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‘Verify’ Product Demonstration:

Validation of Statistical Outputs Using Automation

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ABSTRACT

Validation of statistical outputs of clinical trials is cumbersome and time consuming. Relieving these tasks requires a solution involving automation supported by Machine Learning (ML), an approach that has been proven across many industries, and is considered a game-changer in the world of drug development. Applied to statistical outputs validation, automation can be fundamental to rapidly ensuring sound interpretation of clinical data and, therefore, more efficient regulatory submissions.

‘Verify’ is Beaconcure’s automated output validation solution, based on ML algorithms and created specifically for the pharmaceutical industry. It can read different clinical data formats in any layout into a semantic and dynamic database, to which any required segmentation rule, crosscheck and analysis can be applied. All defined errors and anomalies are identified, with 99.7% accuracy, in a matter of hours, drastically reducing clinical data processing timelines and increasing the quality of the output.
‘Verify’ validates statistical outputs automatically by applying various algorithms to the processed data. The verification algorithms use the base table processing information to identify groups and sub-groups in the data, with the capability of validating single and cross-table content. The system can then flag discrepancies and direct the user to the relevant table for follow-up action and resolution of identified discrepancies.

INTRODUCTION

The majority of validation and Quality Control (QC) of statistical output is performed manually by clinical programmers and biostatisticians. This process is time consuming and error prone. In 2022, Beaconcure conducted an industry survey and received responses from 15 leading companies in the pharmaceutical industry. From the survey, it was found that manual review of a single table takes on average 34 minutes, and can take as much as 28 hours for a small study with 50 outputs. Figure 1 shows the varying amount of time it takes to perform manual QC review. In addition, it was found that the majority of study information exchange is done via email, with tasks assigned and shared using Excel spreadsheets, without a standardized workflow.

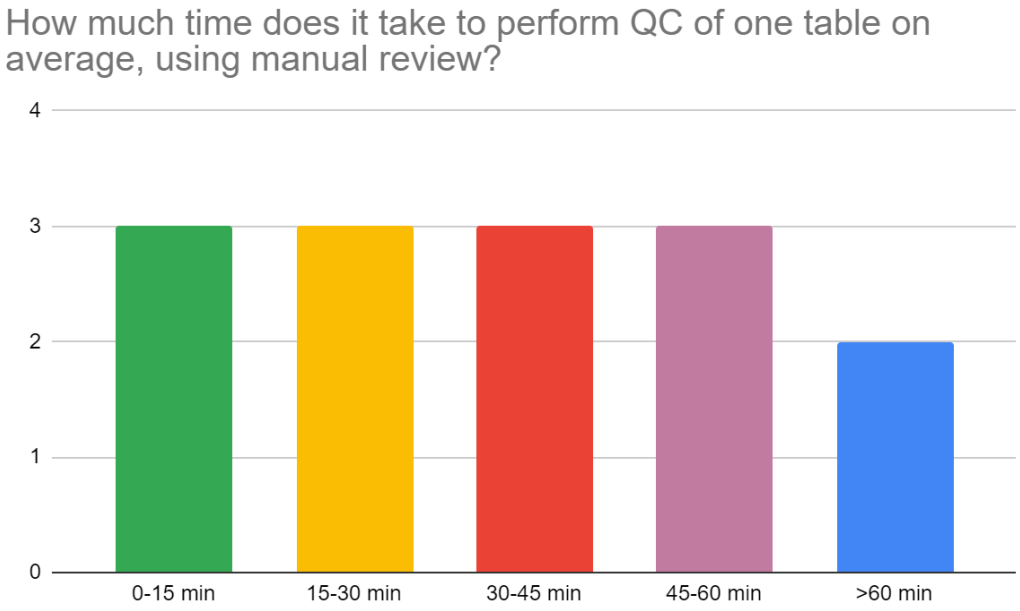

Figure 1: Distribution of responses from the industry survey (2022).

As a result of the manual process, discrepancies are not always found on time and even at times too late in the process. The industry survey also inquired about the sources of discrepancies found during the QC process. The 3 leading reasons for discrepancies in statistical analyses are:

1. Incorrect specifications
2. Data issues
3. Programming errors

Thus, an automated solution that can find discrepancies earlier in the process is crucial for the success of the submission.

THE SOLUTION

In cooperation with Pfizer's statistical programming team, Beaconcure developed Verify. Verify is an automated analytics platform driven by machine learning tools, created specifically to support the QC process of clinical data trials. Verify offers cross-table checks, in-table checks, specs checks, and date checks. It is an intuitive software that saves critical time, reduces human error, and improves quality, accelerating regulatory approval and time-to-market. Customers around the globe use Verify as part of their validation processes, in order to increase data quality and shorten time for submission. With the power of automation, the use of Verify has been expanded to all therapeutic areas and across the range of study phases (I, II, III).

AVAILABLE CHECKS

There are four categories of checks that are performed by Verify.

1. Cross-Table

Cross-table checks validate that numeric values representing the same data point are consistent throughout the study's outputs. An example of a discrepancy in a cross-table check is shown below, where the 'N=' in table headers are compared to a reference table containing the corresponding population and treatment group.

Table 14.1.1.31
Summary of Complete Healing Rate (%) for each population by Treatment (Randomized Population)

Randomized	Drug A (N=118)	Drug B (N=117)	Total (N=235)
	(%)	(%)	(%)
4 weeks ITT	46.7	35.0	40.9
8 weeks ITT	60.0	39.3	49.8
4 weeks (>=1 dose)	47.1	35.0	41.1
8 weeks (>=1 dose)	60.5	39.3	50.0
4 weeks per protocol	57.5	39.3	49.6
8 weeks per protocol	67.3	42.9	57.5

Subjects 001-005 did not receive any treatment and for the ITT analysis is counted as Worsening.
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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Table 1: Header cell is highlighted indicating a discrepancy in the 'N' value when compared to a reference table.

Table 14.1.1.2
Analysis Population

	Drug A	Drug B	Total
Randomized Population	120	117	237
Safety 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 2: Reference table with the cell reference highlighted, indicating a cross reference to the 'randomized population' and 'drug A'.

2. Within-Table

Within table checks validate numeric logics within tables. This includes the sum of numeric values, hierarchy check, etc. The table below shows an example of a discrepancy found in the sum of a mutually exclusive sub-group in the table.

Table 14.1.1.1
Subject Disposition by Site

	Randomized	Treated	Completed 4 weeks of treatment	Completed 8 weeks of treatment	Completed Study	Completed 4 weeks T
Site 001	25	24	24	23	20	1
Site 002	25	25	22	20	19	1
Site 003	24	24	22	22	21	1
Site 004	22	22	19	18	16	1
Site 005	0	0	0	0	0	
Site 006	18	18	14	13	11	
Site 007	25	25	22	20	17	1
Site 008	25	25	22	22	20	1
Site 009	24	23	20	20	18	1
Site 010	25	25	22	21	16	1
Site 011	25	25	22	21	17	1
Total	237	236	209	200	175	1

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Table 3: Example of a ‘within table’ check - discrepancy in a vertical summation is found.

3. Specs

In specs checks, the outputs of source tables are validated against specifications in the LoT and Mock Shell. An example of a discrepancy is shown below, where a difference was found in the titles between the output table and the Mock table.

ae_over_5_safety.rtf Mock shell

Table 14.1.1.16
Treatment Emergent Adverse Events 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)	Total (N=236)
Any TEAEs	61 (51.3%)	69 (59.0%)	130 (55.1%)
Gastrointestinal Disorders	39 (32.8%)	48 (41.0%)	87 (36.5%)
Diarrhoea	25 (21.0%)	35 (29.9%)	60 (25.4%)
Vomiting	20 (16.8%)	30 (25.6%)	50 (21.1%)
Infections & Infestations	10 (8.4%)	10 (8.5%)	20 (8.5%)
Respiratory, Thoracic and Mediastinal Disorders	11 (9.2%)	10 (8.5%)	21 (8.9%)
Cough	10 (8.4%)	8 (6.8%)	18 (7.6%)

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.
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Table 4: difference in the title between the output table and the mock table results in a discrepancy and is highlighted in Verify. The words ‘in study’ do not appear in the mock shell title.

VISUALIZATION

Today, the industry standard is to use an Excel spreadsheet for deliverables management. This may be effective in presenting data discrepancies as a figure, but it does not provide the context of each anomaly. Given the full context, the programmer would be able to understand the source of each discrepancy and eliminate it faster.

The visualization offered by Verify tackles the following challenges:

1. Project (clinical study) tracking
2. Discrepancy tracking
3. Concurrent work due to version misalignments

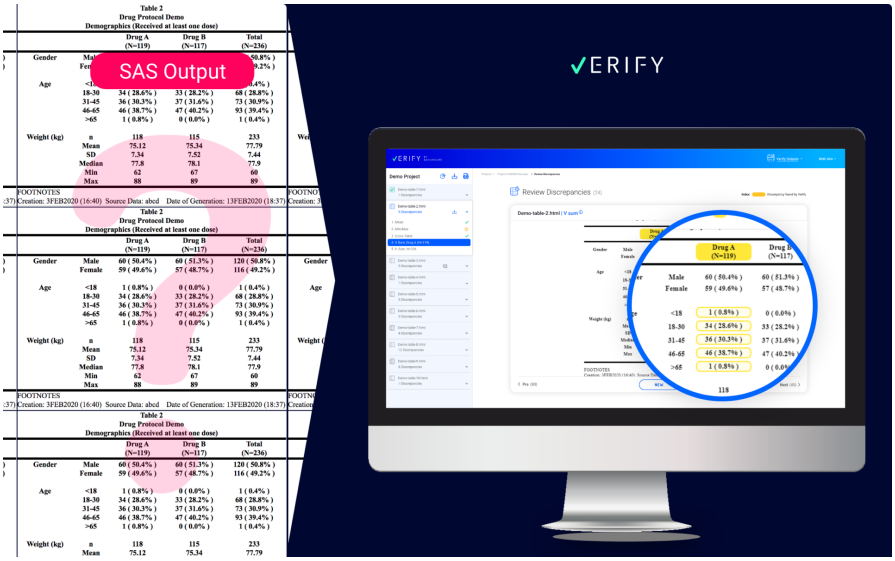

Figure 2: Verify's visualization of output tables.

CONCLUSION

To this day, Verify has processed more than 100 different studies. We can conclude that:

1. Supporting Programmers and Statisticians with automation de-risks the submission through increased quality.
2. Visualizing the discrepancies promotes team discussions within the platform.
3. Finding issues in content and format earlier in the process accelerates delivery.

CONTACT INFORMATION

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