PharmaSUG 2022 - SA-009

The Emerging Use of Automation to Address the Challenge of Cross-Table Consistency Checking of Output Used in the Reporting of Clinical Trial Data

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ABSTRACT

The current gold standard for validation of programs summarizing data from clinical trials is double programming of all analysis datasets, tables, listings, and figures. This approach, however, does not identify cross-table discrepancies, and, we would argue, is not the best method of obtaining the highest quality results. As it is a manual exercise, it is labor intensive and subject to human error. Performing cross-table checks of outputs manually is a common practice performed by biostatisticians in the pharmaceutical industry. Manually validating multiple tables takes a significant amount of time and resources. This repetitive work can be done by a dedicated software, allowing the biostatisticians to focus on the statistical aspects of the study. It also provides a consistent, specified approach, whereas the current checking process is often unspecified and therefore not replicable.

An automation solution developed by Beaconcure cross checks two or more outputs in exactly the same way as figures within and across tables are commonly compared today but it does so in a comprehensive, consistent and faster manner. This technology can be used multiple times as data accumulates, identifying programming errors that lead to discrepancies in the output. It can also be used for all of reporting, such as Interim Analyses, Safety Updates, output for Data Monitoring Committees.

The following article presents multiple examples of cross-table checks as well as the automated process for performing these checks.

THE CHALLENGE

Double programming is commonly used as a Quality Control (QC) tool of clinical statistical analyses to increase the reliability of the data produced. Beconcure has conducted an industry survey and found that out of the participating pharma/CRO companies, 68% double program all outputs, 28% double program the complete tables including their formats, and 44% do additional manual QC checks. Double programming may be useful for specific in-table checks, however, it does not compare the output across tables. In our most recent survey, 68% of companies responded perform cross-table validation, 50% write programs to perform some of the cross-table checks, and 50% have concrete specifications for cross-table review.

Within an individual table, the two programs may produce the same values, but it may not be correct. Comparing the results across tables may identify mistakes in one of the tables. For example, the number of subjects in the safety population in the disposition table may be different from the number of subjects shown in a specific analysis of the safety population, such as adverse events. This type of discrepancy is common and has been observed in our analyses. Another example of a discrepancy we observed exists between the number of adverse events causing withdrawal and the number of subjects withdrawn due to adverse events.

SOLUTION

'Verify', a Solution for table data validation, is a machine learning (ML) based tool. In addition to performing within table checks, can perform cross-table checks quickly and consistently for all deliverables. This would be achieved by running a set of standard cross-table checks defined by statisticians.

The key to success in implementing automation is the combination of the human factor and ML. By adopting an automated platform, pharma companies and CROs can:

- Greatly reduce the time and effort to perform across table checks
- Check the output comprehensively and consistently
- Improve the productivity of statisticians

Beaconcure's 'Verify' Automation is designed to implement cross-table checks throughout the study's output. The technology can be used multiple times as data accumulates, identifying programming errors that lead to discrepancies in the output.

This development can also be used for different kinds of cross-table checks, and are based on the way the study is performed and the company's usual table structure.

Reference Table

In studies where one table defines a group's numbers throughout the study, such as Analysis Sets, Subject Evaluation Group (also known as ADSL) or a Demographic Characteristic table, the automation can perform its comparison based on a reference table. The reference table can be selected either manually by the user related to the study, or by the automation using a consistent rule definition of what the reference should look like. The check is then performed based on the reference table numbers, and a cell match is conducted. If, for any reason, the numbers in a selected table are different from the numbers specified in the reference table, 'Verify' will automatically alert the situation as a discrepancy. An example demonstrating a verified reference table (14.1.1.2) and a compared table (14.1.1.19) sharing relevant features for cell matching is shown below.

Table 14.1.1.2
Analysis Population

	Drug A	Drug B	Total
Randomized Population	120	117	237
Safty Population	**119**	**117**	**236**
Received at least one dose	119	117	236
Completed 4 weeks	89	87	176
Per Protocol Population at 4 weeks	80	61	141
Completed 8 weeks	82	75	157
Per Protocol Population at 8 weeks	48	39	87
Completed Study (12 weeks)	75	69	144

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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	61 (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.
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General Cross-Table

The general cross-table cell match does not require a manual indication of a reference table, the automation is able to identify the different analysis sets, cohorts, phases and match them with one another. Unlike the reference table option, a cell match can be performed for more than two tables in one match. In a study where one or more tables have an anomaly in its cell value, ‘Verify’ will automatically mark the cell as a discrepancy. An example demonstrating a discrepancy for two tables in a cross-table check for “Discontinuation Due to Adverse Events” is shown below.

Table 7
End of Study Disposition

	Drug A (N=119)	Drug B (N=117)	Total (N=236)
Number (%) of Participants	n (%)	n (%)	n (%)
Completed	101 (84.9)	99 (84.6)	200 (84.7)
Discontinued	18 (15.1)	18 (15.4)	36 (15.3)
Treatment Emergent Adverse Events	5 (4.2)	6 (5.1)	11 (4.7)
Death	1 (0.8)		
Lost to Follow-up	7 (5.9)		
Protocol Deviation	3 (2.5)		
Withdrawal by Subject	2 (1.7)		
Other	0		

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Table 4
Overall Summary of Treatment Emergent Adverse Events
(Safety Population)

	Drug A (N=119)	Drug B (N=117)	Total (N=236)
Number (%) of Participants	n (%)	n (%)	n (%)
Any AEs	73 (61.3)	88 (75.2)	161 (68.2)
Any TEAEs	75 (63.0)	85 (7.2)	156 (66.1)
Serious TAEs	3 (2.5)	6 (5.1)	8 (3.4)
Drug Related TEAs	17 (14.3)	27 (23.1)	44 (18.6)
Discontinued due to TEAEs	7 (5.9)	6 (5.1)	13 (5.5)

Summation Cross-Table

Summation cross-table checks are very similar to the general cross-table checks, only the calculation method is based on summation, rather than cell matching. Relevant groups are compared to one another. This function is both a calculation check, and a comparison one. An example demonstrating a verified summation in cross-table check for “Demographic Characteristics” is shown below.

Table 14.1.1.4

Demographics (Received at Least One Dose)

	Drug A	Drug B	Total
Gender			
Male	60 (51.3%)	60 (50.8%)	120 (50.8%)
Female	59 (48.7%)	57 (49.2%)	116 (49.2%)
Age			
<18	1 (0.8%)	0	1 (0.4%)
18-30	34 (28.6%)	33 (28.2%)	68 (28.8%)
31-45	36 (30.3%)	37 (31.6%)	73 (30.9%)
46-65	46 (38.7%)	47 (40.2%)	93 (39.4%)
>65	1 (0.8%)	0	1 (0.4%)
Weight			
n	118	115	233
Mean	75.12	75.34	77.79
SD	7.34	7.52	7.74
Median	77.8	78.1	77.9
Min	62	67	62
Max	88	89	89

Note: Subject 003-005 was randomized to Drug A but received Drug B in error.
Cutoff date: 03MAY2021 Snapshot date: 03MAY2021

Table 14.1.2.4
Overall Summary of Treatment Emergent Adverse Events (Safety Population)

	Drug A (N=119)	Drug B (N=117)	Total (N=236)
Any AEs	73 (61.3%)	88 (75.2%)	161 (68.2%)
0-4 Weeks:			
Any TEAEs	75 (63.0%)	85 (72.6%)	156 (66.1%)
Serious TEAEs	3 (2.5%)	17 (14.3%)	7 (5.9%)
Drug-Related TEAEs	17 (14.3%)	27 (23.1%)	44 (18.6%)
Discontinued due to TEAEs	7 (5.9%)	9 (7.7%)	16 (6.8%)
4-8 Weeks:			
Any TEAEs	48 (40.3%)	38 (32.5%)	86 (36.4%)
Serious TEAEs	1 (0.8%)	3 (2.6%)	4 (1.7%)
Drug-Related TEAEs	12 (10.1%)	20 (17.1%)	40 (16.9%)
Discontinued due to TEAEs	3 (2.5%)	4 (3.4%)	7 (3.0%)
8-12 Weeks:			
Any TEAEs	25 (21.0%)	20 (17.1%)	45 (19.1%)
Serious TEAEs	0 (0.0%)	1 (0.9%)	1 (0.4%)
Drug-Related TEAEs	7 (5.9%)	5 (4.3%)	12 (5.1%)
Discontinued due to TEAEs	1 (0.8%)	1 (0.9%)	2 (0.8%)
0-12 Weeks:			
Any TEAEs	83 (69.7%)	93 (79.5%)	176 (74.6%)
Serious TEAEs	3 (2.5%)	7 (6.0%)	10 (4.2%)
Drug-Related TEAEs	28 (23.5%)	30 (25.6%)	58 (24.6%)
Discontinued due to TEAEs	11 (9.2%)	14 (12.0%)	25 (10.6%)

Note: Subject 003-005 was randomized to Drug A but received Drug B in error.
The Safety Population is all subject who received at least one does of medication.
Any AE is any adverse event that began after the beginning of the screening period.
Any TEAE is any adverse event that began after the first dose.
Cutoff date: 03MAY2021 Snapshot date: 03MAY2021

Footnote Comparison

Cross-table checks in the Footnotes of tables often play a key feature in a clinical study's QC. Cross-table checks in this specific way can validate the coherency and consistency throughout the study, and also validate in comparison with a defined snapshot date. For example, the system can alert a discrepancy when the SDTM date is earlier than the snapshot date in different tables. An example demonstrating a discrepancy for Cross-Table Footnote check, alerting inconsistency is the SDTM date is shown below. '

Table 1:

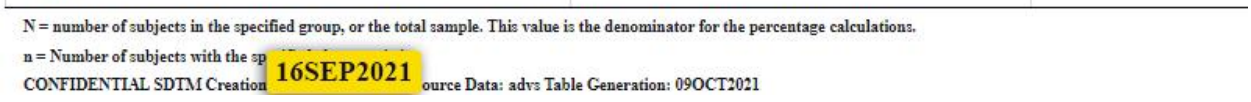
N = number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
n = Number of subjects with the sp
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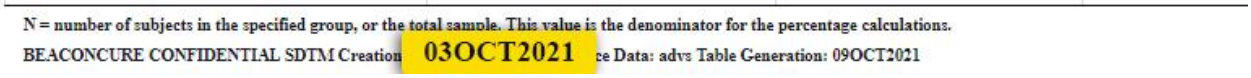
Table 2:


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

The QC process of clinical trials' statistical output is a challenging and cumbersome task to perform, especially when cross-table checks are implemented manually, and discrepancies are missed with double

programming. ‘Verify’ by Beaconcure offers automatic cross-table checks that are tailored to the end-users needs and can be adjusted to varying table structures and specifications.

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