Paper SD10

Analysis Studio: A Tool Framework for Supporting Regulatory Review

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Abstract

Regulatory reviewers in the Center for Drug Evaluation and Research (CDER) are responsible for determining the safety and efficacy of drug products before marketing in the United States. In the course of regulatory review, safety reviewers generate tables and visualizations for regulatory review documents. OCS Analysis Studio is a web-based application comprised of multiple interactive tools for the creation of tabular and graphical analyses ready to incorporate into these documents. Users are empowered to upload their own clinical trial data, customize the inputs according to their needs, and view the outputs, which change in real time according to user-provided criteria. A simple, intuitive, and consistent user interface across tools makes the regulatory review process more dynamic and decreases training time for safety reviewers. Outputs can be exported and saved as Word documents or JSON templates, allowing users to easily copy and paste analyses. The creation of OCS Analysis Studio enhances the efficiency and consistency of regulatory review.

The Need for Easily Crafted, Review-Ready Documents

During a review, clinical reviewers at the FDA are expected to complete numerous analyses. While many services and tools reduce this burden, it can sometimes be made difficult by outputs that are not easily transferred from tools to regulatory review documents. A reviewer can spend substantial time modifying, finalizing, and formatting the output they produce from the different clinical software available. In late 2018, after creating safety analyses for multiple reviewers during a yearlong Safety Support pilot, the Office of Computation Science (OCS) recognized this hardship and took steps to create tools that would solve it. The goals were the following:

1. The software should be intuitive to users and produce critical safety outputs relevant to FDA regulatory reviewers.
2. Output should be in an FDA acceptable format and be easily copied and pasted.
3. The backend code should use open-source technologies to minimize development time and allow for rapid updates to the tools.

The result was Analysis Studio.

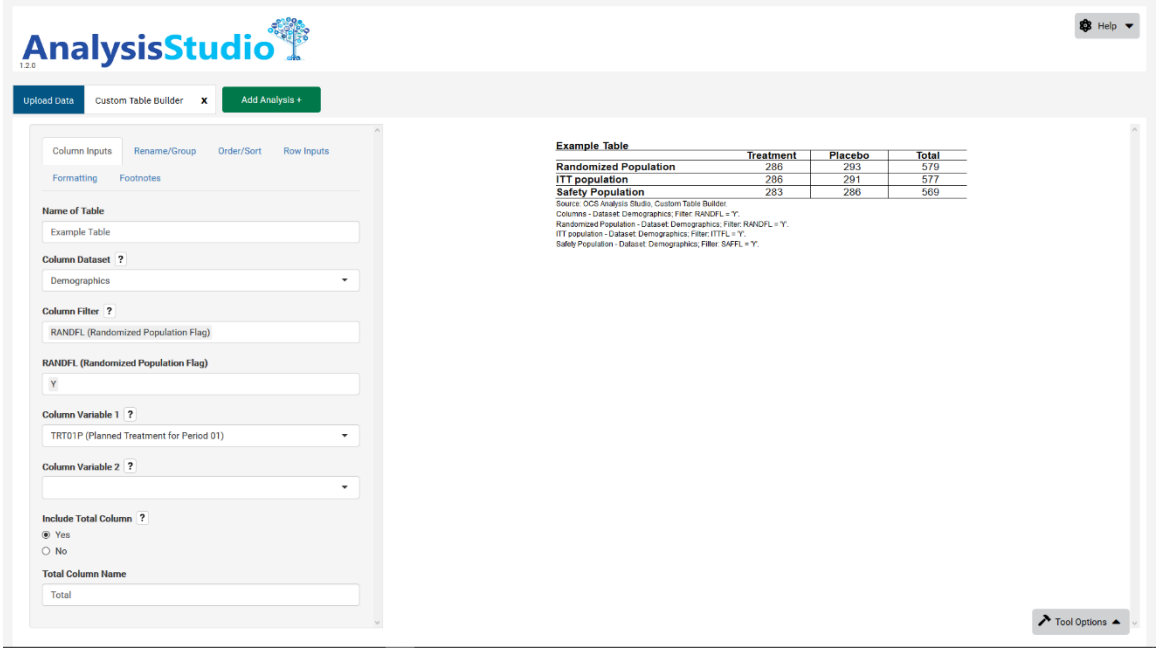
Analysis Studio, A Tool Framework

Analysis Studio is an open-source and web-based tool framework developed internally by OCS. It is a framework in which FDA-specific tools are placed and accessible to all regulatory reviewers. Analyses within this framework were created in collaboration with the OCS Standard Analysis Change Control Board to maximize impact and clinical relevance, while the outputs were designed in partnership with the OND Safety Working Group to ensure they meet standard formatting guidelines. Most significantly, finished and formatted outputs are easily downloaded from the tools and can be easily transferred to review documents. This simple functionality saves reviewers significant time which can then be re-focused on other important review-related activities.

The framework uses several open source technologies including R, R Shiny, JavaScript, and D3 for data visualization. These technologies allow Analysis Studio to remain up-to-date, flexible, cost-effective, and unburdened by the bulk of off-the-shelf solutions. However, the key benefit is speed. By keeping development in-house, the framework web-based, and by using open-source languages, complete tools can be created in weeks. Bug fixes and updates can be pushed in days rather than the months or years it might take to push updates to desktop-based proprietary software. The creation of a uniform user interface (UI) for all tools further reduced development timelines. In the past, new tools necessitated the creation of a bespoke user interface, a time-consuming process. With Analysis Studio, most of the interface already exists before the first line of new code is written. This results in tools being developed, tested and deployed much more quickly than in the “new tool, new UI” paradigm.

From a reviewer’s perspective, a uniform user interface has additional benefits. Training time for new tools is drastically reduced as prior users are already familiar with a layout that utilizes R Shiny’s dynamic input scheme. R Shiny allows developers to build interactive web applications that harness the power of the R programming language while also making them user-friendly and intuitive. For some previous tools, the user had to modify code, which is an error-prone process. For the tools in Analysis Studio, input dropdowns contain the variables of the uploaded data and are prepopulated with variables the tool thinks are relevant, such as population flags or treatment arm variables. When the user modifies inputs, the output changes instantly, which clarifies the relationship between variable inputs and the resulting analysis.

Figure 1. The Analysis Studio user interface.



For all tools, inputs appear on the left side of the screen and output appears on the right side of the screen. Users manipulate the inputs to build output in real time.

After an analysis has been created in Analysis Studio, users are offered two different ways to save their work. The first is to download their output into a Microsoft Word document. The functions used to display the output within Analysis Studio are also used to populate the report. To the user, analyses appear computationally identical and are formatted the same in both locations. The downloaded Word document can also be easily modified by the user. Most importantly, an entire table can be copied and pasted into another document. The current template used by reviewers to outline their review findings is also formatted as a Microsoft Word document which makes moving analyses between Analysis Studio downloads and the template very simple. For traceability purposes, included in the Word output is an audit trail. The audit trail contains information on the datasets, variables, and values used to create the output. An excerpt of an audit trail is provided below:

Table 1. Audit trail excerpt produced by Analysis Studio.

Parameters	Input
Column Dataset	Demographics
Column Filter Values: SAFFL	Y
Column Filter Values: STUDYID	STUDY123
Column Variable 1	STUDYID (Study Identifier)
Column Variable 2	ACTARM (Description of Actual Arm)
Column Variable 2 Order	Treatment 100 mg, Treatment 200 mg, Placebo
Demographic Dataset Unique Key	6d2469c74191c060b782d6

The second method by which Analysis Studio users can save their work is through JSON template files, which store parameters of an analysis. Much like the audit trail described above, this text file contains the variables and values used to build an output. This file can be loaded back into Analysis Studio to populate inputs and restore a previous analysis. This functionality meets two critical needs for reviewers at the FDA. First, it allows users to step away from their work, then come back at a later date and pick up where they left off. But JSON templates also allow for the creation of an analysis template which can be reused for different studies or

submissions (provided the data supports it). For example, if a review division has particular requirements for an analysis, a reviewer can build it to the exact specifications in Analysis Studio then share the template with their colleagues. The rest of the division can then use the template to create their own analyses using different data, but the analysis will be computed and formatted like the original. On a larger scale, this type of functionality encourages analysis standardization among reviewers and encourages review consistency.

Tools in Analysis Studio

The ***Kidney Function Tool*** creates a series of five tables commonly used for the evaluation of kidney function. The tables include a summary of baseline results and a comparison between baseline and a user-chosen endpoint for three labs of interest: creatinine, estimated glomerular filtration rate (eGFR), and albumin-to-creatinine ratio (ACR). Two shift tables are also created, one for eGFR and one for ACR (shown below).

Table 2. Shift table created by the Kidney Function Tool.

		Week 12 Renal Impairment		
Treatment Arm	**Baseline Renal Impairment**	**Normoalbuminuria**	**Microalbuminuria**	**Macroalbuminuria**
Placebo (N = 216)	Normoalbuminuria	195 (90.2%)	5 (2.3%)	0
	Microalbuminuria	1 (0.5%)	9 (4.2%)	0
	Macroalbuminuria	0	2 (0.9%)	4 (1.9%)
Treatment (N = 219)	Normoalbuminuria	159 (72.6%)	20 (9.1%)	5 (2.3%)
	Microalbuminuria	16 (7.3%)	8 (3.7%)	5 (2.3%)
	Macroalbuminuria	0	4 (1.8%)	2 (0.9%)

Subject Count: Subjects with both baseline (LBBLFL = "Y") and Week 12 (VISIT = "Week 12") lab results were included.
Normoalbuminuria: <=30 mg/g; Microalbuminuria: 30-300 mg/g; Macroalbuminuria: >=300 mg/g.

Whereas the Kidney Function Analysis was created for a specific review division, ***Custom Table Builder*** is a highly flexible and powerful tool for creating tables for a variety of purposes. Generally speaking, Custom Table Builder creates pivot tables, which summarize events to count distinct subjects, and are aligned with an OND Safety Working Group standard format. The tool is capable of various data transformations, such as generating a total column, grouping columns together, aggregating one variable's value by another, and sorting analyses to show the most frequently occurring events first.

Table 3. Treatment Emergent Adverse Event count table created by Custom Table Builder.

Example Table: TEAEs by Treatment and Sex (>= 5%)

	Treatment		Placebo	
	Female (N=106)	**Male (N=180)**	**Female (N=119)**	**Male (N=164)**
TEAEs by System Organ Class / Preferred Term				
General disorders and administration site conditions	29 (27.4)	30 (16.7)	24 (20.2)	27 (16.5)
Fatigue	13 (12.3)	5 (2.8)	4 (3.4)	5 (3.0)
Infusion site extravasation	5 (4.7)	9 (5.0)	1 (0.8)	11 (6.7)
Pyrexia	7 (6.6)	5 (2.8)	8 (6.7)	4 (2.4)
Gastrointestinal disorders	20 (18.9)	27 (15.0)	19 (16.0)	24 (14.6)
Nausea	13 (12.3)	16 (8.9)	6 (5.0)	11 (6.7)
Vomiting	7 (6.6)	7 (3.9)	10 (8.4)	5 (3.0)
Diarrhoea	3 (2.8)	2 (1.1)	5 (4.2)	9 (5.5)
Infections and infestations	17 (16.0)	27 (15.0)	18 (15.1)	17 (10.4)
Skin bacterial infection	5 (4.7)	10 (5.6)	6 (5.0)	3 (1.8)
Nervous system disorders	13 (12.3)	23 (12.8)	18 (15.1)	14 (8.5)

Example Table: TEAEs by Treatment and Sex (>= 5%)

	Treatment		Placebo	
	Female (N=106)	Male (N=180)	Female (N=119)	Male (N=164)
Headache	10 (9.4)	19 (10.6)	14 (11.8)	9 (5.5)

Source: OCS Analysis Studio, Custom Table Builder.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
TEAEs by System Organ Class / Preferred Term - Dataset: Adverse Events; Filter: TRTEMFL = 'Y'; Percent Threshold: 5%.

Similar to Custom Table Builder, the ***Listing Tool*** is a very flexible table-creating tool. The key distinction between these two is that Custom Table Builder summarizes by subject counts, whereas Listing Tool simply lists all the events of interest and different variables can be combined together. For example, the tool can be used to show certain adverse events, such as serious adverse events, and demographic information about those who experienced them.

Table 4. Serious Adverse Event table created by the Listing Tool.

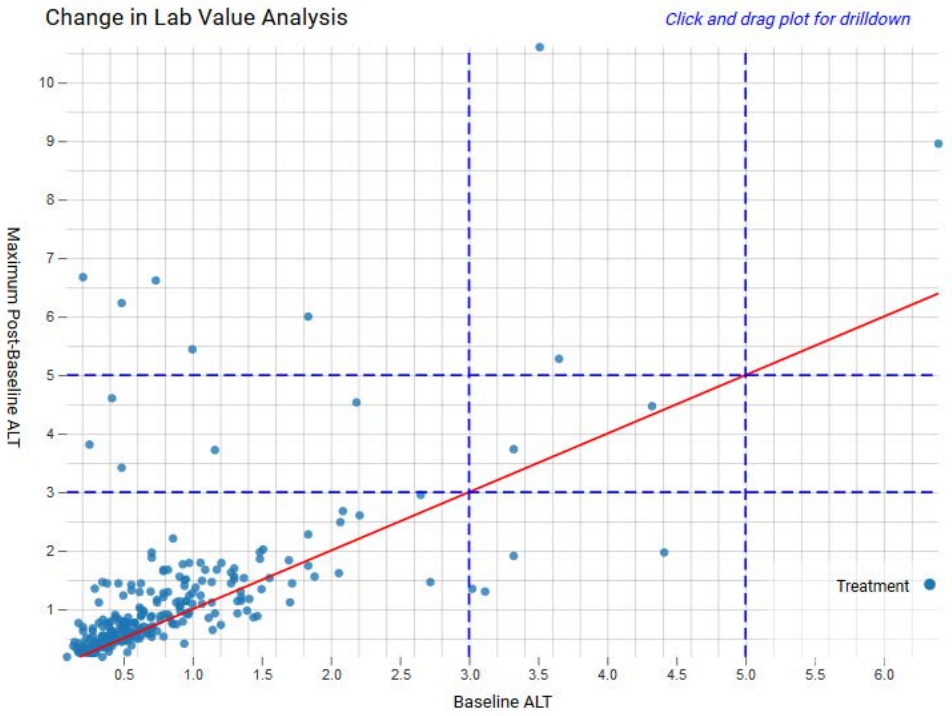
Example Table: Serious Adverse Events in Study ABC123

Subject	Treatment	Age / Sex / Race / Region	Serious Adverse Event	Outcome	Start Day / End Day
ABC123-00001	Treatment	42 / M / WHITE / US	Bursitis infective	RECOVERED	5 / 18
ABC123-00002	Placebo	52 / F / OTHER / Canada	Cellulitis	RECOVERED	8 / 11
			Cellulitis	NOT RECOVERED	34 / <NULL>
ABC123-00003	Treatment	62 / F / WHITE / Europe	Pneumonia	RECOVERING	24 / 39
			Cardio-respiratory arrest	FATAL	45 / 45
ABC123-00004	Placebo	68 / M / WHITE / US	Subcutaneous abscess	RECOVERED	2 / 7
ABC123-00005	Treatment	52 / F / WHITE / US	Cardiac arrest	FATAL	6 / 8
ABC123-00006	Placebo	28 / M / WHITE / US	Bacteraemia	<NULL>	3 / <NULL>

Source: OCS Analysis Studio, Listing Tool.
Subjects - Dataset: Demographics; Filter: SAFFL = 'Y'.
Events - Dataset: Adverse Events; Filter: AESER = 'Y'.

The final tool in Analysis Studio is the ***Shift Table Builder***. This tool compares two sets of lab data, such as baseline vs. post-baseline results for a single lab test, and visualizes the results in two different ways. First, the results are plotted, with one set of values on the x-axis and the other set of values on the y-axis. The points are colored according to treatment arm or another grouping variable chosen by the user. The plot is interactive; when points are selected, information about the subjects appears below the plot including their subject ID and lab results. The tool is flexible enough to use different labs for the x and y axes (such as in a Hy's Law plot) and has the ability to calculate and plot minimum and maximum values by subject.

Figure 2. Scatterplot of Maximum Post-Baseline ALT vs. Baseline ALT created by Shift Table Builder.



The Shift Table Builder also creates a shift table, which is a tabular representation of the graphical data (as depicted in Figure 2). Subject counts are calculated by treatment arm and broken down into different groups according to the cutoffs in the plot. By default, there are three groups of equal width and height based on the minimum and maximum values in each dimension. The number of groups and the cutoff values can be changed if desired. As with other tabular outputs, the footnotes will change in real time to reflect any changes in relevant input parameters.

Table 5. Shift table for ALT readings produced by Shift Table Builder.

		Maximum Post-Baseline ALT		
Grouping Variable	**Baseline ALT**	**Group 1**	**Group 2**	**Group 3**
Treatment (N = 273)	Group 1	254 (93.04%)	5 (1.83%)	5 (1.83%)
	Group 2	4 (1.47%)	2 (0.73%)	2 (0.73%)
	Group 3	0 (0%)	0 (0%)	1 (0.37%)

Source: OCS Analysis Studio, Shift Table Builder
X Cutoffs: Group 1 <= 3 ; 3 < Group 2 <= 5 ; 5 < Group 3
Y Cutoffs: Group 1 <= 3 ; 3 < Group 2 <= 5 ; 5 < Group 3

Conclusion

As of this writing (January 2020), OCS Analysis Studio contains four tools with two more in development. The current suite of tools is intuitive and interactive, thereby empowering reviewers to create critical analyses that can be placed directly into review documents. Analysis Studio's userbase at the FDA is growing and the future remains bright as the OCS JumpStart service has adopted the tool and requests for additional functionality are frequent from the review community. The open-source and easily modifiable nature of Analysis Studio facilitates the rapid incorporation of new reviewer-requested tools.

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