EMBEDDING AN OPEN SOURCE PACKAGE INTO ANALYTICS-BASED AUDITS

webinar

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The Inter coMPany quALity Analytics (IMPALA)
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.
The Inter company Quality Analytics (IMPALA)

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.

Group started on Jul-2019
Established as a non-for-profit consortium on Oct-2022
AGENDA

THE {SIMAEREPE} 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
OPEN SOURCE DEVELOPMENT IN PHARMA
Contributing to Statistical Open Source Software
Pharma Perspective

Collaborative Statistical Open Source Software Development

- Public Repositories

Benefits
- Tailored Solutions
- New Standards
- Efficiency
- Attracting Talent
- Data Harmonisation
- Early Involvement
- Trust through Transparency
- Accelerated Insight from Entrusted Patient Data

Open Source Software Validation Frameworks

- Mango Solutions
- TransCelerate Biopharma Inc.
- Validation Hub
Publishing
Open Source

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}
Calculate AE-Under Reporting Probability

**Bootstrap - Simulations**

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


[https://cran.r-project.org/web/packages/simaerep/](https://cran.r-project.org/web/packages/simaerep/)
[https://openpharma.github.io/simaerep/](https://openpharma.github.io/simaerep/)
## Collaborative Validation of {simaerep}

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

<table>
<thead>
<tr>
<th>Validation Data</th>
<th>Simulate Portfolio Snapshot</th>
<th>Simulate 2 Trials Over Time</th>
<th>AE-related Protocol Deviations</th>
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</thead>
<tbody>
<tr>
<td><strong>High AE Volume Trials</strong></td>
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<td>AE Under-Reporting Detection Rate: 0.5 - 0.75</td>
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<tr>
<td><strong>Medium AE Volume Trials</strong></td>
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<td>AE Under-Reporting Detection Rate: 0.2 - 0.5</td>
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ANALYTICS-BASED AUDITS

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

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<tr>
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<th>6/300 (2%) sites with issues</th>
<th>15/300 (5%) sites with issues</th>
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<tbody>
<tr>
<td>Multi Site Audit (5 sites)</td>
<td>0 site → issue rate 0.2 - 11%</td>
<td>1 site → issue rate 1.4 - 18%</td>
</tr>
<tr>
<td>RAPID Audit 80% detection rate</td>
<td>5-6 sites issue rate 1.6 - 2.4%</td>
<td>12-15 sites with issues issue rate 4-6%</td>
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</table>
RAPID audits
Real-time Audit Package Informed by Data

How are RAPID different to other audits?

Audits

Preparation
01
- Notification to stakeholders
- Refinement of OQs
- Review of objective, scope and purpose
- Audit plan (where applicable)

Conduct
02
- Several days-weeks
- Closing Meeting
- Post audit support meeting

Reporting
03
- 20 calendar days
- Distribution using relevant distribution lists
- Second Post audit support meeting

RAPID

Preparation
01
- Pre-defined OQs
- Pre-defined Methodology
- Audit plan embedded in report
- Requires Onboarding with A&I

Conduct
02
- 2-3 days
- No closing meeting
- Audit outcome shared with study team

Reporting
03
- Aiming at immediate reporting
- Pre-defined scenarios for systemic issues

One time effort for each RAPID
Minimal preparation for Auditors
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

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")

Dashboard

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

Positive Affirmations/Findings
Example - High Risk Late AE Reporting

- 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

- **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 development programs in a short period of time.

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

## Findings

<table>
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<tr>
<th>Minor Finding 1: FIN-011563</th>
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<tbody>
<tr>
<td>Category: Study Conduct</td>
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<tr>
<td>Sub Category: Study Oversight</td>
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<tr>
<td>Impact Factor: Roche Oversight</td>
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<tr>
<td>Sub-Impact Factor: Issue Identification escalation and management</td>
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### 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

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<tr>
<td>ICH GCP 4.11.2</td>
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<tr>
<td>ICH GCP 5.18.4</td>
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<tr>
<td>SOP-0104647: Global: Investigational Site Management</td>
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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/