



More than matching: A statistician's approach to output review

Dr Erika Daly

Director Biostatistics, ICON

Presentations are intended for educational purposes only and do not replace independent professional judgment. Statements of fact and opinions expressed are those of the presenter individually and are not the opinion or position of ICON. ICON does not endorse or approve, and assumes no responsibility for, the content, accuracy or completeness of the information presented.

- Errors detected during Statistical Review
- How to prevent them
- Client Reaction
- Summary

Errors detected during Statistical Review



- **Statistical Review**
 - A review of the entire package for consistency and plausibility of results, to ensure the statistical integrity of the package
- **Consistency Checks**
 - Agreement in the various counts within a table and between tables
- **Plausibility Checks**
 - Appropriateness of the values obtained for derivations, particularly from statistical models

Example 1

Table 14.1.2
Subject Disposition
Safety Population

	Treatment XYZ (N=9)
Completed Study	8 (88.9%)
Discontinued	0 (0.0%)
Primary Reason for Discontinuation of Study Drug	
Unacceptable treatment efficacy	0 (0.0%)
Unacceptable adverse event(s)	1 (11.1%)
Exclusion criteria emerging during the study	0 (0.0%)
Voluntary (and no other reason)	0 (0.0%)
Lost to follow-up	0 (0.0%)
Death	0 (0.0%)
Other	0 (0.0%)

Example 2

Table 14.2.3.2
Analysis of Change from Baseline in Fasting Plasma Glucose (mmol/L) Measurements - LOCF
ITT Population

	Trt A (N=77)	Trt B (N=78)
Change from Baseline to End of Treatment		
n	82	85
LS Mean	-0.91	0.36
SE	0.24	0.24
P-value for comparing with Trt B	<0.001	
LS Mean difference (a)	-1.26	
95% CI for difference with Trt B	(-1.92, -0.60)	

(a) LS Mean difference=LS Mean change of Trt A - LS Mean change of Trt B.

Example 3

Table 14.1.2.8.4
Number of Subjects with Inadequate Response to, Intolerant, or Contraindicated to
Protocol Specified Systemic Treatment for Psoriasis
Full Analysis Set

	Trt A (N=329)	Trt B (N=330)	Trt C (N=335)	Trt D (N=107)	Total (N=1454)
Number of Subjects - n (%)					
Number of Subjects with Inadequate Response, Intolerant, or Contraindicated to Protocol Specified Systemic Therapies					
0	85 (25.8)	96 (29.1)	80 (23.9)	29 (27.1)	643 (44.2)
1	136 (41.3)	126 (38.2)	154 (46.0)	41 (38.3)	457 (31.4)
2	62 (18.8)	71 (21.5)	66 (19.7)	22 (20.6)	221 (15.2)
3	35 (10.6)	29 (8.8)	27 (8.1)	14 (13.1)	105 (7.2)
<3	283 (86.0)	293 (88.8)	300 (89.6)	92 (86.0)	1321 (90.9)
>=3	46 (14.0)	37 (11.2)	35 (10.4)	15 (14.0)	133 (9.1)

Example 4

Table 14.6.2
Analysis of Successful Global Response at EOT
MITT Population

	Group A (N=9)	Group B (N=8)	Overall (N=17)
Global response			
Number of successes	8	5	13
Number of failures	0	1	1
Number of indeterminates	1	2	3
Number of missing	0	0	0
Success Rate (%)	88.9	62.5	59.1
Exact 95% confidence interval (%)	(51.75, 99.72)	(24.49, 91.48)	(50.10, 93.19)

Example 5

Table xxx

	Treatment A (N=94)	Treatment B (N=88)
N	91	85
L.S. Mean	0.480	0.403
S.E.	0.0853	0.0885
L.S. Mean Difference from Treatment A		0.077

(Unacceptable) Responses to Stat Review findings

- “That’s what’s in the dataset”
- “It’s as per SAP and/or ADS specs”
- “No one else raised this before”

Proactive Prevention during Programming



- **Within-table checks**
 - All scheduled visits (where appropriate) are presented in each table.
 - Treatment differences are consistent with treatment values.
- **Between-table checks**
 - Number of subjects in each table agrees with numbers in analysis population table.
 - Number of subjects in each subgroup table agrees with numbers in demography table (or other source of subgroup split), and sum to total.
 - Number of subjects in each subset table (e.g., SAEs) agrees with numbers in master table.
 - Direction of treatment effect is clear and consistent across tables.

- **General**
 - Number of subjects in table is supported by datasets.
 - Randomization codes have been correctly assigned
 - Appropriate ratios of randomization/stratification are maintained in the study
- **Continuous Data**
 - Ranges are sensible and consistent with protocol (check for outliers).
 - Mean and median values are consistent with data range.
 - SD consistent with range (approximately $[\text{range} \div 4]$).
- **Categorical Data**
 - Category numbers are consistent with totals.
 - The denominator for percentages is clear and they sum to 100%.

- **Statistical Inference**

- Pattern of results is consistent with the indication and data
- Direction of treatment effect is clear and consistent across tables
- Treatment differences are consistent with treatment values
- Direction of treatment difference/ratio is consistent with effect values for each individual treatment
- CIs contain the observed value of the statistic they surround, and are consistent with the magnitude of the associated p-values
- 1-sided p-values agree with the direction of the treatment effect
- Model checking and assumptions testing do not indicate any issues with the model or the interpretation

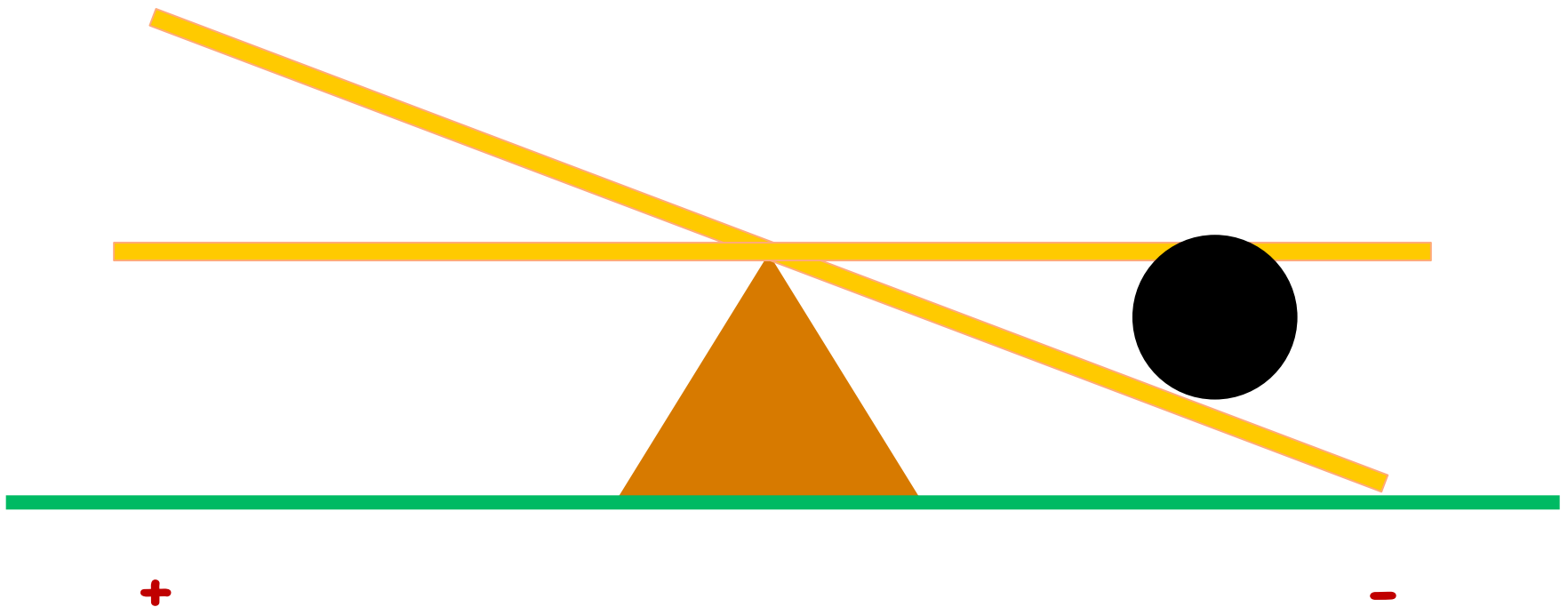
Client Reactions



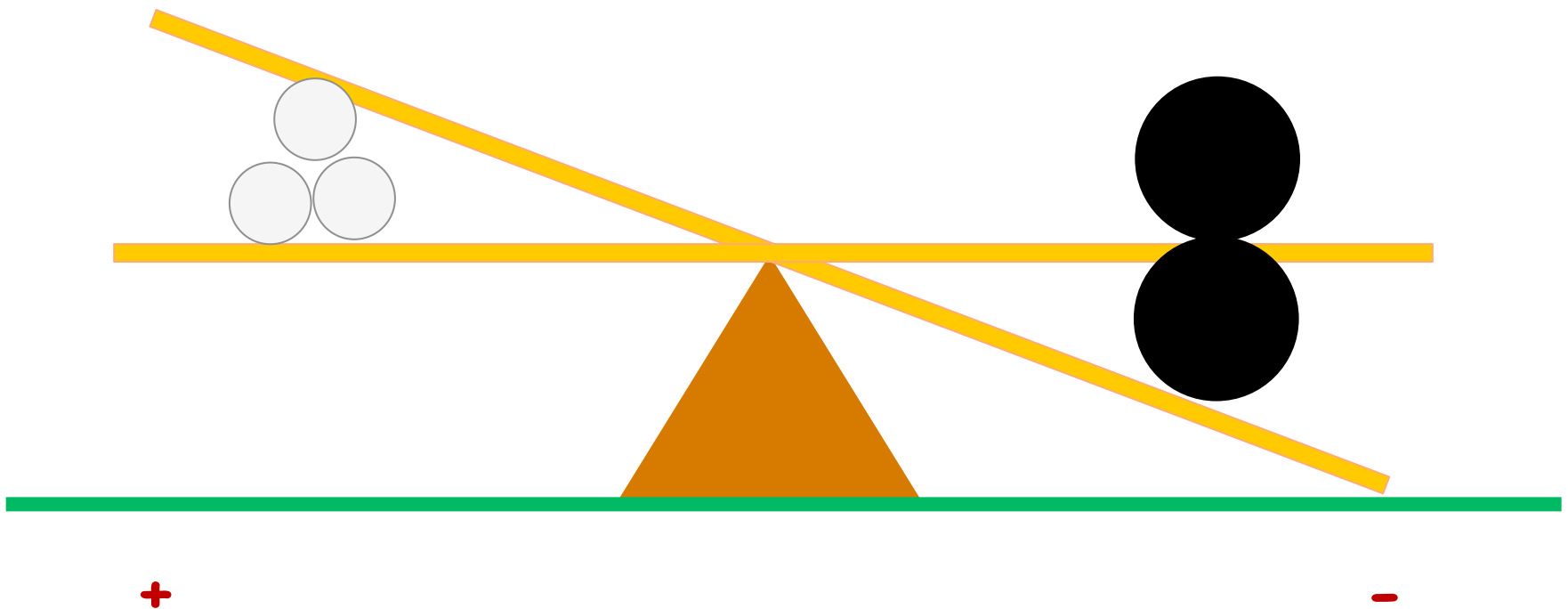
Who is the client?

- External
 - Sponsor
- Internal
 - Project Manager / Lead Statistician
 - Medical Reviewer
 - Medical Writing

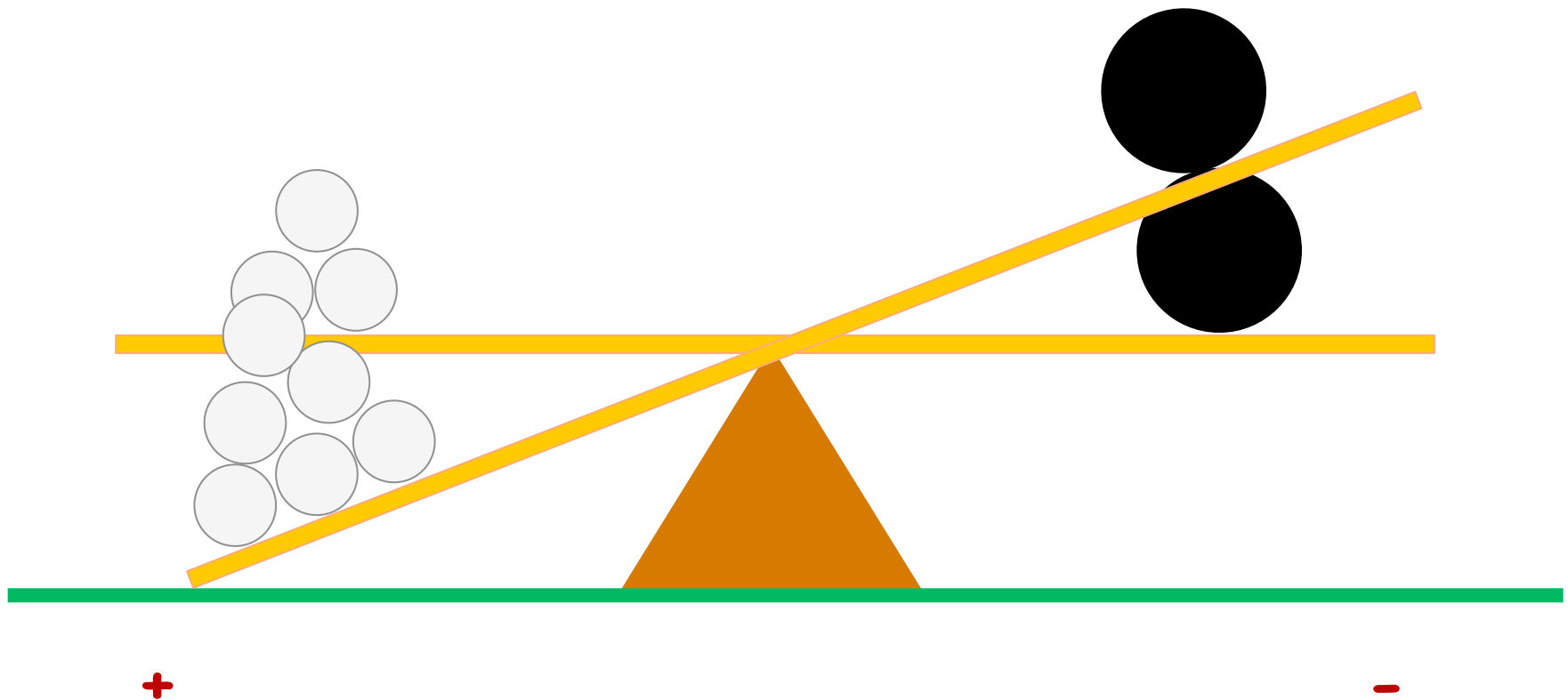
Client Perception



Client Perception



Client Perception



Only as good as your last delivery

- Many repeated “small” errors can be just as damaging as one major error
- When client confidence is eroded
 - New business not awarded
 - Existing business withdrawn
- Projects supported by India may be kept by Onshore teams

Summary



- Take the time to become familiar with the data to be reported
- Don't just assume the programming code will work – you must look at the output too
- Errors occur from source data through to reporting in TFLs
 - Data completion
 - Data entry
 - Mapping
 - Documentation (e.g., SAP, ADaM specs)
 - Derivation
 - SAS 'default' values
- Revert back to source data and work through to output
 - If necessary obtain copies of actual subject CRF pages

No one is perfect

- Trust no one
- Question everything

