

Paper AR02

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OpenRBQM Extended

Endpoint Monitoring, Root-cause Analysis, and Workflows



Overview

Background

Workflow Framework

Extensibility



Background

– Risk-based Quality Management (RBQM)

- *Regulatory-recommended approach for clinical trials*
- *Detect and manage risks throughout study lifecycle (protocol to database lock)*
- *Requires continuous oversight*
- *Comprehensive risk management includes predefined, study-specific risk identification and mitigation*



Background

- **OpenRBQM**
 - *PHUSE-sponsored collaborative effort*
 - *Focused on Risk-Based Quality Management (RBQM)*
 - *Toolbox of open-source R packages*

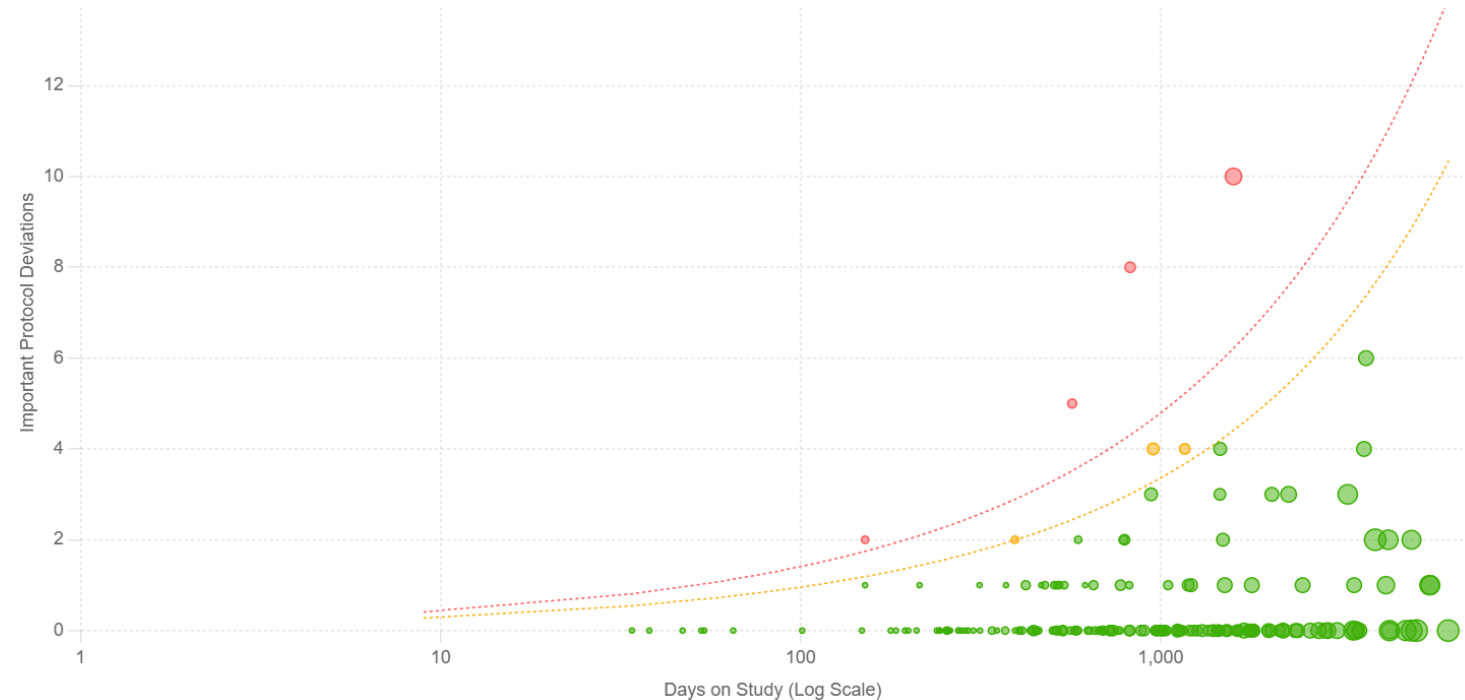


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Risk Based Quality Management

Background

- OpenRBQM tools identify risks with clinical data
 - *Centralized monitoring (CM) teams assess identified risks*
 - *CM team mitigates actionable risks*
- **Adaptable Approach**
 - *Can be applied to any study*
 - *Deployed regularly to identify and mitigate risks*



OpenRBQM 2024 Accomplishments

12 Packages Released

openrbqm

gsm core

{gsm.core}

{gsm.mapping}

{gsm.kri}

{gsm.reporting}

gsm extensions

{gsm.endpoints}

{gsm.simaerep}

{gsm.digitpref}

gsm app

{gsm.app}

{gsm.ae}

utilities

{gsm.template}

{gsm.datasim}

js
gsm.viz

2 Papers Published

Therapeutic Innovation & Regulatory Science (2024) 58:838–844
<https://doi.org/10.1007/s43441-024-00651-4>

DIA

ORIGINAL RESEARCH



Good Statistical Monitoring: A Flexible Open-Source Tool to Detect Risks in Clinical Trials

George Wu¹ · Spencer Childress¹ · Zhongkai Wang¹ · Matt Roumaya² · Colleen McLaughlin Stern² · Chelsea Dickens² · Jeremy Wildfire¹



Contemporary Clinical Trials
Volume 143, August 2024, 107580



Assessing the performance of methods for central statistical monitoring of a binary or continuous outcome in multi-center trials: A simulation study

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Roman Rogoza

Matt Roumaya
Zelos Zhu

Astra Zeneca
Lukasz Bojarski

11:00am–11:30am

Hands-on Workshop

RBQM Workshop – Building
Open-Source Tools Paired
with Central Monitoring Best
Practice

11:30am–12:00pm



GILEAD

Creating Possible

12:00pm–12:30pm

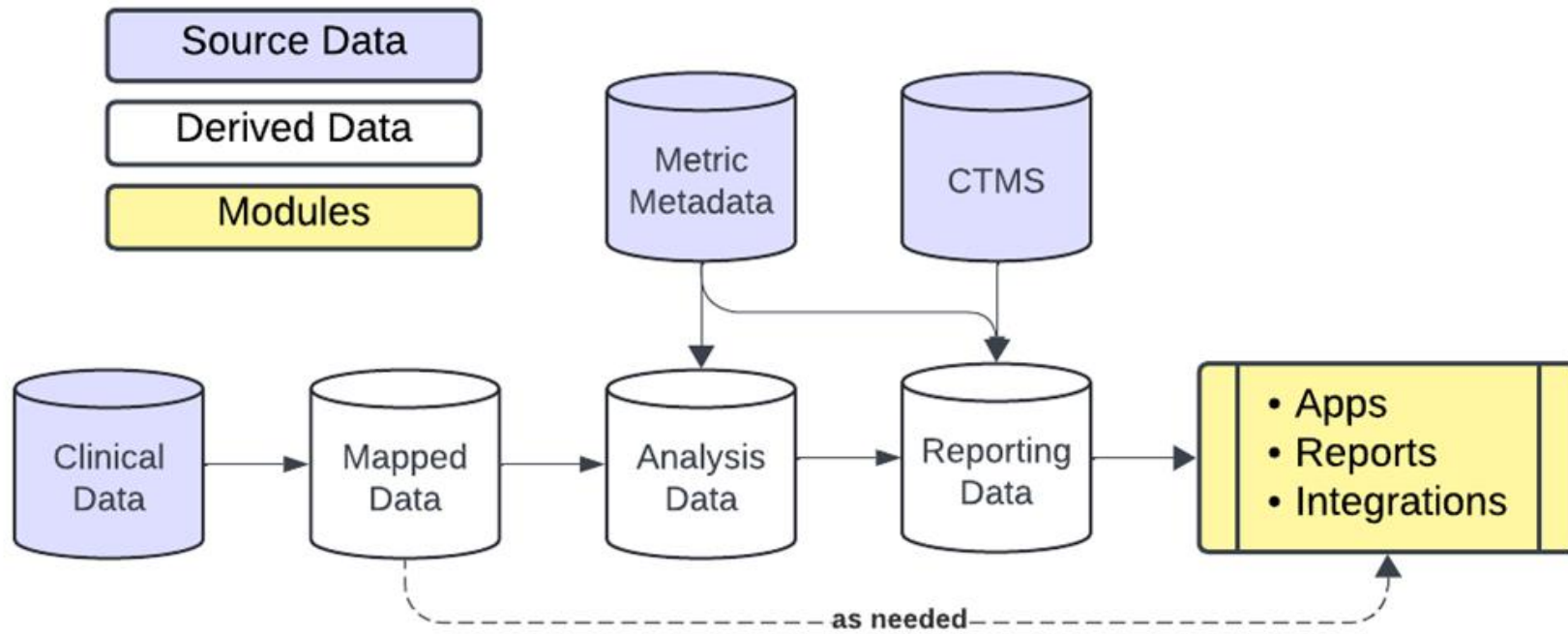
Workshop tomorrow - Tues,
March 18. 11am-12:30pm



Workflow Framework

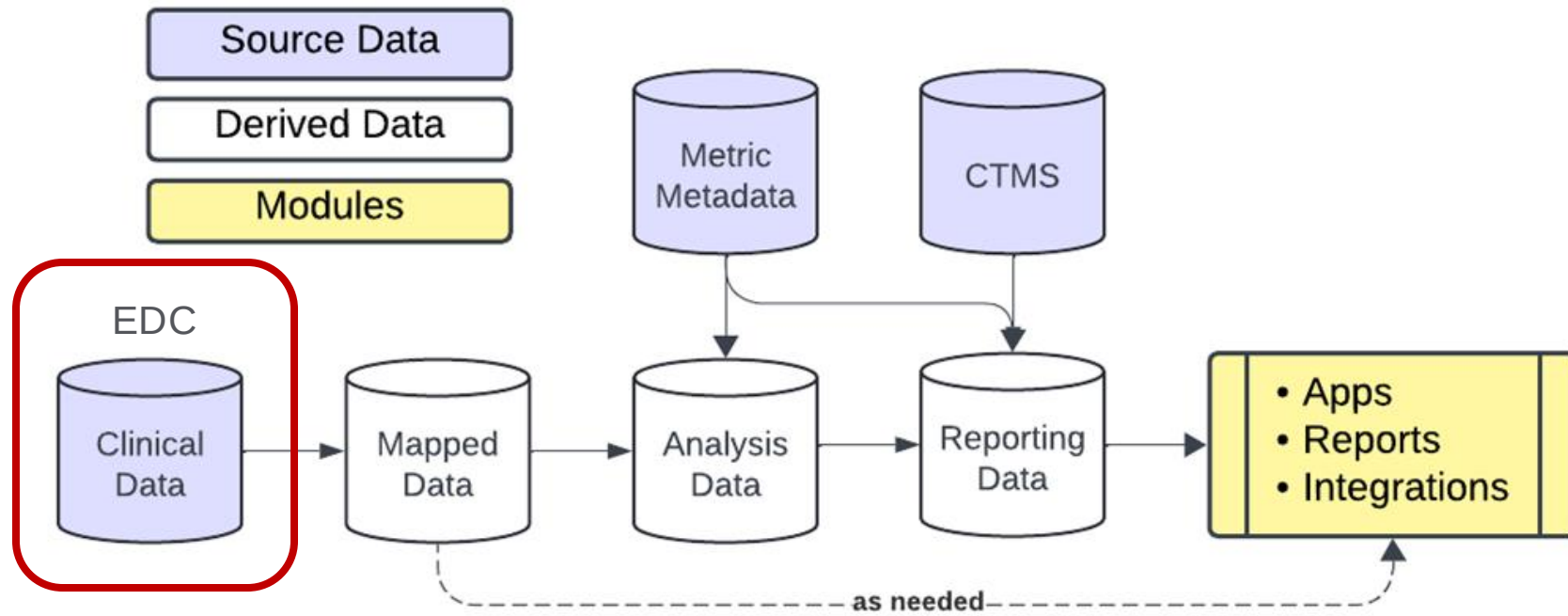
- Structured analysis pipeline orchestrated with {gsm}
 1. *Mapping*
 2. *Analysis*
 3. *Reporting*
 4. *Modules*
- Sequential & Metadata-Driven
 - *Each layer depends on the previous one*
 - *Facilitates adding new metrics and outputs*

Workflow Framework



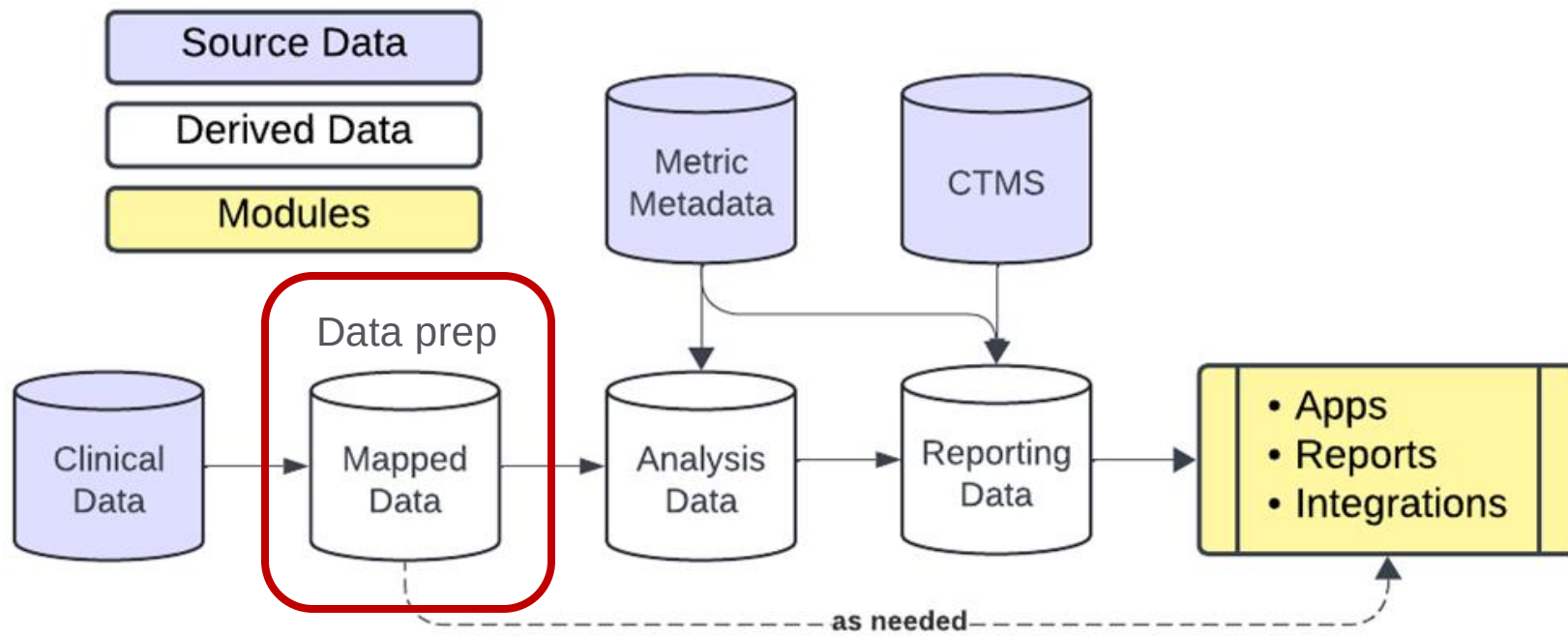
Analysis Pipeline

Workflow Framework



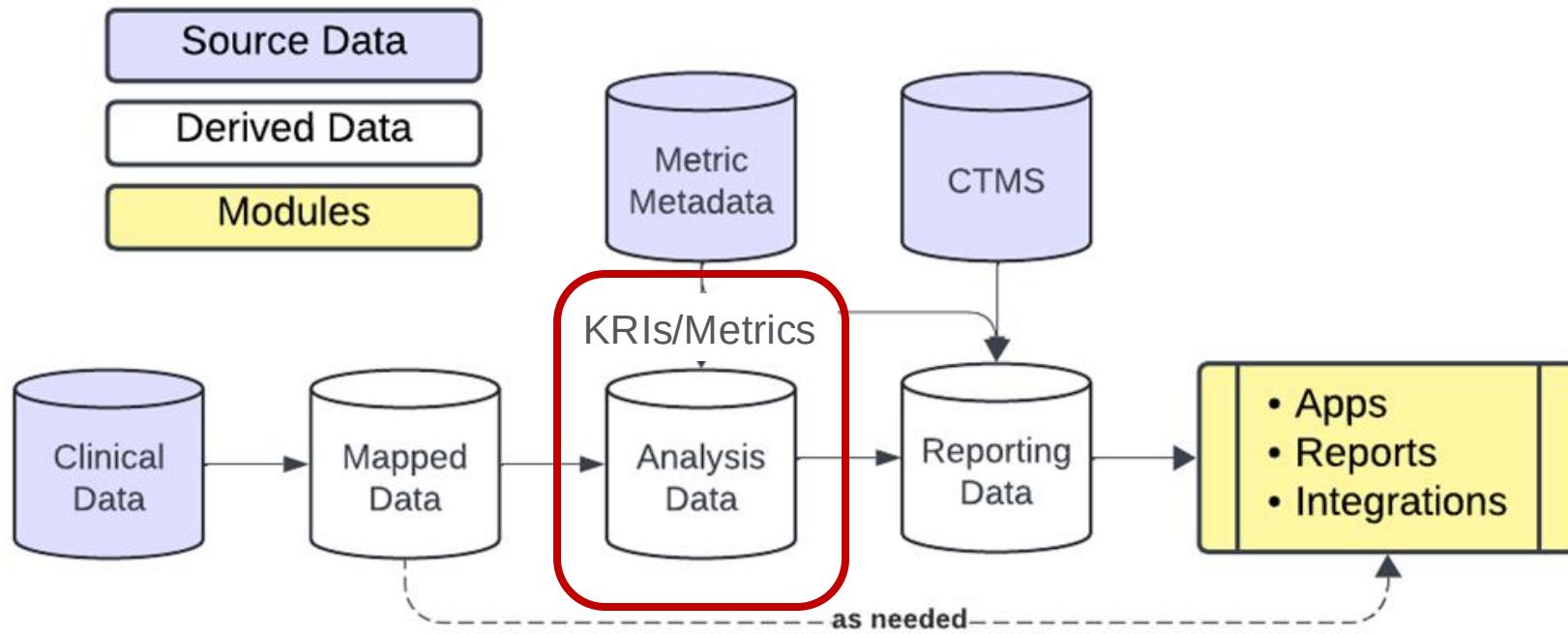
Analysis Pipeline

Workflow Framework



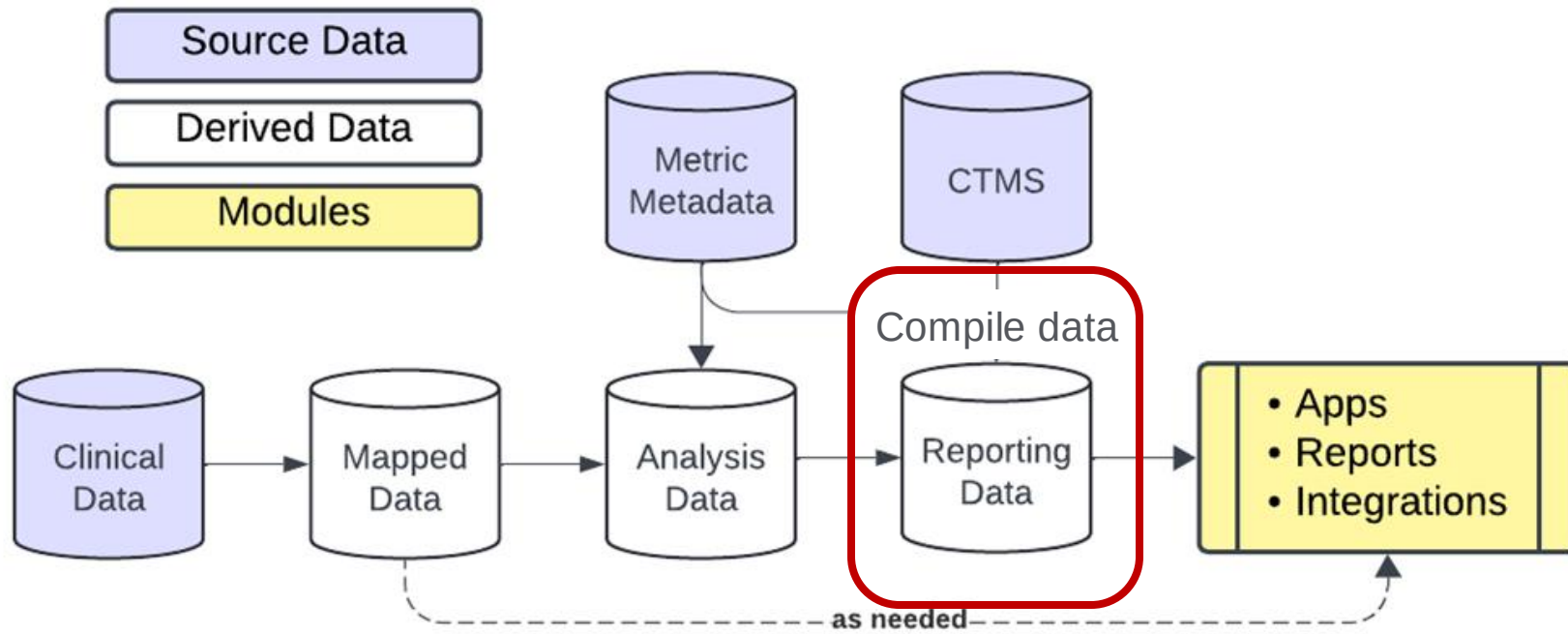
Analysis Pipeline

Workflow Framework



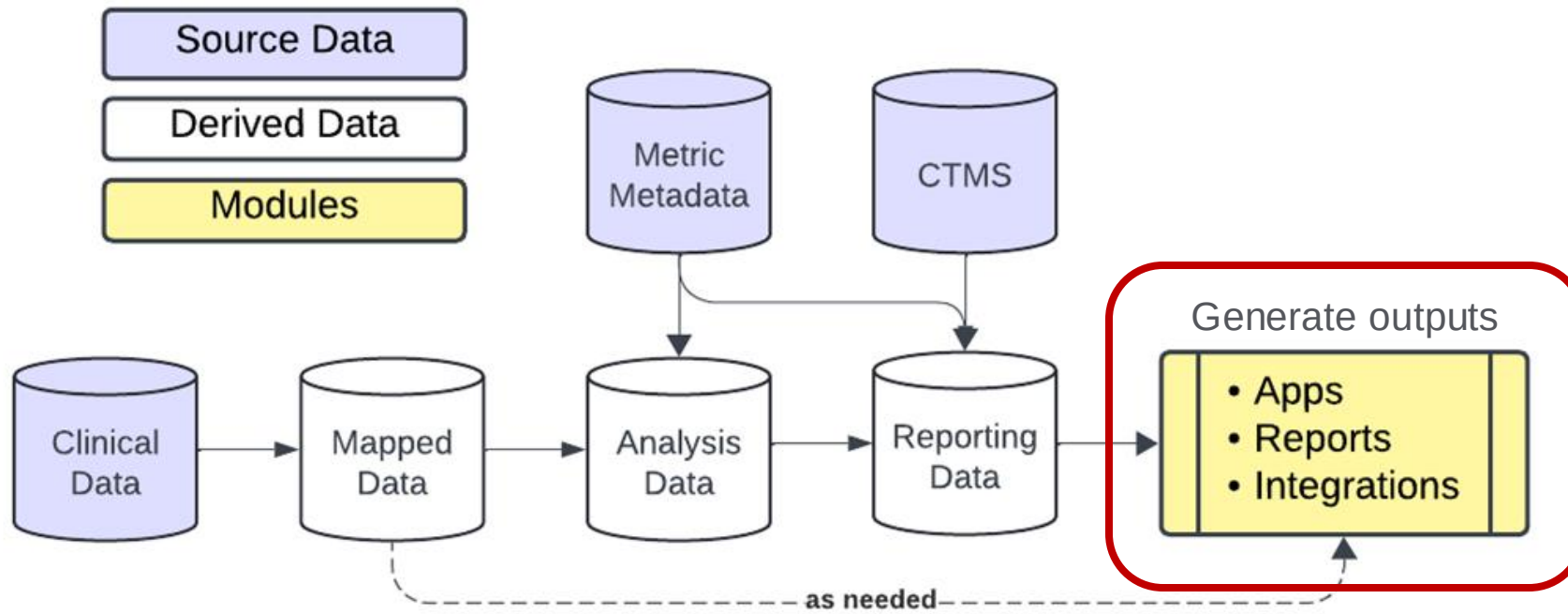
Analysis Pipeline

Workflow Framework



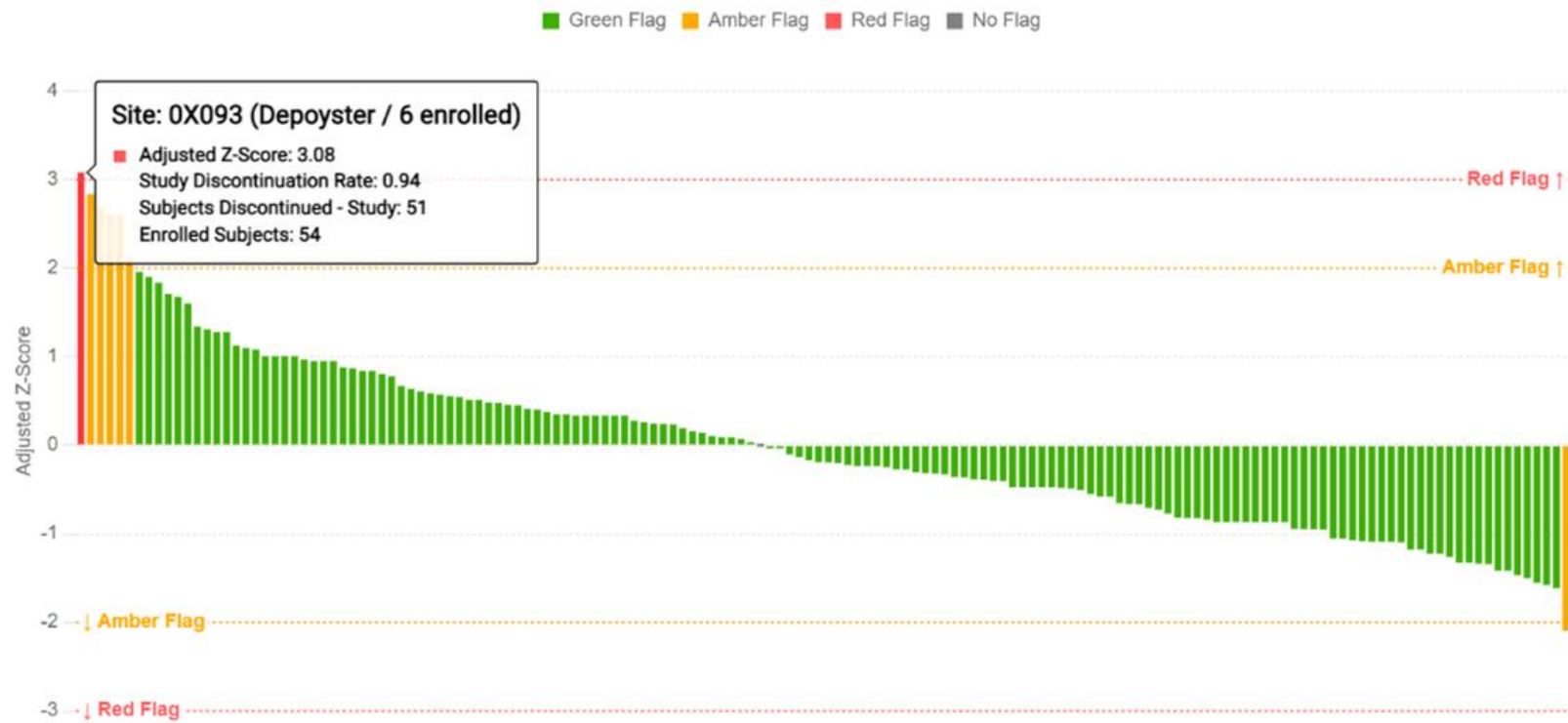
Analysis Pipeline

Workflow Framework



Analysis Pipeline

Workflow Framework



Site by Score with Metric and Site Metadata

Extensibility

– {gsm} refactor

- *Split into component packages for maintainability*
- *“{gsm}” now refers to the suite of packages*

– Component packages

- ***{gsm.core}***: *Statistical analysis & workflow engine*
- ***{gsm.mapping}***: *Data ingestion & mapping*
- ***{gsm.kri}***: *Metric workflows & reporting code*
- ***{gsm.qc}***: *Qualification framework*

Extensibility

- {gsm.app} - a Shiny app for root cause analysis
- Connects risk signals with underlying data
 - *Interactive drill-down for subject matter experts*
 - *Metrics, sites, participants, data domains*
 - *Highly interactive via two-way links between inputs and widgets*
 - *Surfaces all {gsm} data visualizations*



Study Information

Snapshot Date: 2019-11-01

☐ Show Details

Nickname	Protocol Nickname
Status	Active
Site Activation	176 / 190 (92.6%)
Participant Enrollment	1301 / 1300 (100.1%)

Metric

Adverse Event Rate ▾

Site

None ▾

Participant

All ▾

Overview Table

Scatter Plots

24 Red KRIs 22 Amber KRIs

Site Subset: 1+ red flag ▾

Group	Enrolled	Red Flags	Amber Flags	AE	SAE	PD	IPD	LB	SDSC	TDSC	QRY	OQRY	ODAT
0X103 (al-Mona)	5	4	0	✓	⬆	✓	✓	⬆	⬆	⬆	✓	✓	✓
0X027 (Owens)	10	2	1	⬆	✓	⬆	⬆	✓	✓	✓	✓	✓	✓
0X124 (Salas Dominguez)	27	2	1	⬆	✓	⬆	⬆	✓	✓	✓	✓	✓	✓
0X159 (Flores)	33	2	1	⬆	✓	✓	✓	✓	✓	✓	⬆	✓	⬆
0X024 (Rinard)	7	2	0	⬆	✓	✓	✓	⬆	✓	✓	✓	✓	✓
0X170 (Herlin)	4	2	0	✓	✓	✓	✓	✓	⬆	⬆	✓	✓	✓
0X011 (Gallegos)	5	1	1	✓	✓	✓	✓	✓	⬆	⬆	✓	✓	✓
0X016 (el-Shaker)	7	1	1	✓	✓	⬆	⬆	✓	✓	✓	✓	✓	✓
0X064 (al-Mussa)	5	1	1	✓	✓	⬆	⬆	✓	✓	✓	✓	✓	✓
0X180 (Tran)	12	1	1	⬆	✓	✓	✓	✓	✓	✓	✓	✓	✓
0X002 (Biolchini)	1	1	1	✓	✓	✓	✓	✓	—	—	✓	⬆	✓
0X079 (Gomez)	3	1	0	✓	✓	✓	✓	⬆	✓	✓	✓	✓	✓
0X155 (al-Sani)	4	1	0	✓	✓	⬆	✓	✓	✓	✓	✓	✓	✓
0X109 (Nguyen)	1	1	0	✓	⬆	✓	✓	✓	—	—	✓	✓	✓

Extensibility

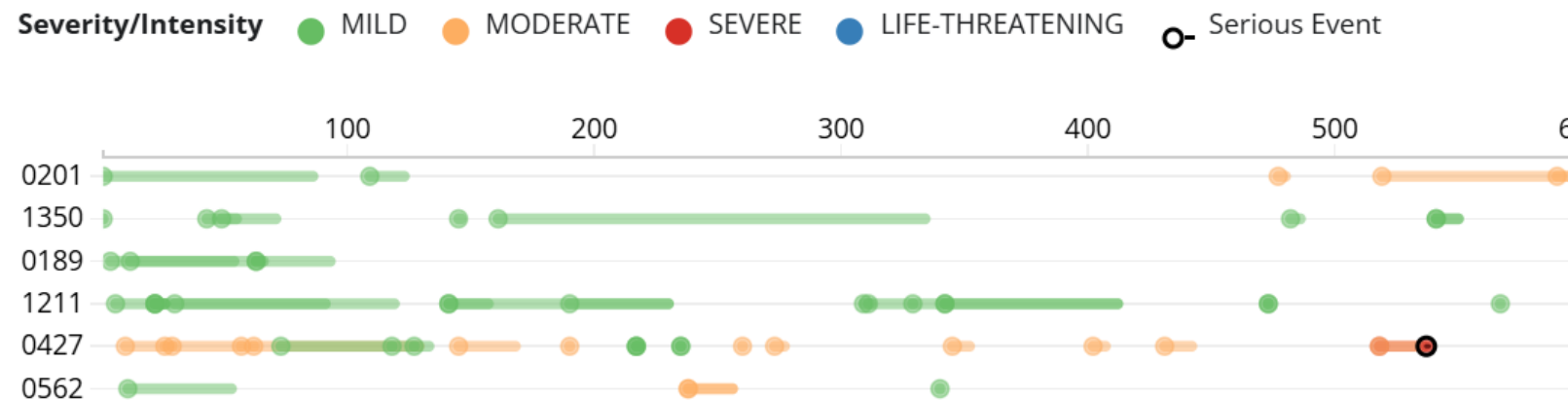
– Deep dive app extensions via “plugins”

- *Self-contained Shiny modules*
- *Dedicated server & UI functions*
- *Present data underlying metrics meaningfully*
- *Fit-for-purpose development based on SME input*

– Current and future plugins

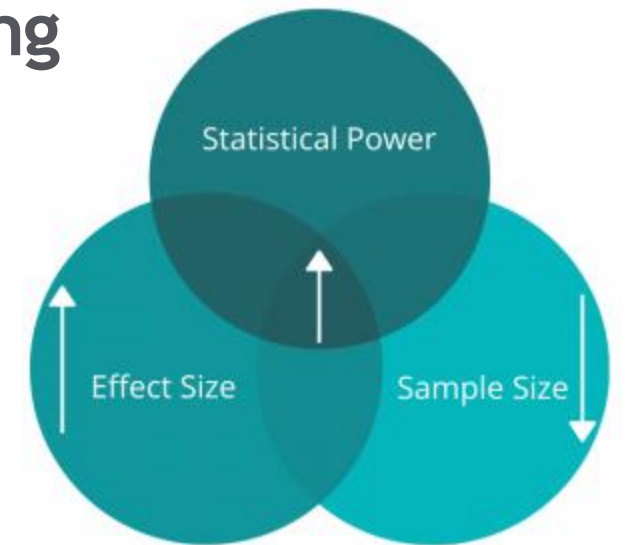
-  *Adverse events*
-  *Protocol deviations*
-  *Data quality*
-  *Site risk score*

– Demo

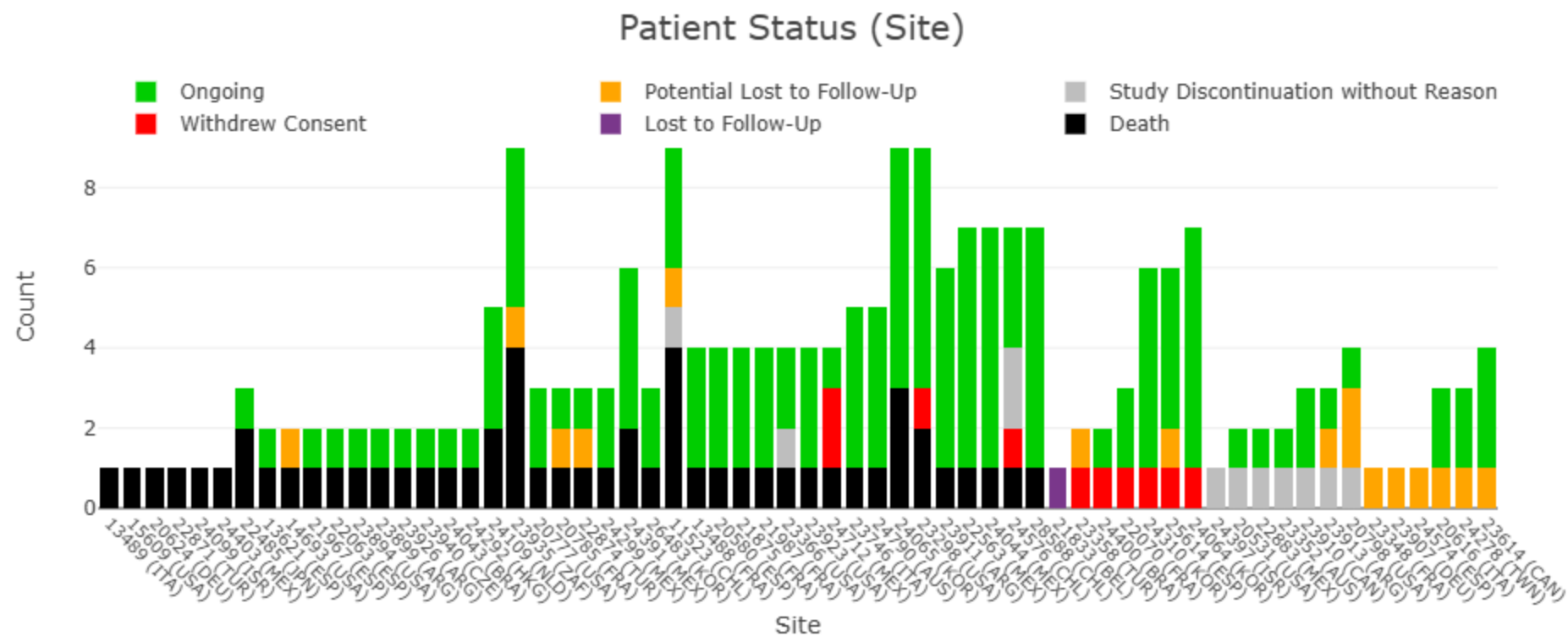


Extensibility

- {gsm.endpoints}: clinical trial endpoint monitoring
- Evaluates risks to study endpoints
 - *General risks: Patient retention*
 - *Therapeutic area-specific risks: Survival in oncology*
- Enables early detection of censoring
- Complex data derivation in mapping layer
- Study-specific, but high benefit for critical risk identification



Extensibility



Patient Retention

Extensibility

– {simaerep} and {gsm.simaerep}: Detect potential under-reporting of AEs

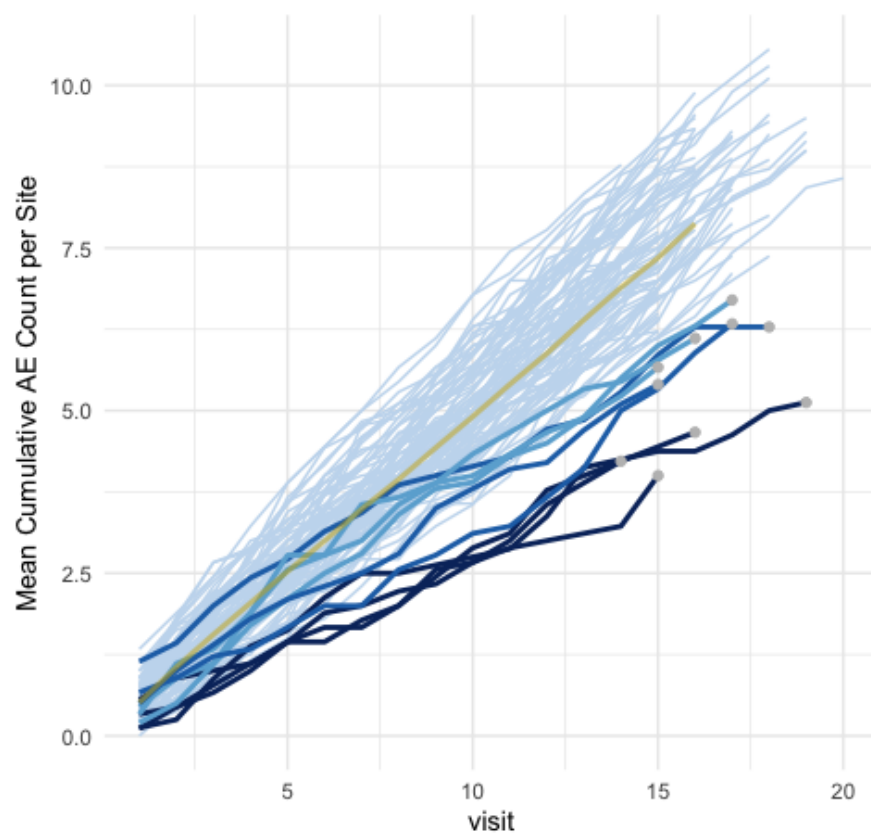
- *Bootstrap-based simulation method*
- *Assigns probability of under-reporting to each site.*

– Key Features

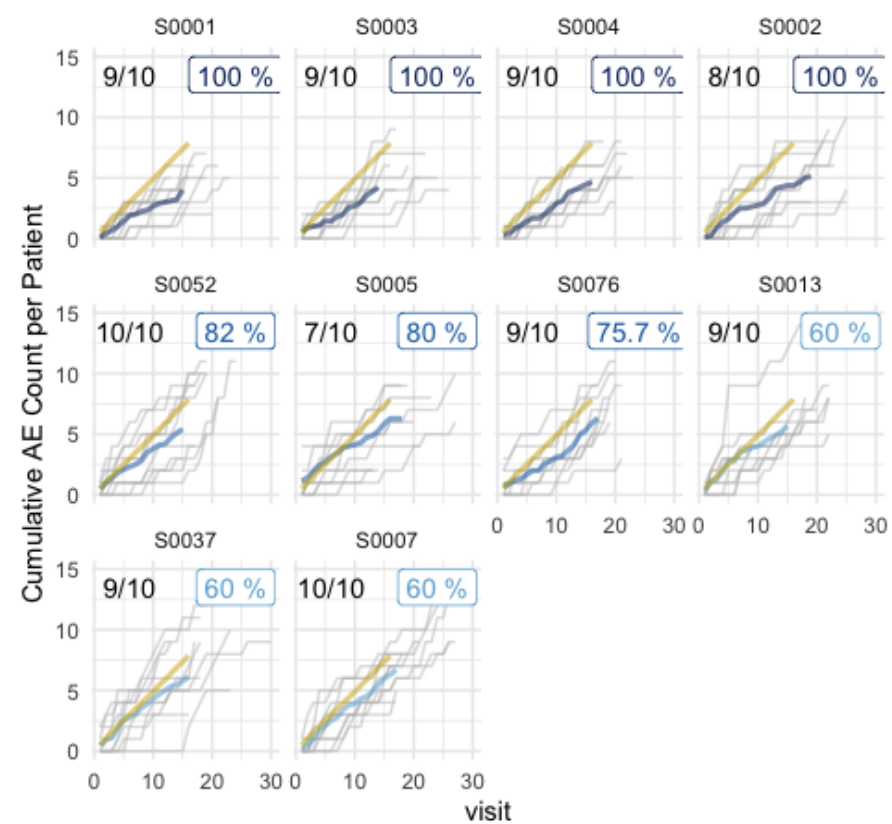
- *Rapid, comprehensive, near-real-time detection*
- *Especially relevant early in a study*
- *Applies to other event-type data domains like protocol deviations*



Extensibility



A



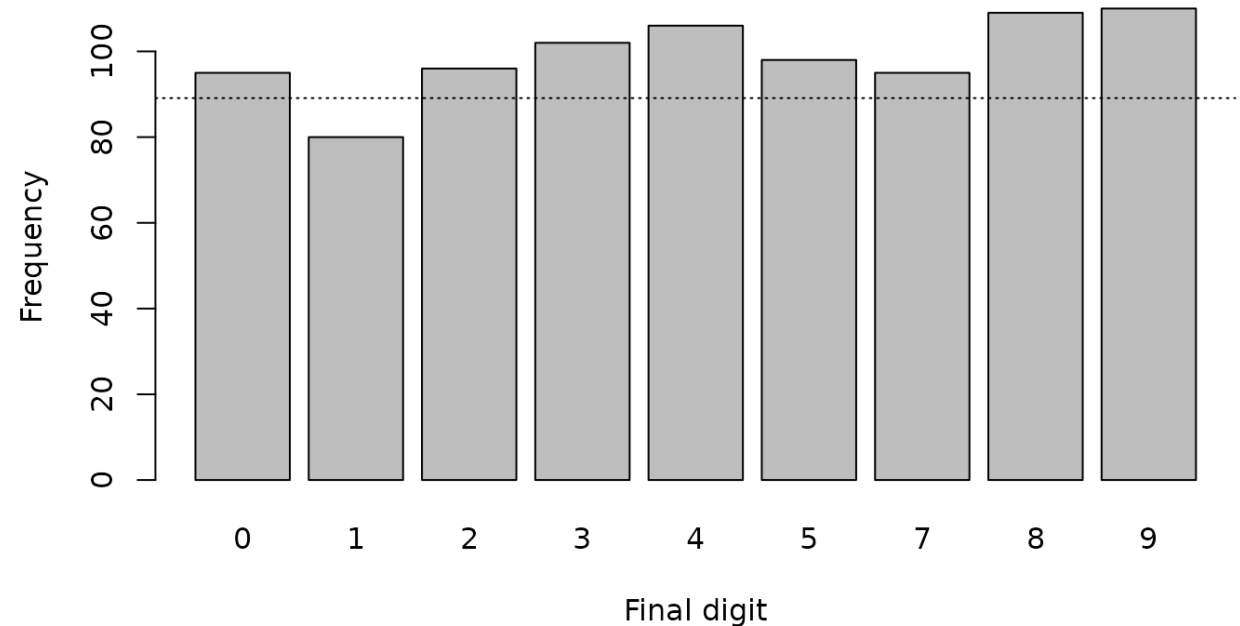
Extensibility

Group	Enrolled	Red Flags	Amber Flags	AE-Simaerep	AE-ZScore	PD-Simaerep	PD-ZScore
0X027 (Owens)	10	4	0	⤴	⤴	⤴	⤴
0X126 (Torres)	20	2	2	⤵	⬇	⤵	⬇
0X014 (Som)	25	2	1	⤴	✓	⤵	⬇
0X024 (Rinard)	7	2	0	⤴	⤴	✓	✓
0X142 (Garnett)	5	2	0	✓	✓	⤴	⤴

Comparison between {simarerep} Method and Normal Approximation

Extensibility

- {gsm.digitpref}: Identify data entry bias
- Detects patterns in numerical attributes
- Compares site vs. study-level digit distribution
- Actionable insights
 - *Focus on critical fields*
 - *Follow-up with sites on best practices*



Conclusion - Summary & Future Directions

- Extensible, workflow-driven framework enables new tools.
- OpenRBQM Contributions:
 - *Domain-specific modules: {gsm.simaerep}, {gsm.ae}, {gsm.query}.*
 - *Therapeutic area metrics: {gsm.endpoints}.*
 - *Data quality evaluation: {gsm.digitpref}.*
- Future Goals:
 - *Expand “qualityverse” to new data domains & therapeutic areas.*
 - *More comprehensive risk understanding.*
- Call to Action:
 - *Implement and/or contribute to OpenRBQM.*
 - *Contact working group leads.*

Thank you!

– Gilead

- *Andy Grannell*
- *Jenn Krohn*
- *Gosia Szczodrak*
- *Zhongkai Wang*
- *George Wu*

– Atorus Research

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- *Xu Fei*
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– Astra Zeneca

- *Lukasz Bojarski*

– And many more