Case Study: Meta-Analysis of Rare Adverse Events

Problem

Occasionally a rare adverse event (AE) is encountered during or post development. As part of the investigation into the risk of the AE with treatment, oftentimes the data from all randomised controlled trials are combined in a meta-analysis. In a similar vein, FDA guidance on the development of anti-diabetic drugs requires the meta-analysis of CV events across controlled trials as a prerequisite of regulatory approval providing the observed risk of such events is acceptable low. A principal difficulty with the meta-analysis of rare events is trials often have just a handful of events with many having only one or even no events. Established methods to estimate relative risk can perform poorly in such situations and exclude trials with zero events. Bayesian meta-analysis provides an alternative approach that includes all trials, even those with zero events.

The meta-analysis of rare AEs is illustrated and a critical regulatory application highlighted.

Rare Adverse Events

Table 1 displays data on CV rare events in 12 placebo controlled randomised trials. The number of events and exposure to randomised treatment (in patient years) are provided together with events rates by treatment and the relative risk, drug:placebo.

Of the 12 trials, 3 have no events and 4 just one event. Of the remaining 5 trials, one has no events on placebo leaving just 4 trials with events on both drug an placebo. Consequently, event rates are not calculable in a number of trials and the relative risk is estimable in only 4 trials. The Mantel-Haenszel (MH) approach was used to combine data across trials since this approach includes all trials with at least one event. The overall RR and 95% CI was estimated to be 0.92 (0.44, 1.92).

In contrast, Table 2 displays the same data but now with a Bayesian analysis. Now (with a *non-informative* prior), event rates can be estimated for drug and placebo in every trial, together with a RR estimate and 95% credibility interval. The overall Bayesian RR and credibility interval was estimated to be 0.94 (0.48, 1.81).

Table 1. CV Rare Adverse Events: Conventional Approach

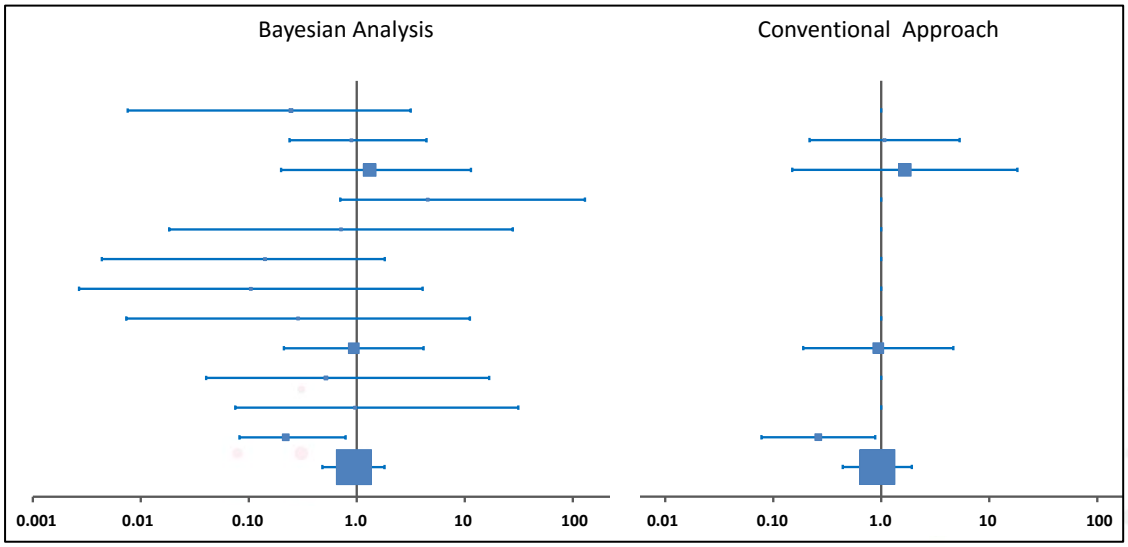
	Events		Exposure pt-years		Event rates				Relative Risk	
Study	Drug	placebo	Drug	placebo	Drug	95% CL	placebo	95% CL	RR	95% CL
1	0	1	59.5	35.3	0.0	(,)	28.3	(4.0 , 201.1)		(,)
2	6	2	100.9	36.1	59.5	(26.7 , 132.4)	55.4	(13.9 , 221.5)	1.07	(0.22 , 5.32)
3	2	1	31.1	25.7	64.3	(16.1 , 257.1)	38.9	(5.5 , 276.2)	1.65	(0.15 , 18.23)
4	7	0	118.1	48.6	59.3	(28.3 , 124.3)	0.0	(,)		(,)
5	0	0	102.8	73.4	0.0	(,)	0.0	(,)		(,)
6	0	1	53.0	18.1	0.0	(,)	55.2	(7.8 , 392.2)		(,)
7	0	0	47.8	5.0	0.0	(,)	0.0	(,)		(,)
8	0	0	121.3	34.7	0.0	(,)	0.0	(,)		(,)
9	3	3	128.9	120.9	23.3	(7.5 , 72.2)	24.8	(8.0 , 76.9)	0.94	(0.19 , 4.65)
10	1	0	90.9	19.5	11.0	(1.5 , 78.1)	0.0	(,)		(,)
11	1	0	52.4	20.9	19.1	(2.7 , 135.5)	0.0	(,)		(,)
12	20	3	948.6	37.2	21.1	(13.6 , 32.7)	80.6	(26.0 , 250.1)	0.26	(0.08 , 0.88)
Total	40	11	1855.3	475.4					0.92	(0.44 , 1.92)

Overall relative risk estimated by the MH approach

Table 2. CV Rare Adverse Events: Bayesian Approach

Events		Exposure pt-years		Event rates				Bayes Relative Risk	
Drug	placebo	Drug	placebo	Bayes rate	95% CI	Bayes rate	95% CI	RR	95% CI
0	1	59.5	35.3	11.6	(0.43 , 62.0)	47.5	(6.86 , 157.8)	0.25	(0.008 , 3.16)
6	2	100.9	36.1	66.1	(27.89 , 129.4)	74.1	(17.14 , 200.1)	0.89	(0.238 , 4.42)
2	1	31.1	25.7	86.0	(19.89 , 232.3)	65.3	(9.42 , 216.8)	1.32	(0.199 , 11.40)
7	0	118.1	48.6	64.9	(29.24 , 122.1)	14.3	(0.52 , 75.9)	4.55	(0.702 , 129.83)
0	0	102.8	73.4	6.7	(0.25 , 35.9)	9.4	(0.34 , 50.3)	0.71	(0.018 , 27.85)
0	1	53.0	18.1	13.1	(0.48 , 69.6)	92.7	(13.38 , 307.8)	0.14	(0.004 , 1.82)
0	0	47.8	5.0	14.5	(0.53 , 77.2)	138.6	(5.06 , 737.8)	0.10	(0.003 , 4.08)
0	0	121.3	34.7	5.7	(0.21 , 30.4)	20.0	(0.73 , 106.3)	0.29	(0.007 , 11.16)
3	3	128.9	120.9	28.5	(8.46 , 68.0)	30.4	(9.01 , 72.5)	0.94	(0.212 , 4.16)
1	0	90.9	19.5	18.5	(2.66 , 61.3)	35.5	(1.30 , 189.2)	0.52	(0.040 , 16.84)
1	0	52.4	20.9	32.0	(4.62 , 106.3)	33.2	(1.21 , 176.5)	0.96	(0.075 , 31.31)
20	3	948.6	37.2	21.8	(13.70 , 32.6)	98.7	(29.30 , 235.7)	0.22	(0.082 , 0.79)
40	11	1855.3	475.4					0.94	(0.480 , 1.81)

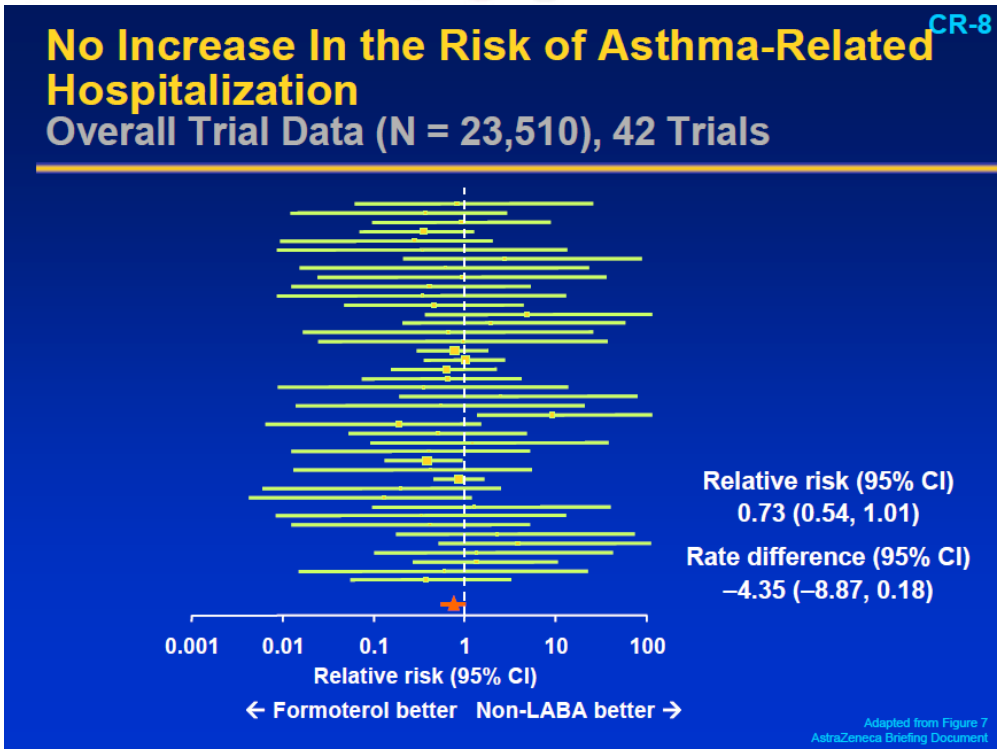
Figure 1. Display of Data: Bayesian vs Conventional Approaches



As a variation of the Bayesian approach, an informative prior for the underlying event rate on placebo can be introduced. This is equivalent to a random effects meta-analysis where there is a common relative risk across trials but a variable placebo effect between trials. When this is done, the Bayesian RR and credibility interval is estimated to be 0.98 (0.58, 1.65).

Figure 1 displays the data for each approach side by side. It is clear that the Bayesian analysis provides a more complete picture of the trial data though it should be noted that the use of 'exact' methodology would provide at least a lower confidence limit for trials that have no events on one arm.
Figure 2 displays a rare events meta-analysis that was submitted to FDA and displayed in a subsequent Pulmonary-Allergy Drugs Advisory Committee (PADAC, March 2008).

Figure 2. Meta-Analysis of Rare Asthma Related Events, PADAC March 2008



Evaluation

Conventional approaches to the meta-analysis of rare events and estimation of relative can mean that event rates in all trials are difficult to estimate and trials with no events are excluded. As an alternative, a Bayesian approach (with non-informative prior) provides an event rate estimates in all trials and includes all trials in the overall analysis to estimate the relative risk.

References:

1. Breslow NE, Day NE. The Design and Analysis of Cohort Studies. 1987, IARC Scientific Publications No. 82 Lyon, France, page 110.
2. Robins J, Breslow N, Greenland S. Estimators of the Mantel-Haenszel variance consistent in both sparse data and large-strata limiting models. 1986, Biometrics 42:311-323.
3. StatXact: Cyrus Mehta and Nitin Patel: StatXact 5®, Statistical software for exact nonparametric inference. User manual vols 1 and 2, CYTEL Software Corporation, Cambridge, MA 02139. 2001. Chapter 13, page 444.
4. Barker L and Cadwell BL. An analysis of eight 95 per cent confidence intervals for a ratio of Poisson parameters when events are rare. Statist. Med. 2008; 27:4030–4037.
5. Cai et al. Meta-analysis for rare events. 2010, Stat in Med. 29:2078-2089
6. FDA Pulmonary-Allergy Drugs Advisory Committee, joint meeting with Drug Safety, Risk Management Advisory Committee and the Pediatric Advisory Committee, December 10 and 11, 2008. http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4398s1-00-index.htm

KJC Statistics Ltd
Sovereign House
Bramhall Village
Cheshire
SK7 1AW
UK
Email: kevin.carroll@kjcstatistics.com
Phone: +44 (0) 161 478 4949
Mobile: +44 (0) 7578 324 824