

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

Steve Ross, Director of Statistics and Life Sciences Consultancy

Ilan Carmeli, Chief Operating Officer

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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)
- Data analysis
- CDISC standards have created a standardized language and structure for clinical trials datasets



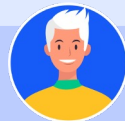
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**Humans are still doing the
repetitive, high-volume
validation tasks that can be
automated by a machine**

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



Production Programmer

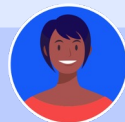
ADaM

+

Specs



TLF



Validation Programmer

ADaM

+

Specs



TLF



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.

Output A

Table 14.1.1.16
TEAE Occurring in >5% of Subjects in at least One Treatment Group in Study by System Organ Class and Preferred Term (Safety Population)

	Drug A (N=119)	Drug B (N=117)
Any TEAEs	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%)
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%)
Anaemia	2 (1.7%)	0
Eosinophilia	4 (3.4%)	0
Leukopenia	8 (6.8%)	0
Lymphopenia	0	30 (25.6%)
Neutropenia	20 (16.8%)	12 (27.4%)
Pancytopenia	4 (3.4%)	57 (48.7%)
Thrombocytopenia	0	27 (23.1%)
Endocrine disorders	2 (1.7%)	5 (4.3%)
Hypothyroidism	0	1 (0.8%)
Hypopituitarism	1 (0.8%)	3 (2.6%)
Hypothyroidism	1 (0.8%)	2 (1.7%)
Metabolism and nutrition disorders	12 (10.1%)	45 (38.5%)
Hyperkalaemia	2 (1.7%)	10 (8.5%)
Polydipsia	5 (4.2%)	14 (12.0%)
Decreased appetite	7 (5.9%)	20 (17.1%)
Hypokalaemia	9 (7.6%)	1 (0.8%)
Psychiatric disorders	1 (0.8%)	0
Insomnia	1 (0.8%)	0

N=119

N=117

Output B

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%)

N = number of subjects in the specified group, or the total sample.
This value is the denominator for the percentage calculations.

BEACONCURE CONFIDENTIAL SDTM Creation: 08OCT2021 (00:55) Source Data:
advs Table Generation: 09OCT2021

**Using AI-enabled
processes for validation,
you can play to the
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Cross-Table Validation of AE Sequence

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Output B

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

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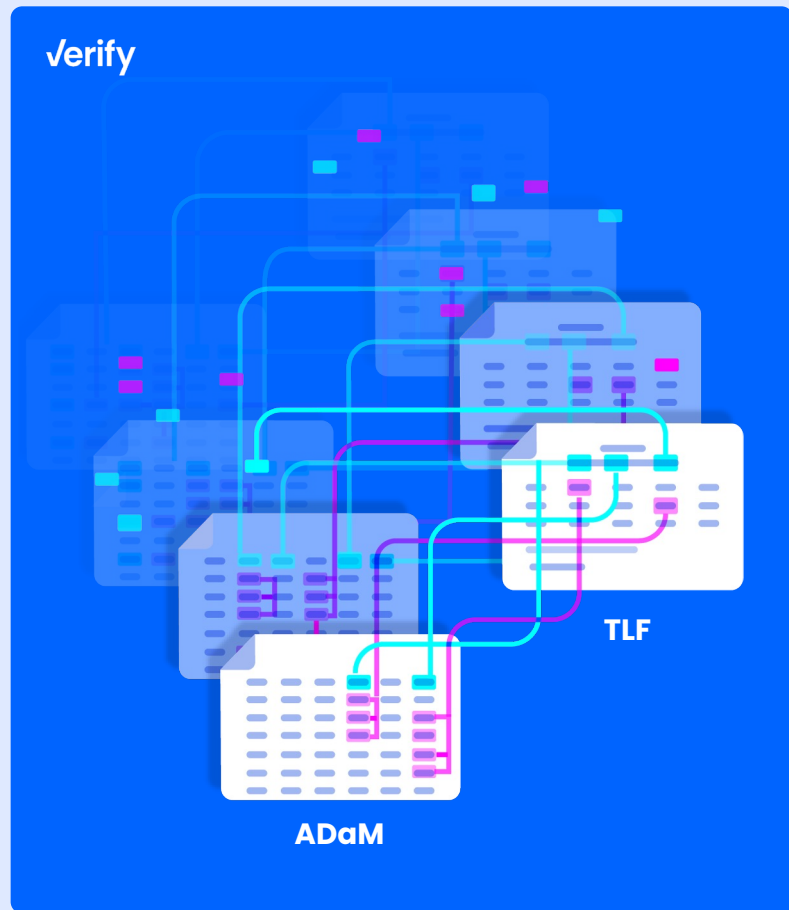
BEACONCURE CONFIDENTIAL SDTM Creation: 08OCT2021 (00:55) Source Data:
advs Table Generation: 09OCT2021

Cross-Table Validation of AE Sequence



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)
 - Pair the ADaM columns to the TLF entities
 - Detect the relevant rows in the ADaM dataset(s) based on the pairing
 - Perform the required statistical analysis on the relevant ADaM data
 - Compare statistical analysis result to data in the TLF
 - Highlight suspected discrepancies



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	SAFPL	PPROTFL	COMPLFL	RANDFL	ISSFL	ARM	ARMCD	ACTARM	ACTARMCD
\$30.	\$1.	\$1.	\$1.	\$1.	\$1.	\$1.	\$50.	200.	200.	200.
A1234567 1001 10015001	Y	Y	Y	Y	Y	Y	DC-0552 43-100mg QD-0	BE-0552543 100mg QD	BE-0552543 100mg QD	C
A1234567 1001 10015002	N	N	N	N	N	N	SCREEN FAILURE	SCRNFIL	SCREEN FAILURE	SCRNFIL
A1234567 1001 10015003	Y	Y	Y	Y	Y	N	Placebo	A	Placebo	A
A1234567 1001 10015004	Y	Y	Y	Y	Y	Y	DC-0552 43-100mg QD-0	BE-0552543 100mg QD	BE-0552543 100mg QD	C
A1234567 1001 10015005	Y	Y	Y	Y	Y	Y	DC-0552 43-100mg QD-0	BE-0552543 100mg QD	BE-0552543 100mg QD	C
A1234567 1001 10015006	Y	Y	Y	Y	Y	Y	DC-0552 43-100mg QD-0	BE-0552543 100mg QD	BE-0552543 100mg QD	C
A1234567 1001 10015007	Y	Y	Y	Y	Y	Y	DC-0552 43-100mg QD-0	BE-0552543 100mg QD	BE-0552543 100mg QD	C
A1234567 1001 10015008	Y	Y	Y	Y	Y	Y	DC-0552 43-100mg QD-0	BE-0552543 100mg QD	BE-0552543 100mg QD	C
A1234567 1001 10015009	Y	Y	Y	Y	Y	Y	DC-0552 43-100mg QD-0	BE-0552543 200mg QD	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)

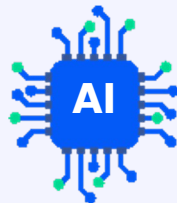
Included data up to 28 days after last dose of study
Subjects were only counted once per treatment per event.
MedDRA v21.1 coding dictionary applied.
BEACONCURE CONFIDENTIAL SDTH Creation: 24APR2020 (01:13) Source Data: adae
Output File: ./A1234567/adae_032_is Date of Generation: 26APR2020 (09:10)

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



Humans

- Design specifications
- Create displays
- Review, understand, and interpret results
- Provide feedback
- Update TLFs based on feedback from reviewers



AI: ML and NLP

- Link variables in ADaMs to metadata captured from the TLFs and mock shell specifications
- Perform repetitive checks on large TLF sets, including:
 - Titles and footnotes
 - Hierarchical checks for decreasing n's
 - Counting
 - Cross-checks across displays

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

Q & A

Thanks for participating!

Steve@beaconcure.com
llan@beaconcure.com

<https://beaconcure.com>

References

“The role of machine learning in clinical research: transforming the future of evidence generation” Weissler et al. Trials (2021) 22:537