



Clinical Data Displays

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Disclaimer

- The views expressed are those of the speaker and do not necessarily reflect the policies and practices of the FDA.

Data Visualizations Usually Found in a Clinical Review

- Risk-Benefit Table
- List of Treatment Options
- Study flow chart
- Study Demographic Table
- AE and SAE Tables
- Shift Tables for Lab Values
- Graphical Displays as needed to convey clinical findings

⇒What considerations are used in selecting data displays in the clinical review process?

Principles of Data Display for Clinical Reviewers

- Data Display (tables, graphs & Charts) have two major roles for clinical reviewers:
 - Help organize the clinical data for analysis and guide decision-making about the benefit/risks considerations for the product(s) under review
 - Help explain the findings of the product evaluation in a succinct fashion in the clinical review document
 - Note: The data display used for the analysis of the clinical data and the final review document do not have to be the same

Principles of Data Display for Clinical Reviewers (cont.)

- Always use the simplest data display that is sufficient for data analysis and/or the clinical review document
- Every Table and Graph should stand on its own
- Complex data displays should only be used if they simplify the visualization for presentation or clinical review of multi-factorial data

Table vs. Graphical Display

- Lists versus Pattern Recognition
- Tables are best for comparing absolute number and frequencies (quantitative) while graphs are better at conveying patterns and structures (qualitative) that can illustrate trends.
- Graph type influenced by variable type, the number of subsets (& how they are defined) and the need for an error distribution

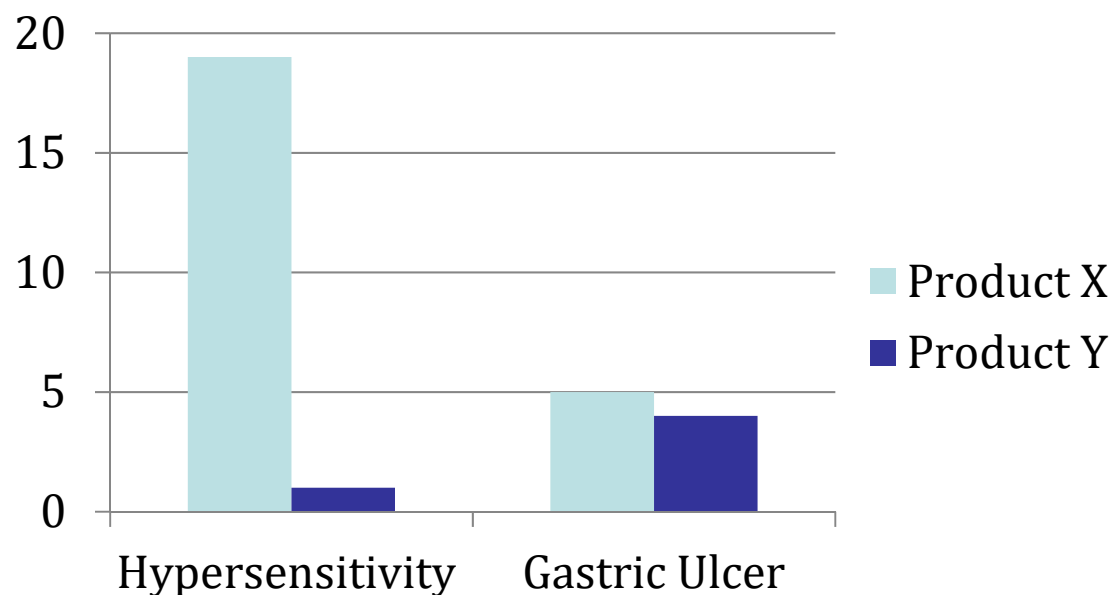
Do not need a graph to emphasize obvious points

TABLE

Events	Product X	Product Y
Hypersensitivity	19	1
Gastric Ulcers	5	4

VS.

GRAPH

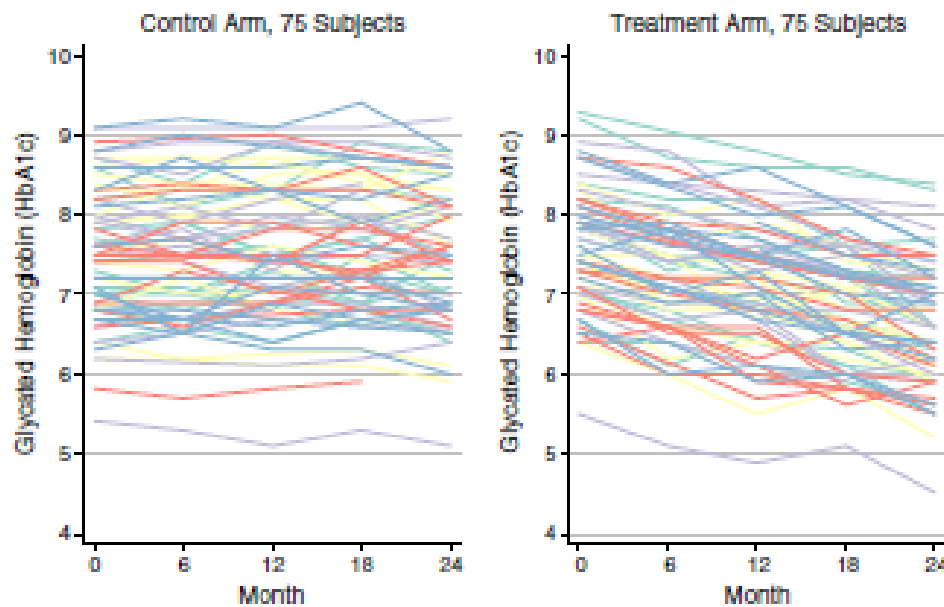


Examples of Complex Graphing Constructs That May Improve Communication

- Spaghetti Plots versus Lasagna Plots
- Napoleon's March Plots

Spaghetti vs. Lasagna Plot

- **Spaghetti Plots** are a collection of line graphs for multiple subjects:
 - Here is an example of 150 subjects in a randomized clinical trial looking at the treatment of diabetes using hemoglobin A1c as an endpoint¹



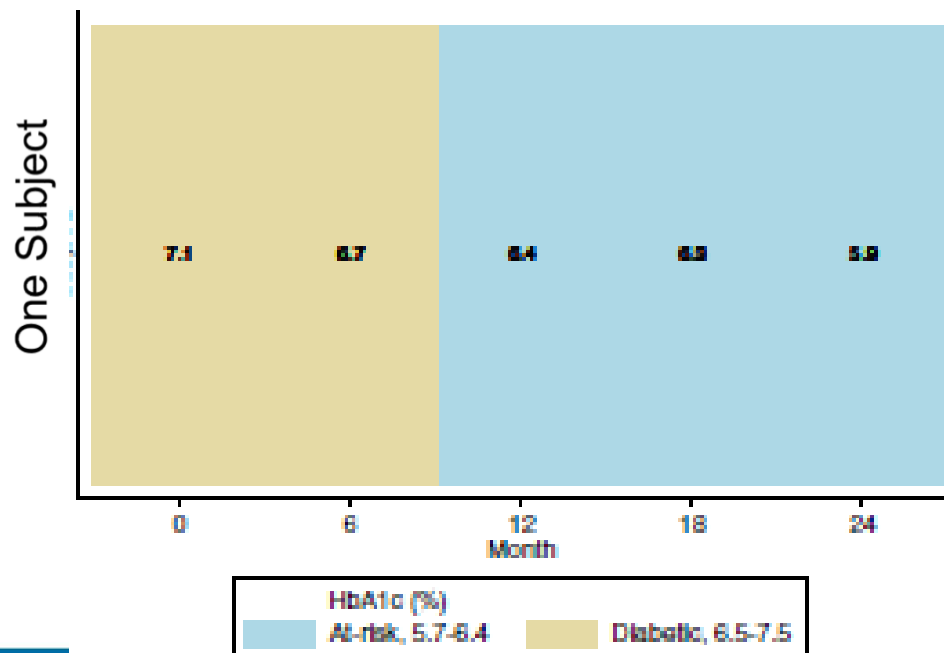
Note: Difficulty in comparing two arms

¹ Excerpted from Duke et al. Statistics in Medicine (2015): 34: 3040-3059

Spaghetti vs. Lasagna Plot (cont.)

- **Lasagna Plots** depict data for each individual subject over time as a row in a matrix plot data
 - Values are represented by gradations in color at each measurement interval
 - Diabetes example: subjects' HbA1c results are grouped into color groups Normal (dark blue), At-Risk (light blue), and various Diabetic ranges (beige to orange to red (most severe))¹

One Data Line Represented By Data Range Grouping

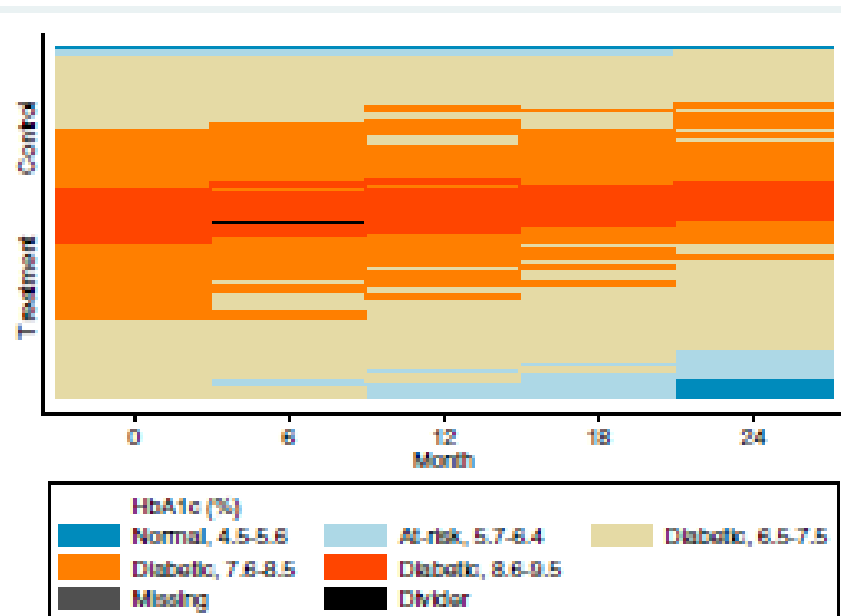
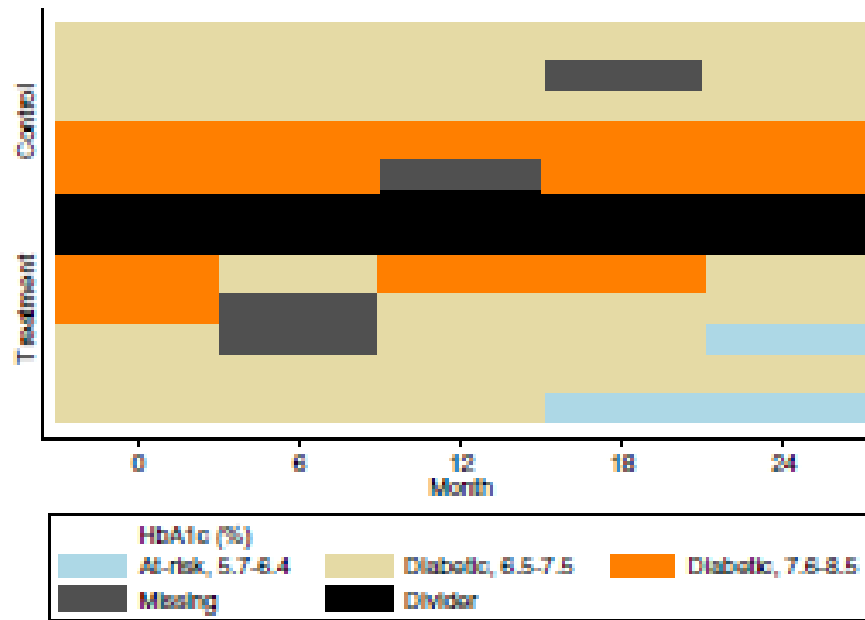


Example of glycated hemoglobin for a single subject (data simulated)

¹ Excerpted from Duke et al. Statistics in Medicine (2015): 34: 3040-3059

Spaghetti vs. Lasagna Plot (cont.)

Lasagna plot of glycated hemoglobin for 10 subjects (data are simulated)¹.



Lasagna plot of glycated hemoglobin for 150 subjects (data are simulated)¹.

¹ Excerpted from Duke et al. Statistics in Medicine (2015): 34: 3040-3059

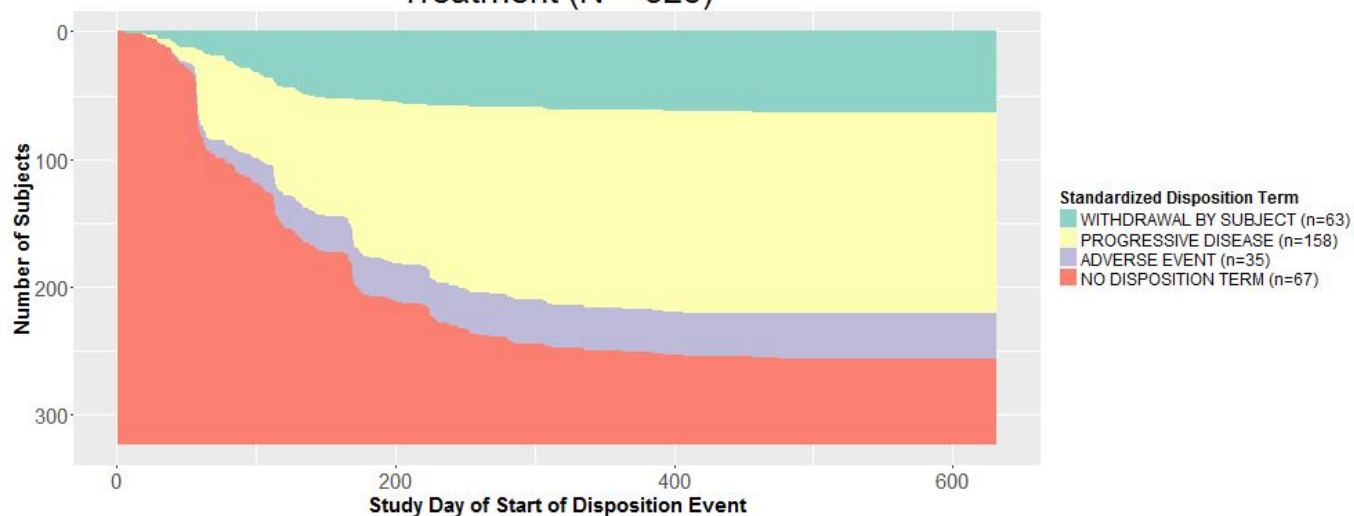
Limitations to Lasagna Plots

- Lasagna plots require readers to decode colors into numbers, which may not be the best way to encode numeric information in a statistical graph
- Many lasagna plots use some grouping of the underlying continuous data based on clinical interpretation (e.g., separating HbA1c into ranges as shown above)

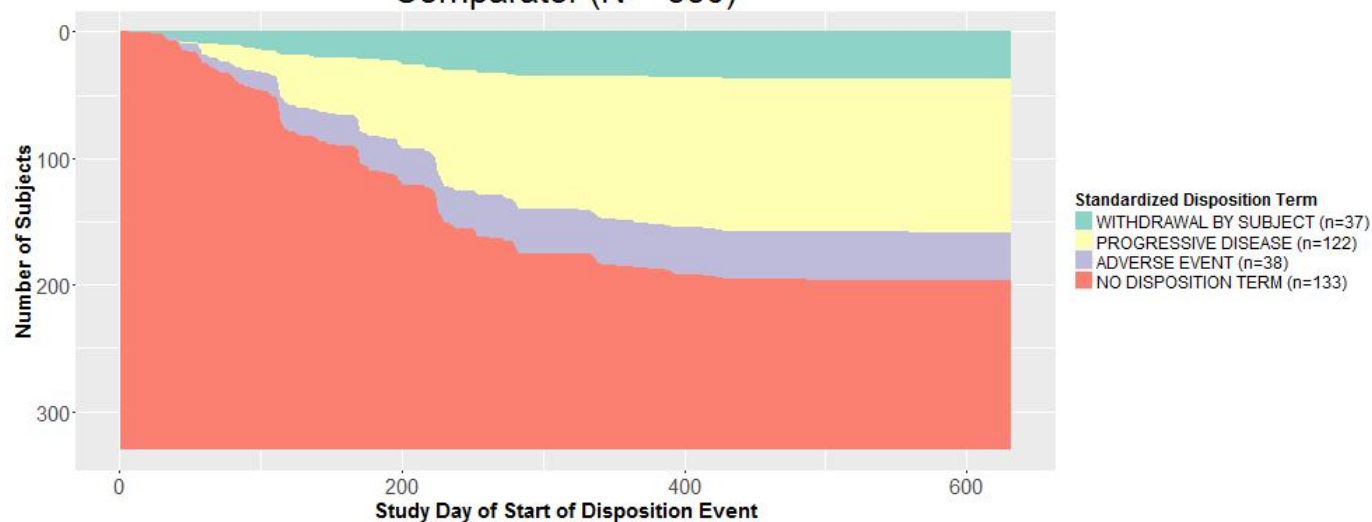
- Carte Figurative** des pertes successives en hommes de l'Armée Française dans la campagne de Russie 1812-1813.
Ouvrage par M. Minard, Inspecteur Général des Ponts et Chaussées en retraite. Paris, le 20 Novembre 1869
- Les nombres d'hommes restants sont représentés par les largeurs des zones colorées à raison d'un millimètre pour dix mille hommes; ils sont de plus écrits en lettres des zones. Le rouge désigne les hommes qui restent en Russie, le noir ceux qui en sortent. — Les renseignements qui ont servi à dresser la carte ont été puisés dans les ouvrages de M. M. Obiers, de Férolard, de Chambray et le journal inédit de Jacob, pharmacien de l'Armée depuis le 28 Octobre.
- Pour mieux faire juger à l'œil la diminution de l'armée, j'ai supposé que les corps de l'Armée Prussienne et du Maréchal Davout qui avaient été détachés sur Moscou et Mielow et un régiment de Cosaques et Wladiw, avaient toujours marché avec l'armée.
-
- TABLEAU GRAPHIQUE** de la température en degrés du thermomètre de Réaumur au dessous de zéro.
- Les Cosaques passent au gélif le Nilman, gélif.
- | Distance (L) | Température (°R) |
|--------------|------------------|
| 0 | -26° le 7 X. |
| 10 | -30° le 6 X. |
| 20 | -24° le 1er X. |
| 30 | -20° le 28 9. |
| 40 | -11° |
| 50 | -25° le 14 0. |
| 60 | -8° le 9 9. |
| 70 | -24° le 24 8. |
- Notes: 1 L. = 3.125 km. 1° R. = 0.5° C.

Example of Napoleon's March Data Display (cont.)

Treatment (N = 323)



Comparator (N = 330)



Example of Napoleon's March Data Display

- Cumulative Tabular Data for Treatment versus Comparator

Treatment (N= 323)

DSDECOD (Reason for Discontinuation)	Cumulative Number of Subjects Discontinuing Study					
	WEEK 1	WEEK 30	WEEK 60	WEEK 90	WEEK 105	After WEEK 105
ADVERSE EVENT	0	108	133	133	133	133
LACK OF EFFICACY	0	58	62	62	62	62
WITHDRAWAL BY SUBJECT	0	6	6	8	8	8

Comparator (N=330)

DSDECOD (Reason for Discontinuation)	Cumulative Number of Subjects Discontinuing Study					
	WEEK 1	WEEK 30	WEEK 60	WEEK 90	WEEK 105	After WEEK 105
ADVERSE EVENT	0	49	84	85	85	85
LACK OF EFFICACY	0	35	49	50	50	50
WITHDRAWAL BY SUBJECT	0	6	8	8	8	8

Conclusion

- Data visualizations that facilitate the analysis of clinical data and communication of data are preferred
 - Keep simple as possible
 - Uncluttered
 - Allow for the identification of trends or patterns
 - Accurately reflect the variability of the data
- Complex Data Displays can be used to analyze data in the following situations:
 - When multiple variables are not easily analyzable with simpler displays
 - Review of multiple displays required to convey the same findings



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Visualization of Nonclinical SEND data

Elaine Thompson, Ph.D.

PhUSE SDE

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SEND Data

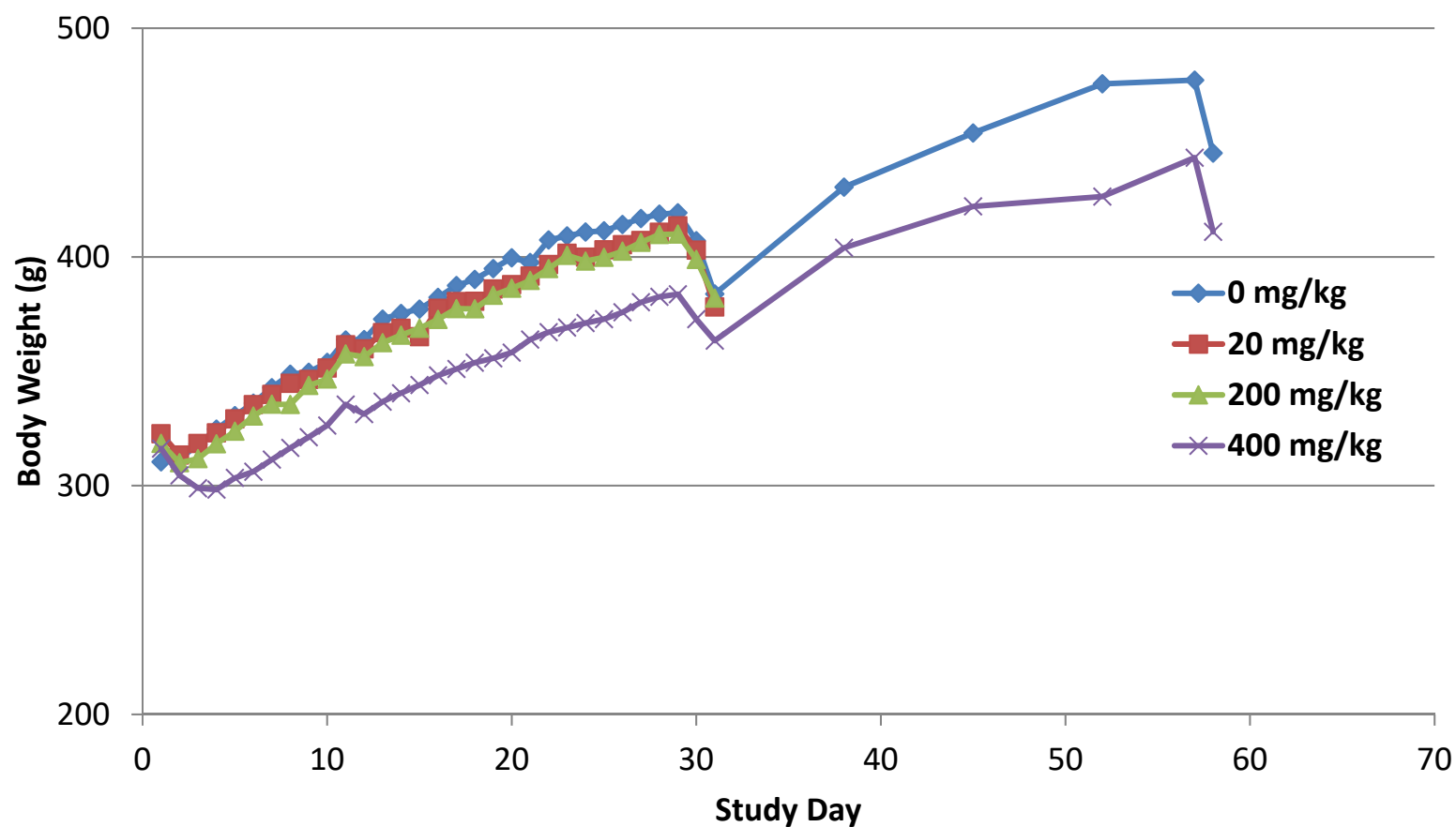
- Electronic submission format allows the automated generation of graphs and tables
- SEND encompasses both quantitative measurements and qualitative observations
- Sample sizes are typically small
- Classic graphs illustrate trends in time series data
- Histopathology and Clinical Observations require different approaches than measured numeric data

Simplest: Summary Statistics

Test		Male				Female			
		0 mg/kg	20 mg/kg	200 mg/kg	400 mg/kg	0 mg/kg	20 mg/kg	200 mg/kg	400 mg/kg
Terminal Body Weight in g	MEAN	422.2	389.9	374.3	366.9	239.9	223.3	201	181.1
	SD	±40.1	±36.0	±20.6	±18.3	±20.2	±15.8	±12.8	±27.9
	N	5	5	5	5	5	5	5	5

- Single time point
- Table allows straight-forward comparison of means
- Sample sizes are present to aid interpretation of standard deviations

Time Series for Visualization of Trends



Clinical Observations Tabular Summary Display

Sign	Day Interval	Male				Female			
		0 mg/kg	20 mg/kg	200 mg/kg	400 mg/kg	0 mg/kg	20 mg/kg	200 mg/kg	400 mg/kg
No Abnormalities	-1-58	1058/15	655/10	665/10	1146/15	1153/15	655/10	665/10	1168/15
Skin Abnormal	1-31	75/5							
Cataract	-1-56	6/3			11/4				2/1
Corneal Opacification	-1-56	6/3			3/1				5/2
Haircoat Abnormal	27-31	5/1							
Persistent Hyaloid Artery	-1-28	2/1			2/1				
Preretinal Bleeding	-1-56	4/3							
Persistent Pupillary Membrane	-1-56	3/1							
Retinal Hyperreflectivity	-1-56	3/1							
Vitreous Hemorrhage	-1-28					2/1			
Ocular Discharge	-1--1	1/1							

- “Day Interval” indicates the range of study days on which the sign was observed
- The display shows #observations / #animals
- Frequent observations appear at the top of the list

Histopathology Heat Map

Finding	Severity	Males			
		0 mg/kg	20 mg/kg	200 mg/kg	400 mg/kg
LIVER					
	#Examined	15	10	10	15
MPS-aggregates multifocal	MILD	10 (66.7%)	4 (40.0%)	6 (60.0%)	5 (33.3%)
	MODERATE	1 (6.67%)	1 (10.0%)	1 (10.0%)	1 (6.67%)
Necrosis	MILD				
	MODERATE				3 (20.0%)
Vacuolization	MILD				
Vacuolization hepatocellular	MODERATE				
GLAND, ADRENAL					
	#Examined	15	10	10	15
Hemorrhage	MILD			1 (10.0%)	1 (6.67%)
Hypertrophy	MILD	1 (6.67%)	1 (10.0%)		
Vacuolization	MILD	1 (6.67%)	2 (20.0%)	7 (70.0%)	12 (80.0%)

Heat map color coding orients the reviewer to the most frequent findings

Conclusions

- Use the simplest appropriate visualization
- Tables summarize data for accurate comparisons
- Graphs are good for visualizing trends in time series data like body weight, or food consumption
- Qualitative data like clinical observations can be viewed in summary tables
- Hybrid tabular/heat map views are more complex but orient the reviewer to the most frequent findings