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DS-400

AI and the Clinical Trial Validation Process – Paving a Rocky Road

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Biographies

Steve Ross

Steve Ross has over 25 years of deep experience in biostatistics and SAS programming, serving in Big Pharma, Small Pharma, CROs, biotech, and consultancy. His work has taken him through all phases of drug development and therapeutic areas, including Infectious Disease (HIV), cardiology, oncology, and dermatology. Steve's current mission at Beaconcure is to help ease the suffering of statisticians and programmers everywhere through using AI-enabled software that shortens and streamlines clinical trial validation.

Ilan Carmeli

Ilan Carmeli brings deep expertise in user-centric machine learning-based software to his leadership at Beaconcure. Leveraging his background in designing innovative products that place customer needs first, Ilan now focuses on creating elegant AI products for statistical clinical analysis. His passion for advancing clinical trials through developing cutting-edge yet intuitive AI solutions aligns closely with Beaconcure's commitment to shaping a responsible and human-centric approach to emerging technology.

Outline

- What's Changed in Validation Processes?
- The High Cost of Manual Validation
- Fit for Purpose: Where AI/ML Fit into a New Validation Methodology
- AI-Enabled TLF Digitization
- AI-Enabled Validation
- Consolidated Collaboration

What's Changed in Validation Processes?

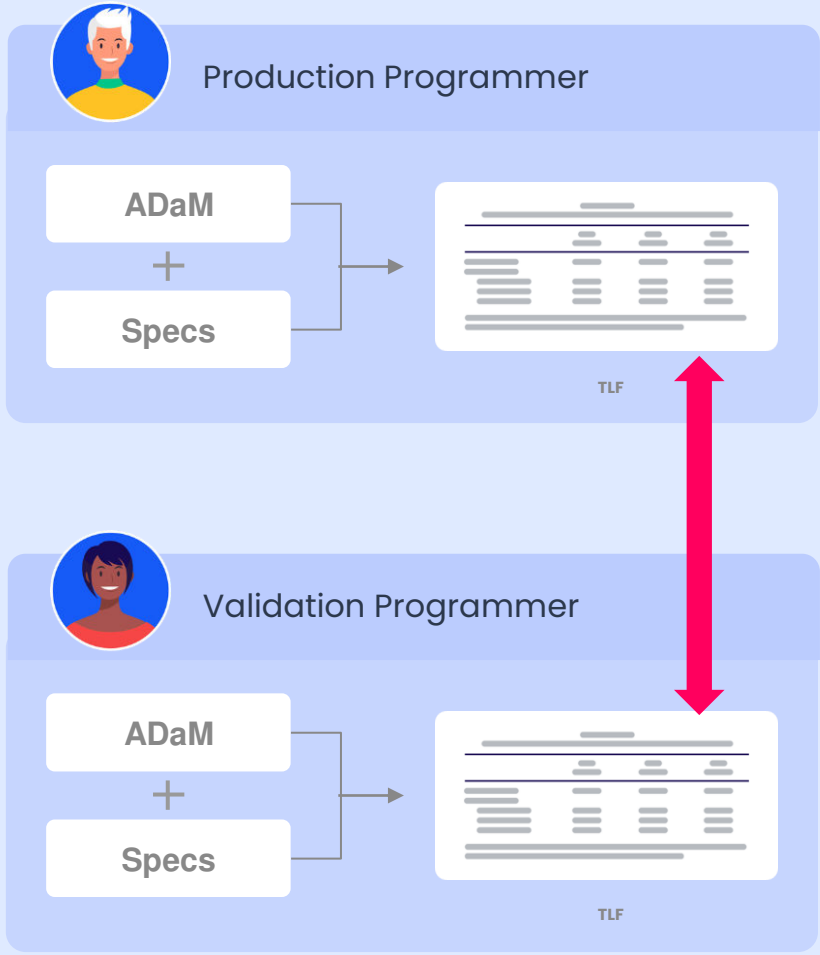
- "PROC EYEBALL" manual review of thousands of pages of outputs
- Data _Null_!
- Vax terminals for programmers; paper outputs for reviewers
- Massive paper submissions deposited at FDA offices
- Non-standard datasets of myriad formats
- Waits of a year to hear whether your NDA has been successful

Generated by CoPilot

What Hasn't Changed?

The High Cost of Manual Validation

- Large labor footprint: duplicative, repetitive, and time-consuming
- Customized code / study-specific configuration
- Double programming
  `"No unequal values were found. All values compared are exactly equal"`
- "PROC EYEBALL" manual visual review of thousands of pages of outputs
- Multiple reviewer spreadsheets



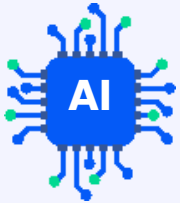
Humans are still doing the **repetitive, high-volume** validation tasks that can be **automated by a machine**

Fit for Purpose:

Where AI/ML Fits into a New Validation Methodology

Humans

- Design studies
- Test hypotheses
- Develop algorithms
- Review, understand, and interpret results
- Evaluate safety and efficacy
- Draw conclusions based on totality of a table set



AI: ML and NLP

- Links like ‘entities’ for comparison using data in varied formats
- Performs high volume, high throughput, repetitive checks on large TLF sets
- Model improves with more data
- Not limited by the parameterization of macro-enabled validation

Using AI-enabled processes for validation, you play to the strengths of human and machine

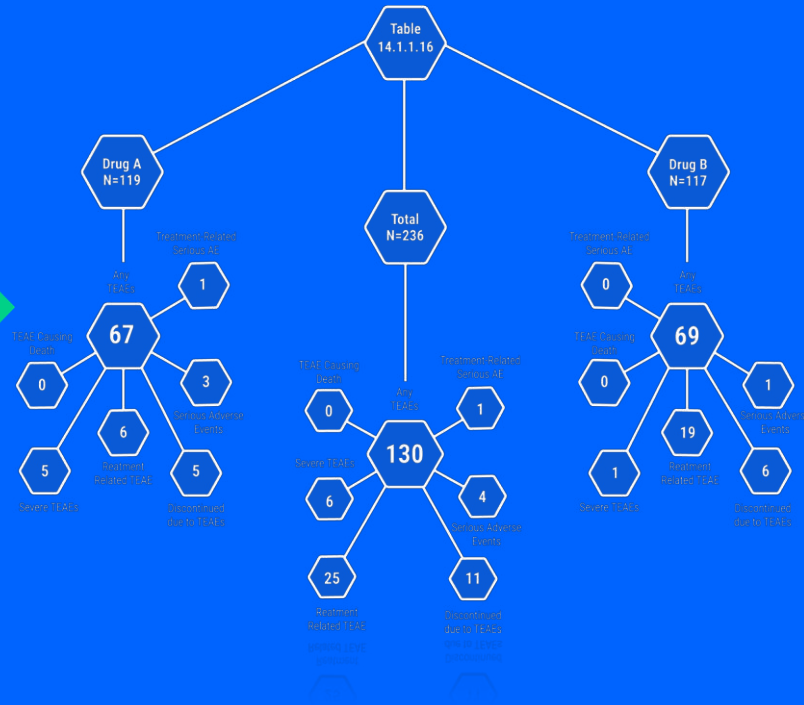
TLF Digitization

AI-Enabled TLF conversion to dynamic database

Table 14.1.1.11
Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

	Drug A (N=119)	Drug B (N=117)
Any Treatment-Emergent Adverse Events	61 (51.3%)	69 (59.0%)
Gastro Disorders	53(32.8%)	48 (41.0%)
Diarrhea	25 (21.0%)	35 (29.9%)
Vomiting	20 (16.8%)	30 (25.6%)
Infections & Infestations	10 (8.4%)	10 (8.5%)
Influenza	10 (8.4%)	10 (8.5%)
Respiratory, Thoracic and Mediastinal Disorders	11 (9.2%)	10 (8.5%)
Cough	11 (9.2%)	10 (8.5%)
Blood and lymphatic system disorders	29 (24.4%)	62 (53%)
Anemia	2 (1.7%)	0
Eosinophilia	4 (3.4%)	0
Leukopenia	8 (6.8%)	0
Lymphopenia	0	30 (25.6%)
Neutropenia	20 (16.8%)	32 (27.4%)
Pancytopenia	4 (3.4%)	57 (48.7%)
Thrombocytopenia	0	27 (23.1%)
Metabolism and nutrition disorders	12 (10.1%)	45 (38.5%)
Hyperkaliemia	2 (1.7%)	10 (8.5%)
Polydipsia	5 (4.2%)	14 (12.0%)
Decreased appetite	7 (5.9%)	20 (17.1%)
Hypokalemia	9 (7.6%)	1 (0.8%)
Psychiatric disorders	1 (0.8%)	0 (0.0%)
Insomnia	1 (0.8%)	0 (0.0%)

N = number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
Subjects are only counted once per event in each row.
BEACONCURE CONFIDENTIAL SDTM Creation: 08OCT2021 (00:55) Source Data: advs Table Generation: 09OCT2021



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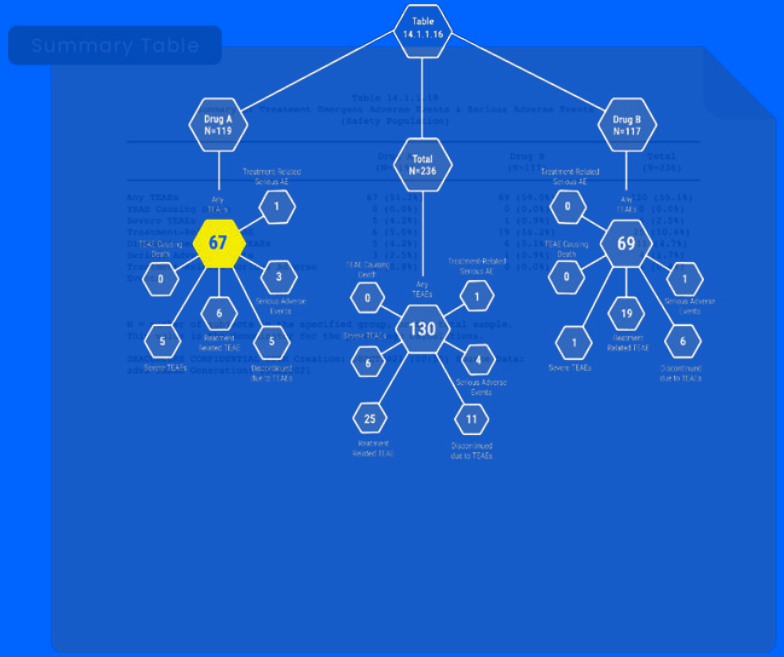
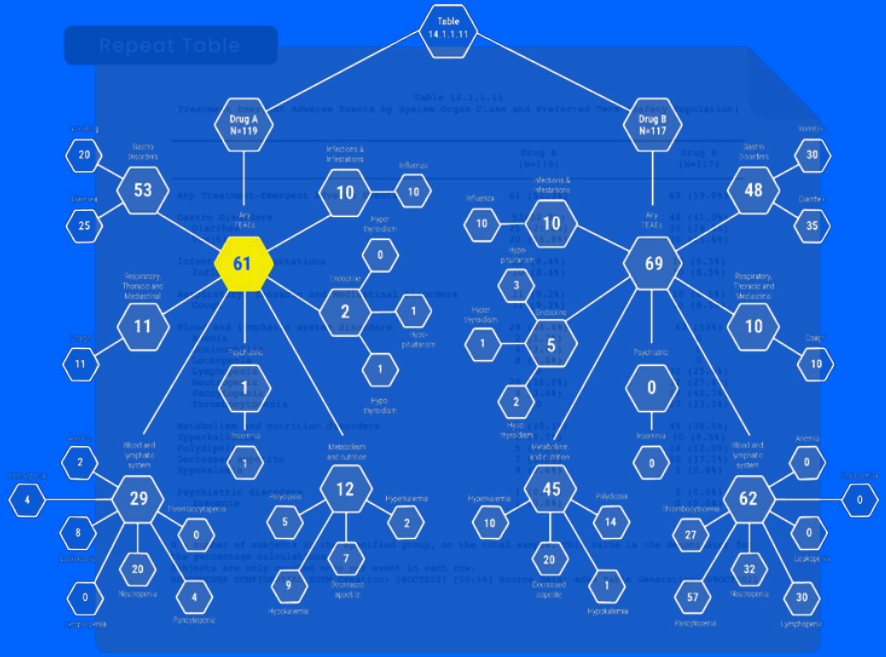
TLF Digitization

Shared Metadata Facilitates Automated Analysis





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Verify Validation Checks

Arithmetic and Hierarchies within TLFs

- Adverse Events Hierarchy
- Baseline Hierarchy
- CI Range
- Disposition Phases Hierarchy
- H Sum
- V Sum
- Kaplan-Meier Legend
- Subject Proportion with AE
- Q2: N Hierarchy
- Q2: p-Value Range
- Q2: Percent Sum

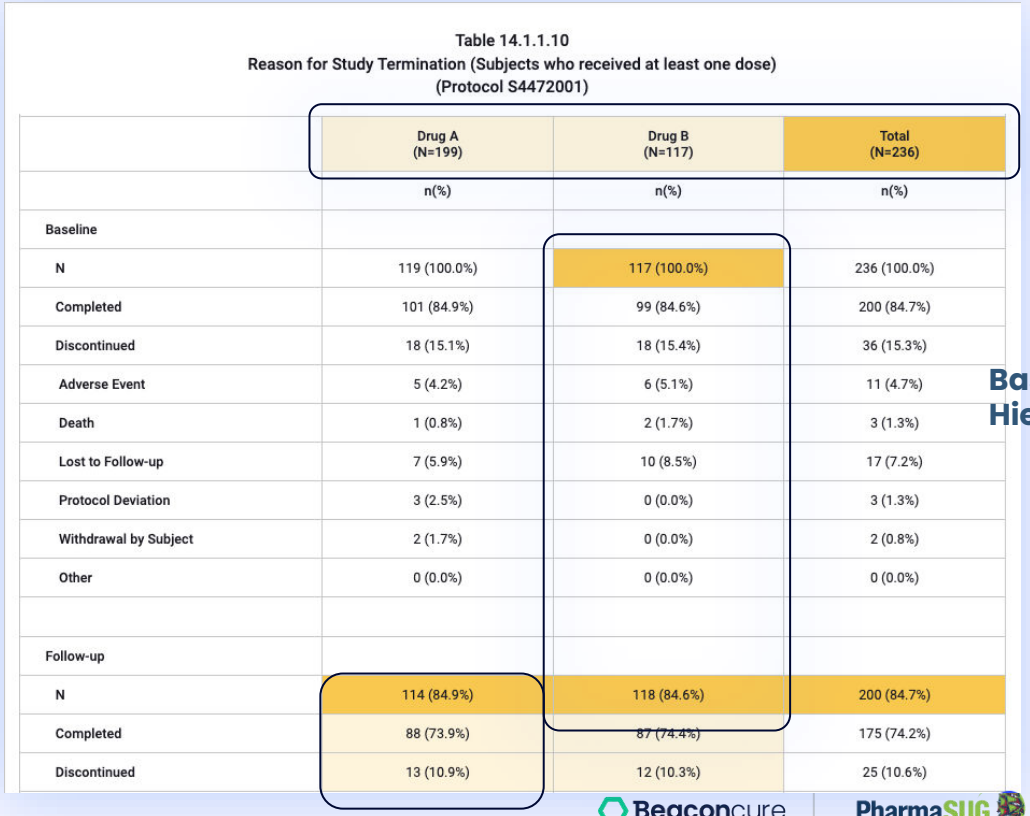

Table 14.1.1.10
Reason for Study Termination (Subjects who received at least one dose)
(Protocol S4472001)

	Drug A (N=199)	Drug B (N=117)	Total (N=236)
	n(%)	n(%)	n(%)
Baseline			
N	119 (100.0%)	117 (100.0%)	236 (100.0%)
Completed	101 (84.9%)	99 (84.6%)	200 (84.7%)
Discontinued	18 (15.1%)	18 (15.4%)	36 (15.3%)
Adverse Event	5 (4.2%)	6 (5.1%)	11 (4.7%)
Death	1 (0.8%)	2 (1.7%)	3 (1.3%)
Lost to Follow-up	7 (5.9%)	10 (8.5%)	17 (7.2%)
Protocol Deviation	3 (2.5%)	0 (0.0%)	3 (1.3%)
Withdrawal by Subject	2 (1.7%)	0 (0.0%)	2 (0.8%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)
Follow-up			
N	114 (84.9%)	118 (84.6%)	200 (84.7%)
Completed	88 (73.9%)	87 (74.4%)	175 (74.2%)
Discontinued	13 (10.9%)	12 (10.3%)	25 (10.6%)

H Sum

Baseline Hierarchy

V Sum

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AI-Enabled Validation

Validate N Consistency in Tables against ADaM

ADaM Dataset N=6

Table N=5

Unique Subject Identifier	Full Analysis Set Population Flag	Safety Population Flag	Per-Protocol Population Flag	Completers Population Flag	Randomized Population Flag	Immunogenicity Sub-study Analysis Flag	Description of Planned Arm	Planned Arm Code	Description of Actual Arm	Actual Arm Code
USUBJID	FASFL	SAFFL	PPROTFL	COMPLFL	RANDFL	ISSFL	ARM	ARMCD	ACTARM	ACTARMCD
$30.	$1.	$1.	$1.	$1.	$1.	$1.	$60.	200.	200.	200
A1234567 1001 10015001	Y	Y	Y	Y	Y	Y	BE-0552543 100mg QD	C	BE-0552543 100mg QD	C
A1234567 1001 10015002	N	N	N	N	N	N	SCREEN FAILURE	SCRNFAIL	SCREEN FAILURE	SCRNFAIL
A1234567 1001 10015003	Y	Y	Y	Y	Y	N	Placebo	A	Placebo	A
A1234567 1001 10015004	Y	Y	Y	Y	Y	Y	BE-0552543 100mg QD	C	BE-0552543 100mg QD	C
A1234567 1001 10015005	Y	Y	Y	Y	Y	Y	BE-0552543 100mg QD	C	BE-0552543 100mg QD	C
A1234567 1001 10015006	Y	Y	Y	Y	Y	Y	BE-0552543 100mg QD	C	BE-0552543 100mg QD	C
A1234567 1001 10015007	Y	Y	Y	Y	Y	Y	BE-0552543 100mg QD	C	BE-0552543 100mg QD	C
A1234567 1001 10015008	Y	Y	Y	Y	Y	Y	BE-0552543 100mg QD	C	BE-0552543 100mg QD	C
A1234567 1001 10015009	Y	Y	Y	Y	Y	Y	BE-0552543 200mg QD	C	BE-0552543 200mg QD	C

Table 14.3.2.5.2
BE-0552543 Protocol A1234567
Treatment-Emergent Adverse Events by System Organ Class (Treatment Related, Immunogenicity Sub-study Analysis Set)

Number of Subjects Evaluable for AEs	Placebo (N=9)	BE-0552543 100mg QD (N=5)	BE-0552543 200mg QD (N=11)
Number (%) of Subjects: by SYSTEM ORGAN CLASS	n (%)	n (%)	n (%)
With Any Adverse Event	0	0	1(9.1)
Nervous System Disorders	0	0	1(9.1)

Included data up to 28 days after last dose of study
Subjects were only counted once per treatment per event.
MedDRA v22.1 coding dictionary applied.
BEACONCURE CONFIDENTIAL SDTM Creation: 24APR2020 (01:13) Source Data: adae
Output File: ./A1234567/adae_s032_is Date of Generation: 26APR2020 (09:10)

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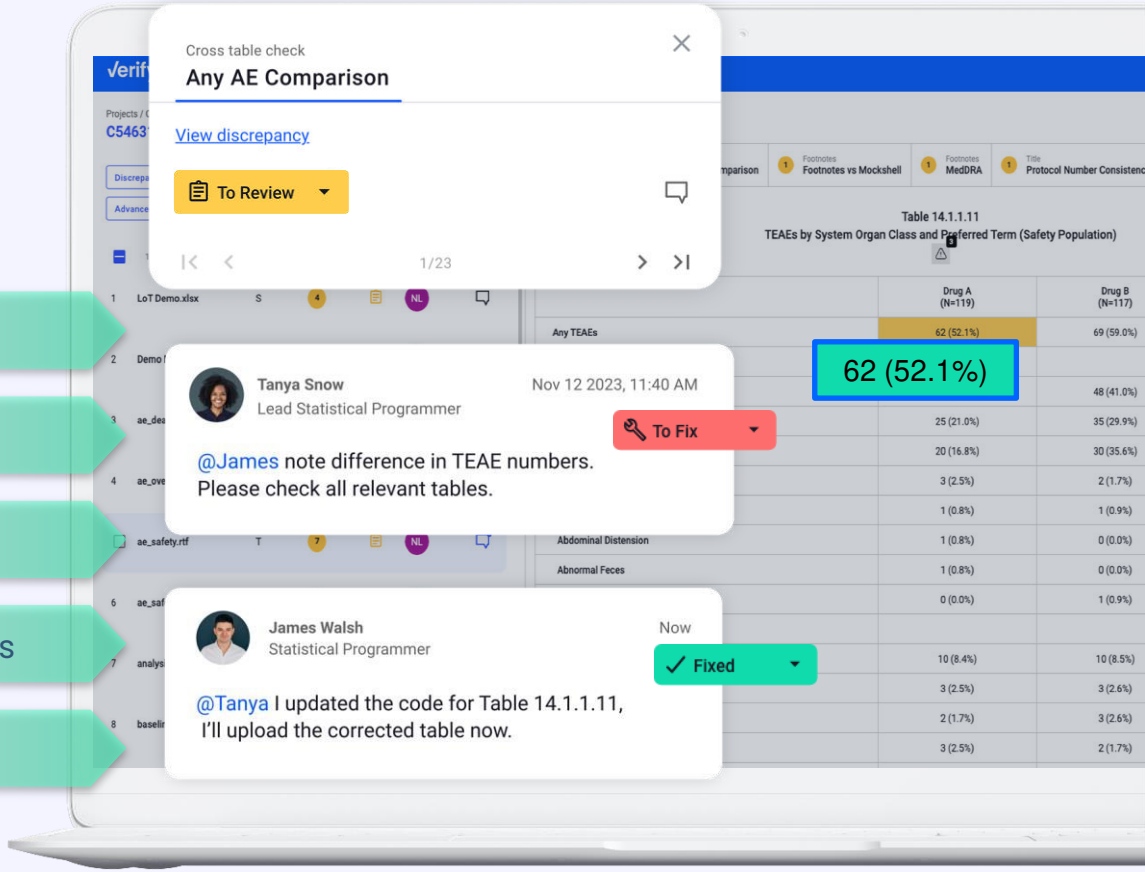
Transparent, free-flowing communication helps smooth validation processes

Consolidate Validation Review Communication

- Programmer QC spreadsheet
- Internal reviewer spreadsheet
- External reviewer spreadsheet
- Multiple emails with varied distribution lists
- Reviewer comments in marked-up PDF



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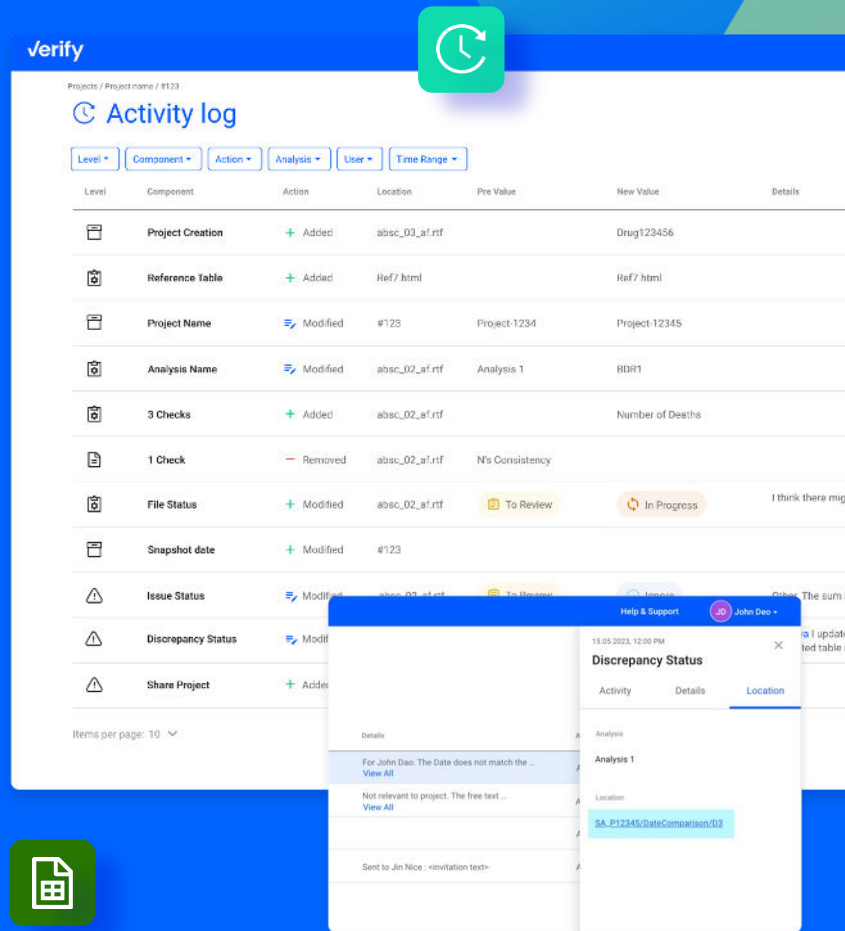
Automated Record of All Review Actions

- Unify communication between multiple reviewers on a single platform
- Facilitate review of single and multiple displays in a single deliverable, or over multiple deliverables
- Remove ambiguity about how decisions are made
- Preserve the conversation for future deliverables



Using AI to Pave the Rocky Road of TLF Validation

- **Digitized TLFs** enable quick, efficient, and accurate execution of high volume, repetitive tasks
- An AI model is easily adapted to new data, such as new formats and new logical groupings
- **AI-enabled validation checks** on large TLF sets are generalized and repeatable to a high degree of accuracy
- TLF, ARM, and ADaM data reflected in the AI model become part of the 'knowledge base' of study information – allowing for comparisons across multiple outputs and across multiple deliverables
- **Unified collaboration flows** facilitate a fully transparent discussion of deliverables

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Q & A

Thanks for listening!

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