EMBEDDING AN OPEN SOURCE PACKAGE INTO ANALYTICS-BASED AUDITS

webinar

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The Inter coMPany quALity Analytics (IMPALA)

IMPALA

HOUSEKEEPING

Attendees are automatically muted throughout the webinar.

The webinar is being recorded.

There will be a Question and Answer Session at the end of the presentation. We ask that attendees kindly hold any questions until then.

IMPALA

The Inter coMPany quALity Analytics (IMPALA)

Group started on Jul-2019

Established as a *non-for-profit* consortium on Oct-2022

In scope

- Knowledge sharing and best practices for GCP/PV quality and analytics
- Joint Health Authorities engagement for GCP/PV quality 2.0
- Co-development of open source tools: analytics packages, templates, methodologies, etc.
- Analytics for GCP/PV quality; quality for AI/ML (e.g. validation); quality briefs; etc.

Roche
Biogen
J&J
MERCK
BAYER
Pfizer
MSD
Boehringer Ingelheim
Bristol Myers Squibb
NOVARTIS
astellas
sanofi
Lilly
Galápagos
AMGEN
GSK
AstraZeneca

AGENDA

THE {SIMAEREP} OPEN SOURCE PACKAGE

Methodology, testing, validation between IMPALA member companies, release as open source R package

ANALYTICS-BASED AUDITS

Implementation into routine audit practice, incl. change management and how analytics-based audits can provide QA evidence generation at scale

IMPALA

OPEN SOURCE DEVELOPMENT IN PHARMA

Contributing to Statistical Open Source Software

Pharma Perspective

Collaborative Statistical Open Source Software Development

Public Repositories

Open Source Software Validation Frameworks

MANGO SOLUTIONS

TransCelerate BIOPHARMA INC.

Validation Hub

Benefits

- Tailored Solutions
- New Standards
- Efficiency
- Attracting Talent

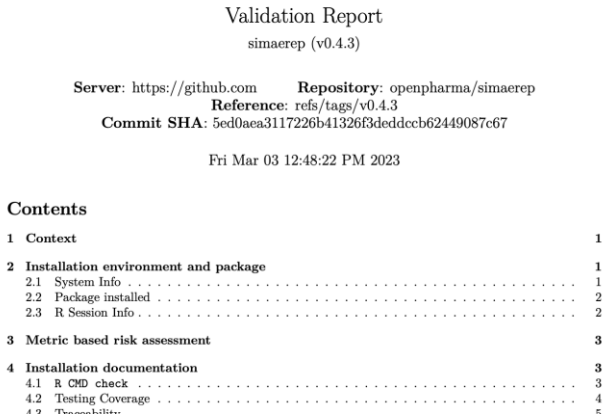
FDA

- Data Harmonisation
- Early Involvement
- Trust through Transparency

- Accelerated Insight from Entrusted Patient Data

Publishing

Open Source



Validation Report

simaerep (v0.4.3)

Server: https://github.com **Repository**: openpharma/simaerep
Reference: refs/tags/v0.4.3
Commit SHA: 5ed0aea3117226b41326f3deddccb62449087c67

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Contents

Statistical Software Package

- Standardized Structure
- Reusable
- Testable
- Documentation Framework

Public Code Hosting Platform

- Version Control
- Documentation Hosting
- Automated Testing

Package Validation Frameworks

- external Vendors
- in house validation
- public open source solutions

DETECTING AE UNDER-REPORTING {simaerep}

{simaerep} Calculate AE-Under Reporting Probability

Bootstrap - Simulations

https://cran.r-project.org/web/packages/simaerep/
https://openpharma.github.io/simaerep/

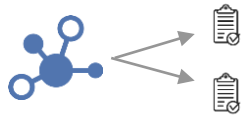
Advantages

- Only needs visit and AE data from a single study
- Low false positive rate
- No assumption about statistical distributions (non-parametric)

Detailed Video Presentation: https://impala-consortium.org/clinical-safety-reporting-work-product-stream/

Collaborative Validation of {simaerep}

Under review - Preprint available on https://doi.org/10.21203/rs.3.rs-3506170/v1

simaerep	Roche	MERCK	Boehringer Ingelheim
Validation Data	 Simulate Portfolio Snapshot	 Simulate 2 Trials Over Time	 AE-related Protocol Deviations
High AE Volume Trials	AE Under-Reporting Detection Rate: 0.5 - 0.75		
Medium AE Volume Trials	AE Under-Reporting Detection Rate: 0.2 - 0.5		

ANALYTICS-BASED AUDITS

Implementation into routine audit practice, incl. change management and how analytics-based audits can provide QA evidence generation at scale

IMPALA

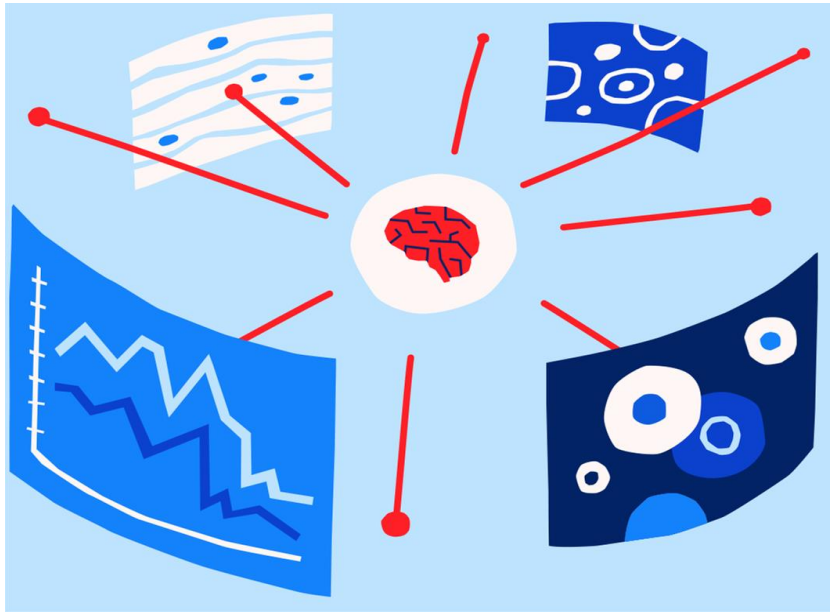
RAPID Audits

Real-time Audit Package Informed by Data

With our development portfolios doubling or tripling in the coming years, we need to find new ways of delivering quality in a more scalable manner.

Industry Narrative

GOAL: Generate 90% of evidence for select focus areas through routine, analytics-enabled audits



RAPID Audits

- RAPID Audits are conducted to industry audit standards
- The main characteristics of RAPID audits are that they are **primarily based on data analytics** and they follow a **pre-defined methodology**
- This enables them to obtain **evidence** and draw conclusions on a **large volume of data** in a **short period of time** and identify issues that are systemic in nature

Increasing Statistical Confidence in Quality with RAPID

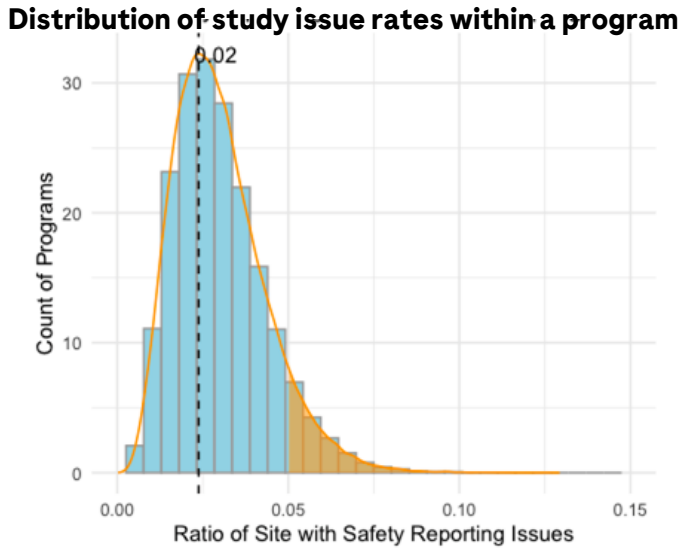
RAPID vs sample-based Multi Site Audit (5 Sites)

Audit Goals

- Detect/Mitigate Site Issues
- Detect/Mitigate Program Issues

RAPID audits

- Detect more sites with issues than sample-based audits
- Provide good estimates on the total development program issue rate
- Resource requirements are massively reduced:
  - 10-20 FTE (RAPID) vs 120 FTE (sample-based)



	6/300 (2%) sites with issues	15/300 (5%) sites with issues
Multi Site Audit (5 sites) 100% detection rate	**0 site → issue rate 0.2 - 11% 1 site → issue rate 1.4 - 18%**	
RAPID Audit 80% detection rate	**5-6 sites issue rate 1.6 - 2.4%**	**12-15 sites with issues issue rate 4-6 %**

RAPID audits

Real-time Audit Package Informed by Data

How are RAPID different to other audits?

Audits

01 Preparation

- Notification to stakeholders
- Refinement of OQs
- Review of objective, scope and purpose
- Audit plan (where applicable)

02 Conduct

- Several days-weeks
- Closing Meeting
- Post audit support meeting

03 Reporting

- 20 calendar days
- Distribution using relevant distribution lists
- Second Post audit support meeting

RAPID

01 Preparation

- **Pre-defined** OQs
- **Pre-defined** Methodology
- **Audit plan embedded** in report
- Requires **Onboarding** with A&I

One time effort for each RAPID

Minimal preparation for Auditors

02 Conduct

- 2-3 days
- No closing meeting
- Audit outcome shared with study team

03 Reporting

- Aiming at **immediate** reporting
- Pre-defined scenarios for systemic issues

Streamlined execution and ability to repeat

RAPID-*ADVERSE EVENT* AUDIT

Safety Data Acquisition in Clinical Trials

Why do we need to find a different path to quality assurance?

Delayed AE reporting can impact the ability to detect safety signals in a timely manner

Poor quality of AE reporting will adversely affect the interpretation of the safety data.

Timely reporting of all relevant details is important in order to support our interpretation of causality.

RAPID-AE Audit Objective Question

Focus Areas: Safety Data Acquisition & Sponsor Oversight

Can Roche demonstrate that all Adverse Events across the study have been reported to Roche in a timely manner?

- **Are AEs reported by investigator sites to the sponsor at expected rates and volume consistently across the study?**
- **Where reporting issues occur, is there evidence that these have been identified and recorded in site monitoring and issue management systems?**

RAPID-AE audit methodology

Data Sources

- RAVE
- eTMF
- CTMS

Dashboard

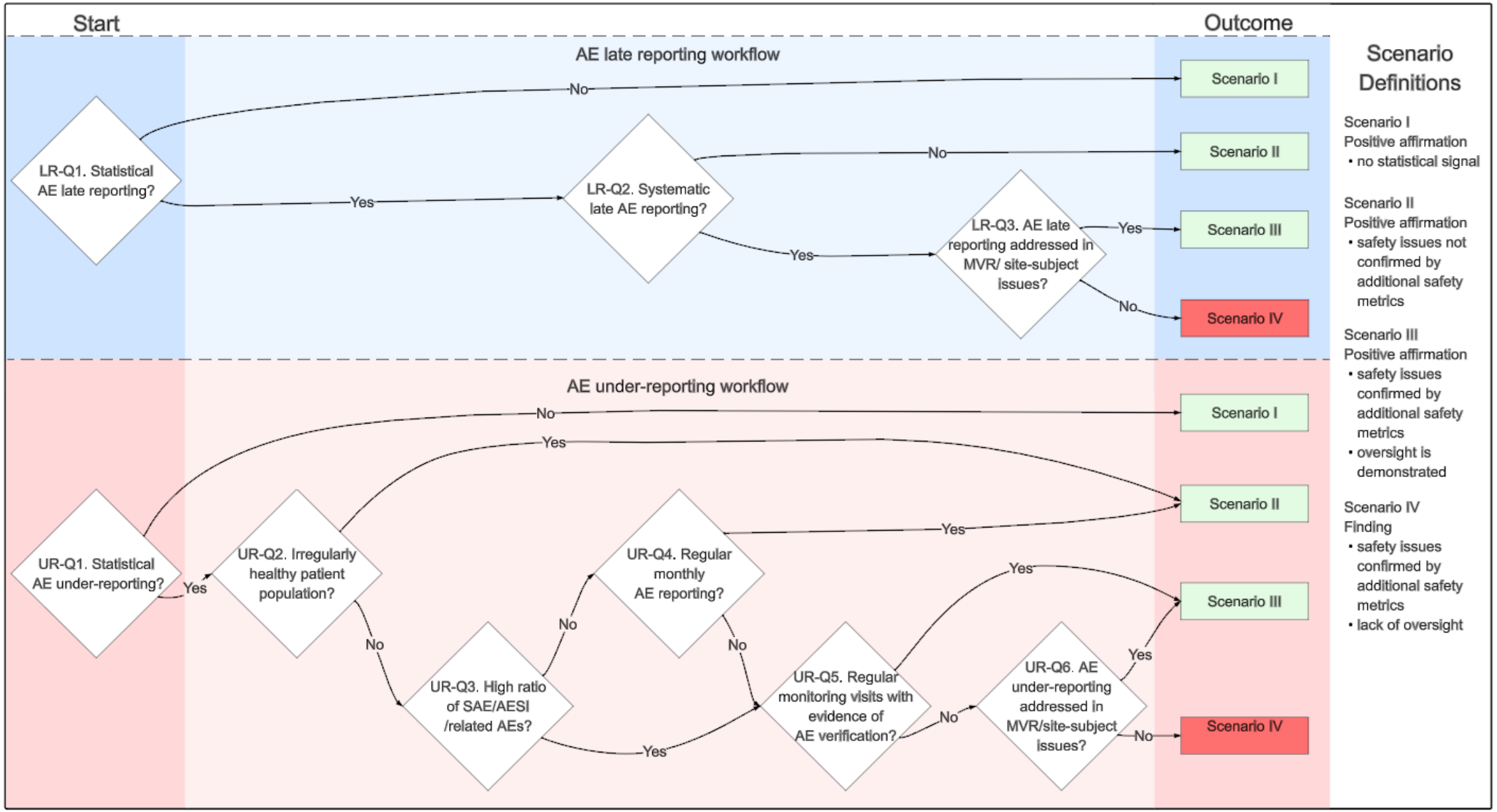
Evidence obtained from the **Review & Interpretation** of Data presented in the Dashboard

What we are looking at?

- AE underreporting and late AE reporting over time
- MVRs:Extracts with key sections (Source data review, AE/SAE reviews)
- Description of AE related issues/PDs (“Keywords”)

Positive Affirmations/Findings

Audit Workflow



Example - High Risk Late AE Reporting

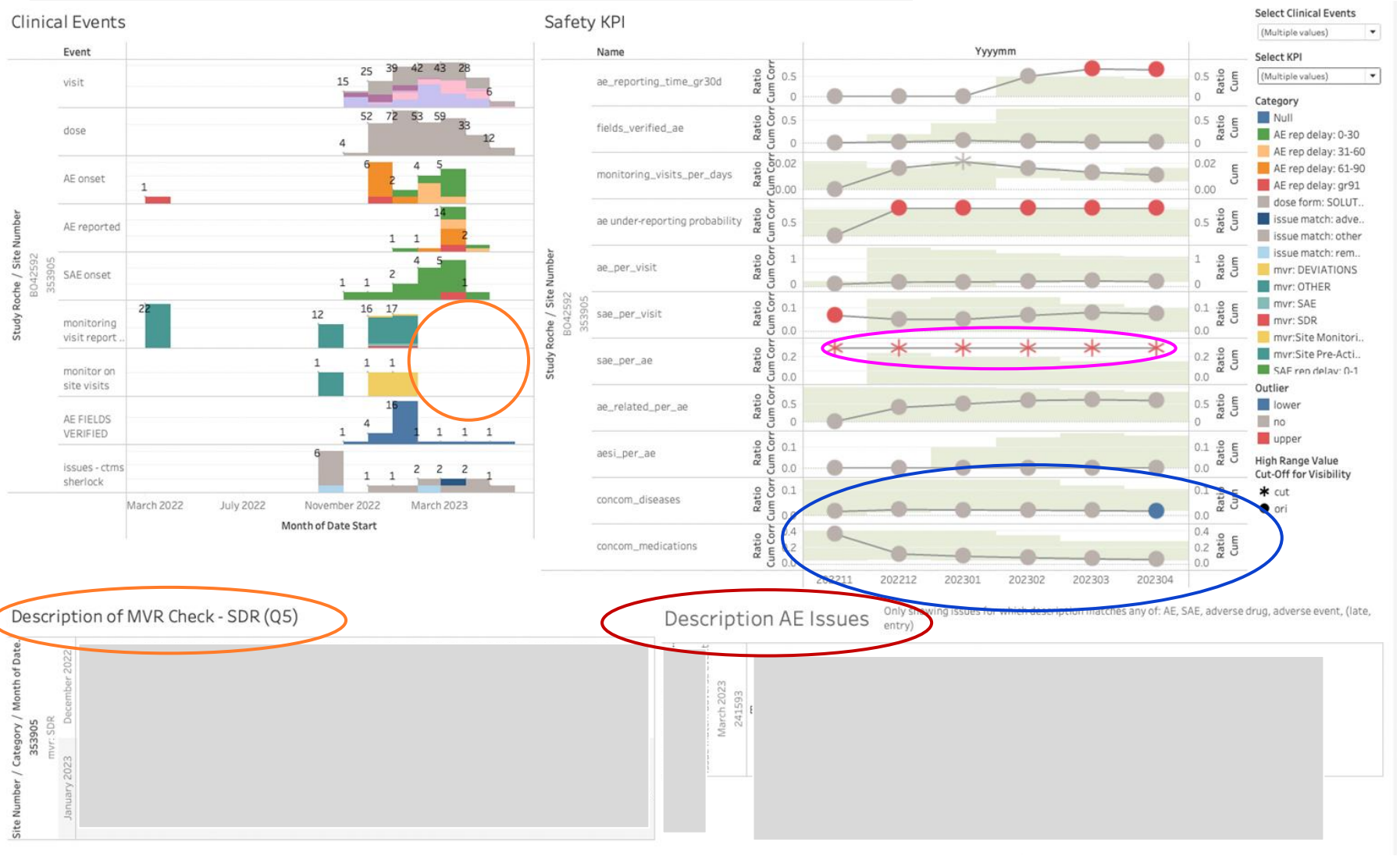
Study Roche	Site Number	Site Platinum Country Name	Pi Platinum Full Name	Site Platinum Name	AE reporting status	N Pat Tot	N Pat Disc	Perc Enr
					late	18	4	33.3%

- LR-Q1 statistical late-reporting flag? (yes)
- LR-Q2 systematic late reporting patterns? (yes)
- LR-Q3 Issues addressed in MVRs or site/subject issues (no)

Finding:
Site late reporting not addressed in site & subject issues

Example - High Risk AE Under-Reporting

Study Roche	Site Number	Site Platinum Country Name	Pi Platinum Full Name	Site Platinum Name	AE reporting status	N Pat Tot	N Pat Disc	Perc Enr
					under	15	2	60.0%



- UR-Q1 under-reporting? (yes)
- UR-Q2 healthy patients? (unclear)
- UR-Q3 high ratio SAEs? (yes, 0.4)
- UR-Q5 Regular monitoring visits with evidence of AE verification? (no, monitoring visits since earthquake)
- UR-Q6 Missing AEs addressed in MVRs or site/subject issues (no, only addressing late entry)

Finding:
Site under-reporting supported by additional safety KPI and lack of oversight

Impact

Innovative approach to audit will create evidence for deve
programs in a short period of time.

- executed on several programs
- easy onboarding
- fast timelines
- well received by study teams

Findings

Minor Finding 1 : FIN-011563	
Category: Study Conduct	**Sub Category:** Study Oversight
Impact Factor:	**Sub-Impact Factor:**
Roche Oversight	Issue Identification escalation and management
Finding Description	

Finding Note	
Late Reporting delay ranges observed for the 9 sites were as follows: 32% of late AEs 31-60d late 23% of late AEs 61-90d late 44% of late AEs >91d late	
Reference	
ICH GCP 4.11.2 ICH GCP 5.18.4	
SOP-0104647: Global: Investigational Site Management	
Responsible for Finding Response:	
Minor Correction	
CA1: Country Operations teams to follow-up with the identified sites to discuss the instances of late reporting of AEs and document the discussion and reasons for late reporting in a CTMS issue. PA1: Country Operations teams to retrain the sites regarding AE and SAE reporting requirements and document the retraining in the associated CTMS issue. PA2: Global Clinical Operations Leads to retrain all CRAs for all sites to review AE reporting timelines on an ongoing basis with their sites per the TMP. PA3: Country Operations teams to share reasons for delays with the global team to understand trends or challenges around timely AE reporting	

Questions & Answers

- As a preferred way, please use the chat function to ask questions
- You also can raise your hand and you will be unmuted to ask your questions

https://impala-consortium.org/

Also on LinkedIn - https://www.linkedin.com/company/86955237/