Paper DV07

Visualizing your protocol objectives

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ABSTRACT

With the increasing complexity of study designs and the use of composite endpoints, we often struggle to effectively communicate the objectives of their studies beyond a table of numerical results. To better visualize the most important outcomes of a study and show how they relate to individual endpoints, it is important to develop and utilize effective figures that can provide a clearer representation of the study's objectives. By doing so, researchers can better showcase the relevance and significance of their trial results to stakeholders. Effective use of visual aids can also help to improve the overall understanding of the study outcomes, making it easier for stakeholders to draw meaningful conclusions and make informed decisions based on the results.

INTRODUCTION

STUDY DESIGNS AND ENDPOINTS

STUDY DESIGNS

Healthcare sector is always in race to develop more efficient drugs. This demands more challenging clinical trial study designs. These designs help in bringing multiple parameters to the trial equation and evaluate all of them at once. The choice of a study design is driven by specific objectives and nature of intervention.

Complex study designs like adaptive trials bring higher precision and sensitivity to the study especially to a evaluate subtle effects. In case of targeted therapies, complex study designs with biomarker and genomics data help in understanding responses in multiple subpopulations. These designs now enable us to utilize more advanced statistical methodologies which were previously beyond the scope of traditional methods.

Let's look at few complex study designs,

Adaptive Clinical Trials represent a novel means of conducting medical research, constantly adjusting trial design according to accumulating results. They provide flexibility like the change in sample size, treatment allocation and even endpoints at an operational plan stage based on interim analysis. Adaptive trials attempt to improve efficiency, with potential cost savings, shorter trials, and a focus on patients by quickly finding effective treatments. Such trials lessen the chances of undertaking futile research because it enables making alterations where feasible. Nevertheless, these are associated with certain limitations, particularly concerning the issue of fake positives and clean data that necessitate sophisticated techniques for management. In basket trial, for example patients with different cancers but same genetic mutation or molecular alteration are pooled together into one basket. These similar genetic defects or molecular alterations despite different cancers can be evaluated together. These provide benefit of potential personalized medicine tailored to a genetic profile. Umbrella Trials, in contrast to basket trials have multiple therapies targeted to one clinical condition. Cluster randomized trials (CRTs) have randomized groups or clusters of subjects rather than individual subjects. These clusters can either be schools, hospitals, communities, or even entire regions. CRTs are preferred when it is not feasible to randomize subjects. Sequential Multiple Assignment Randomized Trial (SMART) trials are multistage trials, where a subject can be randomized at multiple stages based on the outcome of previous stages.

ENDPOINTS

Endpoints are measures used to evaluate the safety and efficacy of drugs, medical devices, surgical procedures, or behavioral therapies. They help us determine whether a treatment had a positive or meaningful impact on patient. Endpoints come in various types and complexities based on study designs. Very primitive one being binary endpoint, which is defined by categorical equivalent of yes or no. For example, alive vs dead, or responder vs non responder. These binary endpoints sometimes are derivatives are more complex, multiple endpoints. In survival studies we see another kind of endpoint which are time to event endpoints. These endpoints measure time taken for an event of interest to occur. If endpoints are continuously monitored over long period of time capturing trends, patterns there are termed as longitudinal endpoints. In When multiple outcomes are evaluated for an objective, these are considered as composite endpoints. In composite endpoints where a hierarchy is present like primary, secondary there are considered as hierarchical endpoints. In complex trials where benefit vs risk of a treatment is evaluated, they are termed as net clinical benefit endpoint. Apart from clinical endpoints, patients' subjective experiences like Pain,

HRQoL (Health-Related Quality of Life), symptom severity are accessed as Patient Reported Outcome (PRO). These types of endpoints help bridge the gap between clinical data and the patient's experience adding to patient centric treatment.

VISUAL AIDS

Graphical representation of data are power visual aids to present the clinical trial data and convey complex information to key stake holders. They distill enormous amount of data into simple representations which bring simplicity and clarity to the table. They are powerful storytelling tools compared to tables or listings. They are more vivid and allow us to add a narrative to the data. They facilitate comparative analysis allowing us to see differences or similarities between data points. They have more impact on the audience, enabling fast processing of large data, longer retention and more engaging. We can consider them as universal language. They also help us in predicting the outcome by pattern recognition or trends. Figures are highly effective when used appropriately. They might not be sometime as accurate as tables to represent that data, but a well-designed and labelled figure can bring on more insights of clinical trial data.

APPROACH

In further of this paper, we will be exploring various scenarios from sample protocols where complex endpoints are broken down to individual data points and simpler graphical elements. We will also see how these simpler elements when aligned, help us seeing the big picture of the trial.

SCENARIO 1

A sample study, where we want to evaluate efficacy of multiple combinations of treatments. We see that response rate of each arm is defined by response rate from a composite endpoint.

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the efficacy of each combination treatment arm	• Response rate for the composite endpoint (anemia improvement of ≥ 1.5 g/dL and no spleen volume progression and no symptom worsening) at the end of Cycle 6.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the proportion of subjects in each treatment arm who achieve an Hb improvement of ≥ 1.5 g/dL	• Proportion of subjects achieving improvement of Hb level of ≥ 1.5 g/dL from baseline
• To evaluate changes in symptoms in each treatment arm using patient reported outcomes (PROs)	• Change in PRO scores from baseline
• To evaluate the changes in spleen size in each treatment arm	• Change in spleen length from baseline. Change in spleen volume from baseline.

Figure 1: Image of table showing objectives and endpoints of a sample study.

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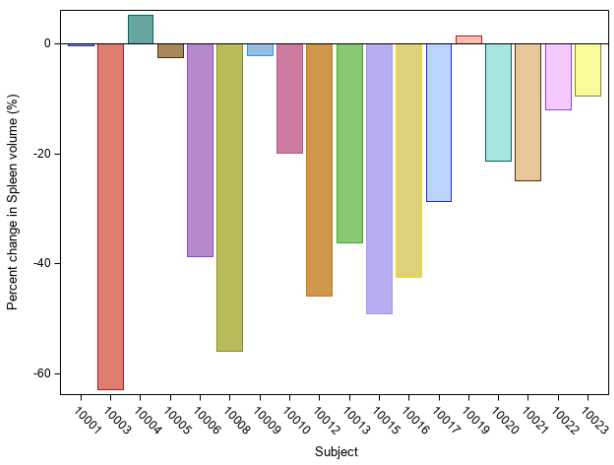
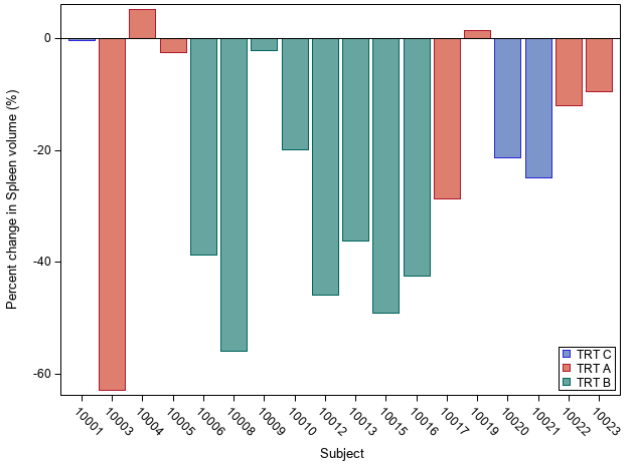
Let's begin with bring all the available data corresponding to endpoints to the table. Assuming all subjects had anemia improved irrespective of the i.e., and hence would not be add any value to the discussion. We see that spleen volume changes had variation and we would like to see the endpoint data with spleen volume, PRO scores in the picture.

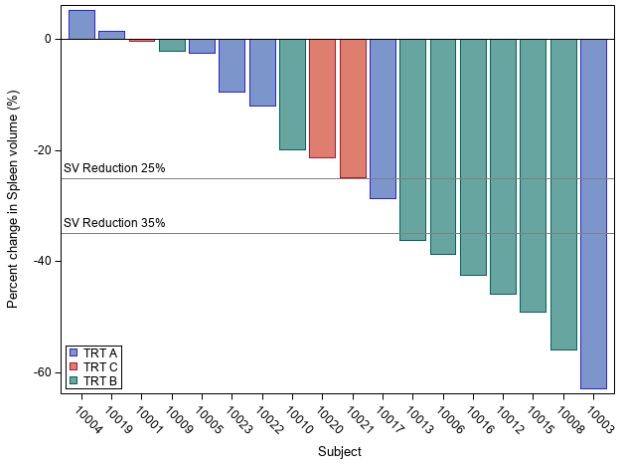
We need to explore a way to represent all this data in a figure. Firstly, let put all the data in a simple bar chart.

SUBJID	TRT01P	AVISIT	PARAM	PARAMCD	AVAL	BASE	CHG	PCHG
10001	TRT C	Cycle 7 Day 1	Spleen Volume(mL)	SPLVOL	3400	3410	-10	-0.293255132
10003	TRT A	Cycle 7 Day 1	Spleen Volume(mL)	SPLVOL	200	540	-340	-62.96296296
10004	TRT A	Cycle 7 Day 1	Spleen Volume(mL)	SPLVOL	200	190	10	5.263157895
10005	TRT A	Cycle 7 Day 1	Spleen Volume(mL)	SPLVOL	400	410	-10	-2.439024391
10006	TRT B	Cycle 7 Day 1	Spleen Volume(mL)	SPLVOL	1000	1630	-630	-38.65030675
10008	TRT B	Cycle 7 Day 1	Spleen Volume(mL)	SPLVOL	300	680	-380	-55.88235294
10009	TRT B	Cycle 7 Day 1	Spleen Volume(mL)	SPLVOL	1900	1940	-40	-2.061855567
10010	TRT B	Cycle 7 Day 1	Spleen Volume(mL)	SPLVOL	2100	2620	-520	-19.84732824
10012	TRT B	Cycle 7 Day 1	Spleen Volume(mL)	SPLVOL	3100	5720	-2620	-45.80419580
10013	TRT B	Cycle 7 Day 1	Spleen Volume(mL)	SPLVOL	1800	2820	-1020	-36.17021277
10015	TRT B	Cycle 7 Day 1	Spleen Volume(mL)	SPLVOL	300	590	-290	-49.15254237

Figure 2: Sample spleen volume data.







In figure 3, all the data is first represented as bar chart showing percent change in spleen volume at end of cycle 6. We see overall decrease in spleen volume in all subjects.

Later they are grouped by treatment. This brings insights of TRT B subjects having more decrease in spleen volume. Upon sorting that data by increasing negative percent change, see the first flavor of water fall chart.

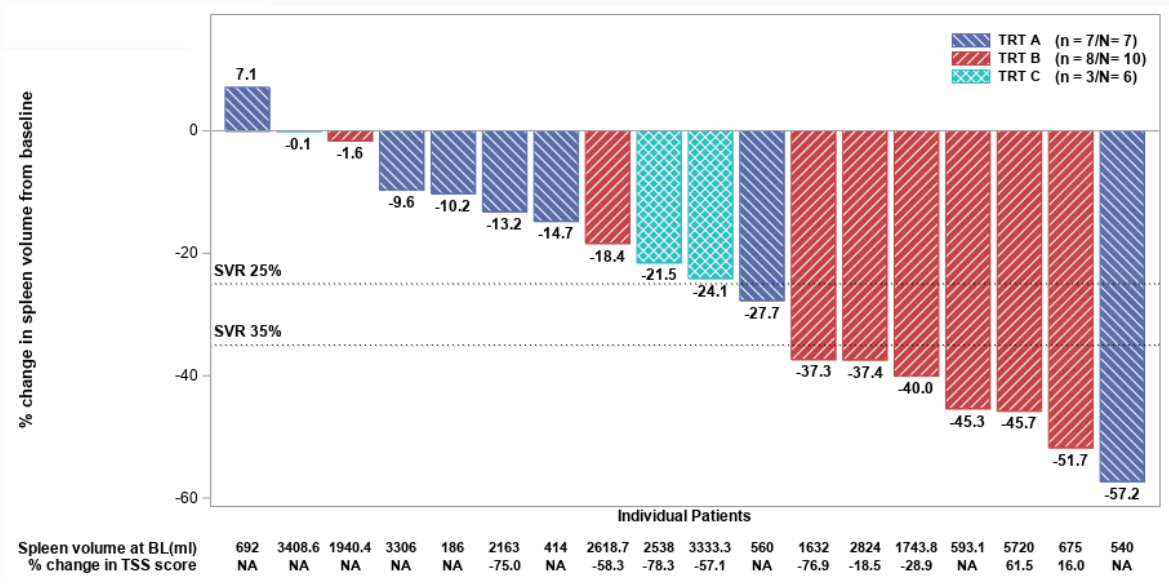


Figure 3: Figure construction flow from bar chart to waterfall plot

We can add multiple other data points and elements to the chart to bring more added value to the graph. Adding a reference line can help us see any specific ranges of interest say to show subjects having at least 25 % reduction in spleen volume. We can add legends with counts showing counts as n/N, to see the evaluable subjects. We can also add axis table to figure to bring correlation of PRO data of individual subjects. These answer the questions like are subjects seeing clinical benefit along with improve in symptoms?

SCENARIO 2

Another sample study, where we want to evaluate efficacy of single treatment by assessing multiple types of response at various time intervals. In this kind of study design, it is important to see a picture of patients journey throughout the journey.

Table 2-3 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
To measure the activity of treatment in patients with disease assessed by Overall Response Rate (ORR) at Day 28.	• Overall response rate (ORR) at Day 28, defined as the proportion of patients demonstrating a complete response (CR) or partial response (PR) without requirement for additional systemic therapies for an earlier progression, mixed response or non-response.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• **Key Secondary** To assess the rate of durable ORR at Day 56	• Proportion of all patients who achieve a CR or PR at Day 28 and maintain a CR or PR at Day 56
• To estimate ORR at Day 14	• Proportion of patients who achieved ORR (CR+PR) at Day 14
• To assess Duration of response	• Duration of response (DOR) is assessed for responders only and is defined as the time from first response until disease progression or the date of additional systemic therapies. Progression to chronic condition, or death without prior observation of progression are considered as competing risks

Figure 4: Image of table showing objectives and endpoints of a sample study.

In response-based studies, lot of data points are collected to draw a conclusion. We need to identify and review the data collected to better visualize the endpoint.

SUBJID	FACAT	FADTC	FADY
10001	PROGRESSION TO CHRONIC	2021-03-12	379

SUBJID	Dosage form	Date of Death
10001	Tab	.

SUBJID	New Systemic Therapy Date
10001	2020-08-05

SUBJID	Parameter	Parameter Code	orrd28fl
10001	Overall Response Rate at Day 28	ORRD28	Y

SUBJID	Parameter	Parameter Code	durd56fl
10001	Durable Overall Response Rate at Day 56	DURRD56	Y

For above example, we have data regarding disease progression, systemic therapy, dosage forms, response.

Such individual timepoints are identified and can be plotted against the study period to see the events on interest in a chronological order. Let put these as data points as a scatter plot.

Figure 5: Various data points related to out sample endpoints

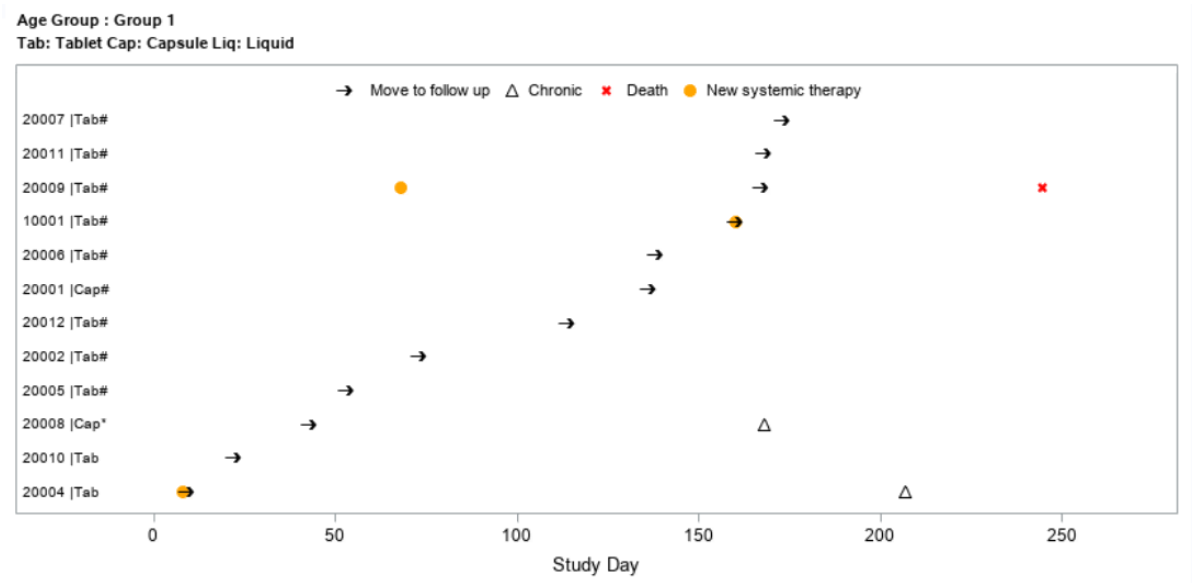


Figure 6: scatter plot of multiple datapoints on timeline scale

Derived datapoints are those which require some derivation prior to adding them to the figure. They could be simple derivation like summary statistics or little more complex like we have in below example.

SUBJID	VISIT	FADTC	FASTRESC	AVAL	FADY
10001	Week 1	2020-03-06	PROGRESSION	4	8
10001	Week 2	2020-03-13	PROGRESSION	4	15
10001	Week 3	2020-03-19	COMPLETE RESPONSE	1	21
10001	Week 4	2020-03-27	COMPLETE RESPONSE	1	29
10001	Week 5	2020-04-03	COMPLETE RESPONSE	1	36
10001	Week 6	2020-04-10	COMPLETE RESPONSE	1	43
10001	Week 7	2020-04-17	COMPLETE RESPONSE	1	50
10001	Week 8	2020-04-23	COMPLETE RESPONSE	1	56
10001	Week 12	2020-05-21	COMPLETE RESPONSE	1	84
10001	Week 16	2020-06-18	COMPLETE RESPONSE	1	112
10001	Week 20	2020-07-16	MIXED RESPONSE/NO RESPONSE	3	140
10001	EOT	2020-08-04	MIXED RESPONSE/NO RESPONSE	3	159

Data transformation

SUBJID	VISIT	FADTC	FASTRESC	AVAL	FADY	START	END
10001	Week 1	2020-03-06	PROGRESSION	4	8	8	20
10001	Week 3	2020-03-19	COMPLETE RESPONSE	1	21	21	139
10001	Week 20	2020-07-16	MIXED RESPONSE/NO RESPONSE	3	140	140	159

Data visualization

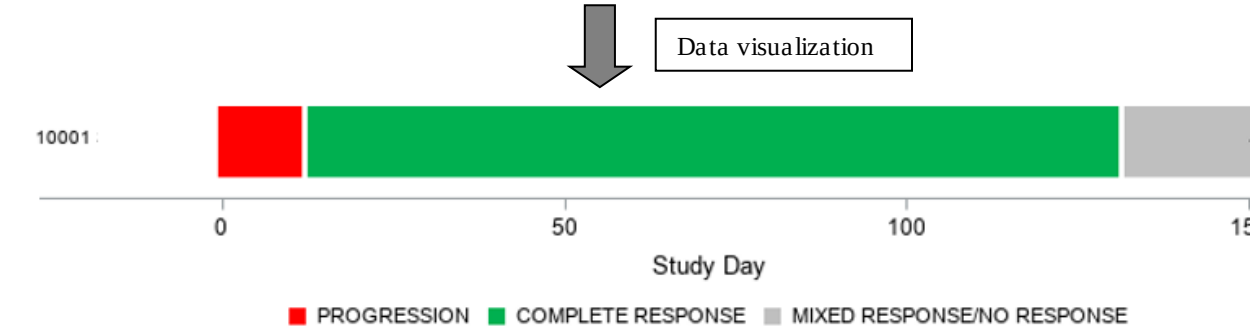


Figure 7: Data transformation for response data

In the above example, response information is collected at each visit. We convert this data into more concise form to better fit the graph and understanding. Similar continuous responses are combined to form on sequence. This data can be plotted against timeline to visualize the subject's progression in the study.

A new opportunity arises to combine the scatter plot and the high-low plot. This will help us bridge individual data points with the subject's state of response.

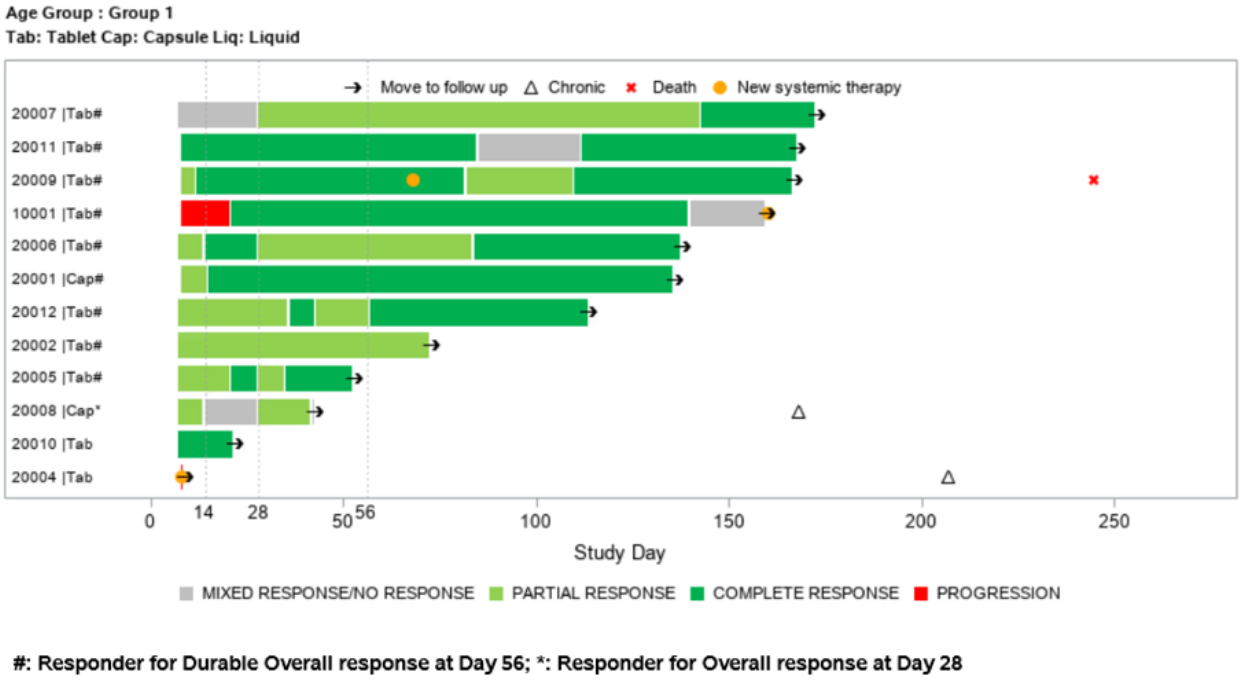


Figure 8: Swimmer plot showing over clinical response and associated endpoints.

This swimmer plot will now be able answer new set of questions like in what state was subject in during death, was additional therapy the cause for improvement in response or the study drug and so on.

CONCLUSION:

Visualizing your protocol would require deep understanding of the study design, rationale of each decision making. The ability to interrelate the objective with end point and understanding the available data plays a major role in visualizing your protocol. Putting together all data in one visual does not all meet the purpose instead can make it worse. We need to see that practicality, have active discussions with the stakeholders, understanding their need and asking right questions like need of visualization, what kind of value does it bring to the outcome? Always remember to enjoy the process of this discussion.

CONTACT INFORMATION

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