Reporting Cumulative Proportion of Subjects with an Adverse Event Based on Data from Multiple Studies

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Reference

- Chuang-Stein C, Beltangady M. (2011) "Reporting cumulative proportion of subjects with an adverse event based on data from multiple studies", *Pharmaceutical Statistics,* 10(1):3-7.

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Outline

- Motivating example of a cumulative proportion from multiple studies
- Simpson's Paradox
- Two examples of product package insert (label)
- Approaches for reporting cumulative proportions
- Observations
- Summary

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Clinical Summary of Safety

Study	Drug A	# of Pts	Drug B	# of Pts
1	8%		4%	
2	7%		6%	
3	1%		1%	
4	1%		2%	
5	21%		20%	
6	8%		10%	
Total Avg	13%	1000	9.5%	750

13% vs 9.5%: a two-sided P-value of 0.023 for testing equal proportions.

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Clinical Summary of Safety

Study	Drug A	# of Pts	Drug B	# of Pts
1	8%	100	4%	100
2	7%	100	6%	100
3	1%	100	1%	100
4	1%	100	2%	100
5	21%	500	20%	250
6	8%	100	10%	100
Total Avg	13%	1000	9.5%	750

95% CI for the diff (A – B) using inverse variance weighting is (-0.017, 0.018) with a point estimate of 0.001. ***What happens?***

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Clinical Summary of Safety

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5	21%	500	20%	250
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Total Avg	13%	1000	9.5%	750

The study with the highest AE rates had twice as many subjects on Drug A as on Drug B.

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Simpson's Paradox

Treatment	Study I		Study 2	
	Event	No Event	Event	No Event
New	180 (60%)	120 (40%)	60 (30%)	140 (70%)
Control	60 (60%)	40 (40%)	60 (30%)	140 (70%)
Total	New: 300 Control: 100		New: 200 Control: 200	

- Within each study, the two groups have the same event rates.
- Study 1 randomized patients 1:1:1:1 to 3 doses and 1 control.
- Study 2 randomized patients 1:1 to one dose and control.

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Results Pooled over Studies

Treatment	Event	No Event	Combined
New	240 (48%)	260 (52%)	500
Control	120 (40%)	180 (60%)	300

- Pooling produces an event rate of 48% for the new treatment and 40% for the control.
- The chi-square statistic has a two-sided P- value = 0.028. Conducting un-stratified (un-adjusted) analysis in this case leads to an erroneous conclusion.

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Results from Multiple Studies

- A stratified analysis is necessary to yield proper comparative statistics and appropriate p-value.
- ***But, how should we report the proportions?***
- Package inserts are used to inform public about the safety of approved medicines. In the first example, do we report 13% for Drug A and 9.5% for Drug B?

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Table 1 – Celebrex US Label (Jan 2011)

	CBX N=4146	Placebo N=1864	NAP N=1366	DCF N=387	IBU N=345
Gastrointestinal					
Abdominal Pain	4.1%	2.8%	7.7%	9.0%	9.0%
Diarrhea	5.6%	3.8%	5.3%	9.3%	5.8%
Dyspepsia	8.8%	6.2%	12.2%	10.9%	12.8%
Flatulence	2.2%	1.0%	3.6%	4.1%	3.5%
Nausea	3.5%	4.2%	6.0%	3.4%	6.7%
Body as a whole					
….					
….					

Table 1 lists all adverse events, regardless of causality, occurring in ≥ 2% of patients receiving CELEBREX in 12 controlled RA or OA studies that included a placebo and/or a positive control group.

CBX: Celebrex 100-200 mg BID or 200 mg QD; NAP: Naproxen 500 mg BID; DCF: Diclofenac 75 mg BID; IBU: ibuprofen 800 mg TID

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Table 2 – Cymbalta US Label (Sept 2011)

	Cymbalta (N=6020)	Placebo (N=3962)
Nausea	24	8
Headache	14	13
Dry mouth	13	5
Fatigue	10	5
Somnolence	10	3
Insomnia	10	6
Dizziness	10	5
Constipation	10	4
Diarrhea	9	6
Decreased appetite	8	2
Hyperhidrosis	7	2

Table 2 gives incidence (%) of TE adverse reactions in placebo-controlled trials for approved indications that occurred in 5% or more of patients treated with duloxetine and with an incidence greater than placebo.

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Test an Overall Treatment Effect

- Let d_j represent the risk difference in the jth study. A common approach is to form a weighted average and construct a test statistic for the overall effect as

$$\hat{d} = \frac{\sum_j w_j \hat{d}_j}{\sum_j w_j}$$

$$X^2 = \frac{\hat{d}^2}{\mathrm{var}(\hat{d})}$$

X^2 has an asymptotic chi-square distribution with 1 degree of freedom if $\Sigma_j w_j d_j = 0$.

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Choice of Weight – Inverse Variance

- Inverse variance – $\{w_j\}$ is equal to the inverse of the sample variance of $\hat{d}_j$. In this case, X^2 will be

$$X^2 = \frac{\left(\sum_j w_j \hat{d}_j\right)^2}{\sum_j w_j}$$

When $d_j = d$ (the risk difference is uniform across the strata), the inverse variance weighting produces the minimum variance estimate for the common risk difference d, which is unbiased for large samples. This method is favored by meta analysts.

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Choice of Weights – CMH

- CMH method – n_{ij} is the sample size for treatment i in study j, a "+" means summation over that subscript. $\{w_i\}$ is equal to the inverse of the harmonic mean of n_{1j} and n_{2j}. This method produces the X^2 test by Cochran, which is asymptotically equivalent to the MH test.

$$X_C^2 = \left(\sum_j \bar{p}_j(1-\bar{p}_j)\frac{n_{1j}\,n_{2j}}{n_{+j}}\right)^{-1}\left(\sum_j \frac{n_{1j}\,n_{2j}}{n_{+j}}\hat{d}_j\right)^2$$

$$X_{MH}^2 = \left(\sum_j \bar{p}_j(1-\bar{p}_j)\frac{n_{1j}\,n_{2j}}{n_{+j}-1}\right)^{-1}\left(\sum_j \frac{n_{1j}\,n_{2j}}{n_{+j}}\hat{d}_j\right)^2$$

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Reporting Cumulative Proportions

- Let p_{ij} be the observed proportion for the *ith* treatment in the *jth* study. Intuitively, one might consider

$$p_{i(adj)}^{(IV)} = \left(\sum_j \text{var}(\hat{d}_j)^{-1}\right)^{-1}\left(\sum_j \text{var}(\hat{d}_j)^{-1} p_{ij}\right)$$

$$p_{i(adj)}^{(CMH)} = \left(\sum_j \frac{n_{1j}n_{2j}}{n_{+j}}\right)^{-1}\left(\sum_j \frac{n_{1j}n_{2j}}{n_{+j}} p_{ij}\right)$$

$$p_{i(aadj)}^{(SS)} = \sum_j \left(\frac{n_{+j}}{n_{++}}\right) p_{ij}$$

SS: Study Size Approach

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Weights under Three Options

	Study	IV	CMH	SS
	1	0.07	0.12	0.114
	2	0.07	0.12	0.114
→	3	**0.43**	0.12	0.114
	4	0.29	0.12	0.114
→	5	0.09	**0.40**	**0.430**
	6	0.05	0.12	0.114
Adjusted proportion	New	4.1%	11.4%	11.9%
	Control	4.0%	10.8%	11.2%

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Observations

- For the same design, IV approach gives the largest weight to the study with a proportion furthest from 50%.
- We do not recommend IV weighting for deriving adjusted cumulative proportions.
- We consider both CMH and SS approaches reasonable.
- The CMH approach has the advantage that the difference between the adjusted cumulative proportions is the point estimate for the risk difference under the CMH approach.
- The SS approach provides standardized proportions, using $\{n_{+j}/n_{++}\}$ to reflect the composition of the population.

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CMH vs SS Approach (3 Scenarios)

Sample Size (New, Con)		Observed Proportion (New) Three Scenarios		
(100, 100)		5%	10%	15%
(200, 100)		10%	15%	5%
(300, 100)		15%	5%	10%
CMH	Adj Prop (Std Dev)	10.7% (1.2%)	9.8% (1.3%)	9.6% (1.3%)
SS	Adj Prop (Std Dev)	11.1% (1.3%)	9.4% (1.2%)	9.4% (1.2%)

One approach does not always produce a lower adjusted proportion.

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Summary

- We should apply a meta analytical approach when generating P-values and confidence intervals for the chosen risk measure in the clinical summary of safety.
- Adjusted cumulative proportions are not necessarily less than the proportions from naïvely pooled data.
- If all studies use 1:1 randomization, CMH- and SS-adjusted proportions will be similar to the naively pooled proportions.
- When different doses were used for different populations, displaying doses side-by-side could be misleading because dose and population are confounded.
- Adjusted proportions have not been part of label discussions, but should be.

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