Beaconcure

ET06

Optimizing Clinical Research: Using AI for Automated Validation of Output Tables against ADaM

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Agenda

- Technological Transformation in Clinical Trial Processes
- Traditional Approach to TLF Validation
- AI-Enabled TLF Validation
- Example 1: Cross-Table Validation of AE Sequence
- Example 2: Validate N-Consistency in Tables against ADaM
- Wider Applicability and Benefits of AI-Enabled Validation

Gone Are the Days of…

- Hand-checking thousands of pages of output
- Massive paper submissions being deposited at the offices of FDA
- Non-standard datasets of myriad formats
- Waits of a year to hear whether your NDA has been successful

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What's Changed?

The conduct of clinical trials has been dramatically reshaped in our lifetime. Technology has been a key driver of this transformation, creating efficiencies in:

- Identifying novel drug candidates (drug discovery)
- Patient identification/recruitment/retention
- Electronic data capture (EDC) and cleaning
- Study Design (adaptive designs, synthetic control arms, modeling, simulation)
- Advancement of statistical techniques (MMRM)
- CDISC standards have created a standardized language and structure for clinical trials datasets

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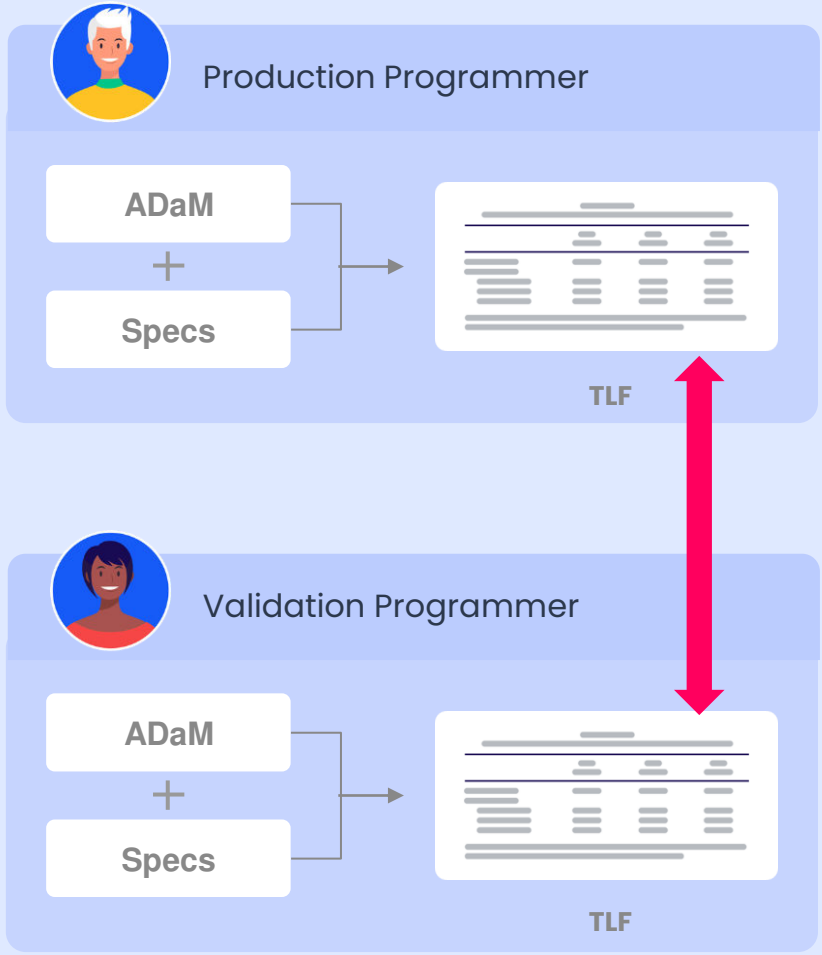
Humans are still doing the **repetitive, high-volume** validation tasks that can be **automated by a machine**

Traditional Approach to TLF Validation

“Duplication by Design”

- Customized code
- Study-specific configuration
- Large labor footprint
- Double programming and visual review
- Duplicative, repetitive, and time-consuming



Traditional Approach to TLF Validation

Cross-Table Validation of AE Sequence

- Double programming to independently generate counts, percents, univariate statistics, p-values, etc.
- Visual review of formats, decreasing n's, sums, etc.

Overall AE Table

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

Summary Table

Table 14.1.1.19
Summary of Treatment Emergent Adverse Events & Serious Adverse Events
(Safety Population)

	Drug A (N=119)	Drug B (N=117)	Total (N=236)
Any TEAEs	67 (51.3%)	69 (59.0%)	130 (55.1%)
TEAE Causing Death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe TEAEs	5 (4.2%)	1 (0.9%)	6 (2.5%)
Treatment-Related TEAE	6 (5.0%)	19 (16.2%)	25 (10.6%)
Discontinued due to TEAEs	5 (4.2%)	6 (5.1%)	11 (4.7%)
Serious Adverse Events	3 (2.5%)	1 (0.9%)	4 (1.7%)
Treatment-Related Serious Adverse Events	1 (0.8%)	0 (0.0%)	1 (0.4%)

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advs Table Generation: 09OCT2021

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

AI-Enabled TLF Validation

Cross-Table Validation of AE Sequence

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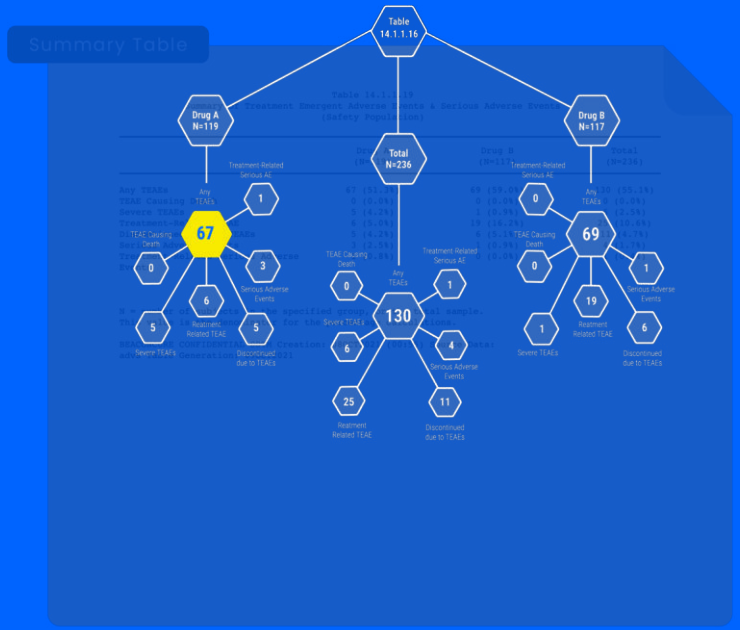
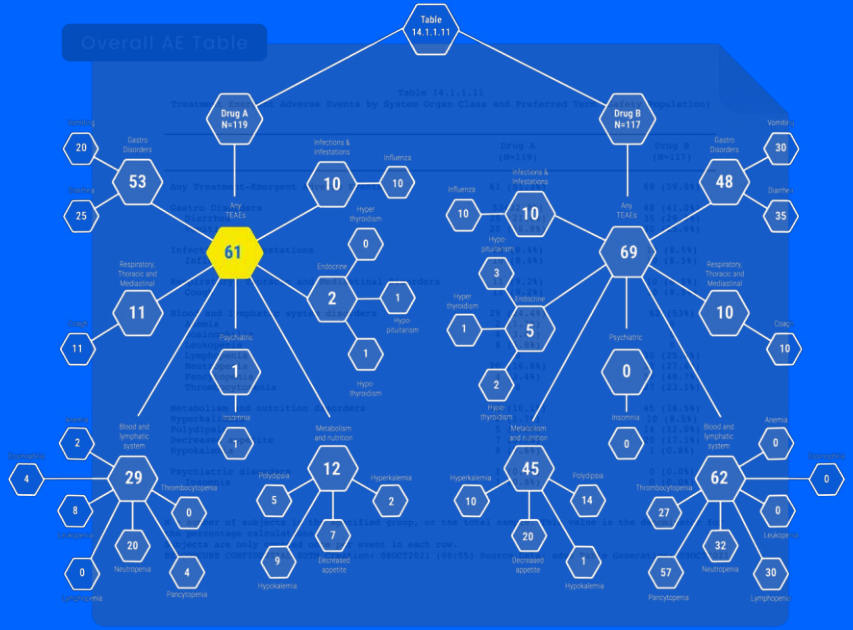
AI-Enabled TLF Validation

Cross-Table Validation of AE Sequence

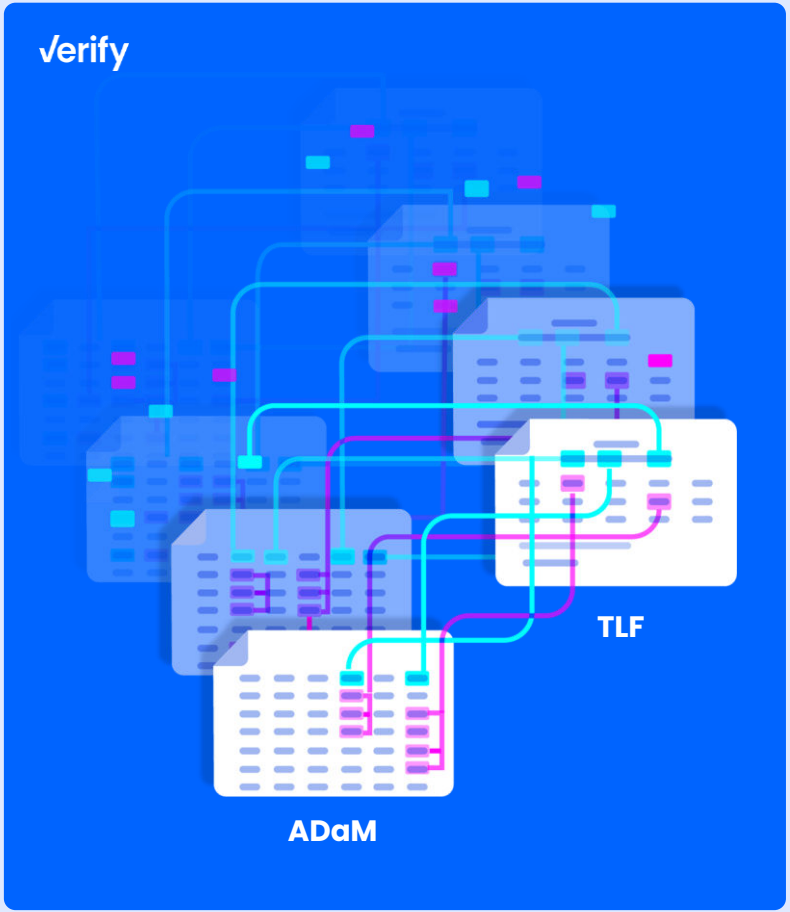




AI-Enabled TLF Validation

Validate N-Consistency in Tables against ADaM

1. Upload ADaM datasets
2. Classify columns' types in the ADaM data
3. For each TLF:
   - Digitize TLF
   - Detect and extract TLF entities (metadata)
   - Link ADaM variables to the TLF entities for subsetting and summarization
   - Compare analysis results to data in the ADaMs
   - Highlight suspected discrepancies



AI-Enabled TLF 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)

AI-Enabled Validation:
Wider Applicability and Benefits

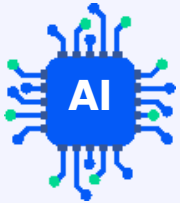
- **Validation is generalized**
  - Not limited to a specific set of initial tables or specs
  - Can be applied to understand any table introduced at any stage of development, allowing updates applied at the format review stage to be captured for future deliverables

- **Machine learning models improve over time as more data are incorporated**
  - TLF and ADaM data reflected in the AI model become part of the 'knowledge base' of study information, and can be reused to compare multiple outputs, and across multiple study outputs
  - An AI model is easily adapted to new data, such as new formats and new logical groupings

AI-Enabled Validation:
Playing to the Strengths of Human and Machine

Humans

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



AI: ML and NLP

- Linking like ‘entities’ for comparison using data in varied formats
- Perform high volume, high throughput, repetitive checks on large TLF sets, including:
  - Titles and footnotes
  - Hierarchical checks for decreasing n’s
  - Counting
  - Cross-checks across displays

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Q & A

Thanks for participating!

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References

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"Landscape Analysis of the Application of Artificial Intelligence and Machine Learning in Regulatory Submissions for Drug Development From 2016 to 2021," Liu, Q. *et al.* Clinical Pharmacology & Therapeutics (2023) 113:4