compliance for reactogenicity
- Reactogenicity Symptom resolution dates

Innovative Data Validation tools

Use of Artificial Intelligence/machine learning enabled tools to assist in performing certain data reviews/cross checks, which reduce review and query generation time

Examples of reviews in scope:

- eDiary reconciliation
- AE cross checks
- IRT reconciliation
- Free text review

Recap

Healthy Volunteers with quick enrollment

Common elements in Vaccines studies are reactogenicity and immunogenicity

Very specific data structure requirements for submission at FDA

Vaccines are crucial to public health in preventing the spread of contagious, dangerous, and deadly diseases. Rather than treating a disease after it occurs, vaccines prevent us from getting sick in the first place

Q and A