Statistical Considerations

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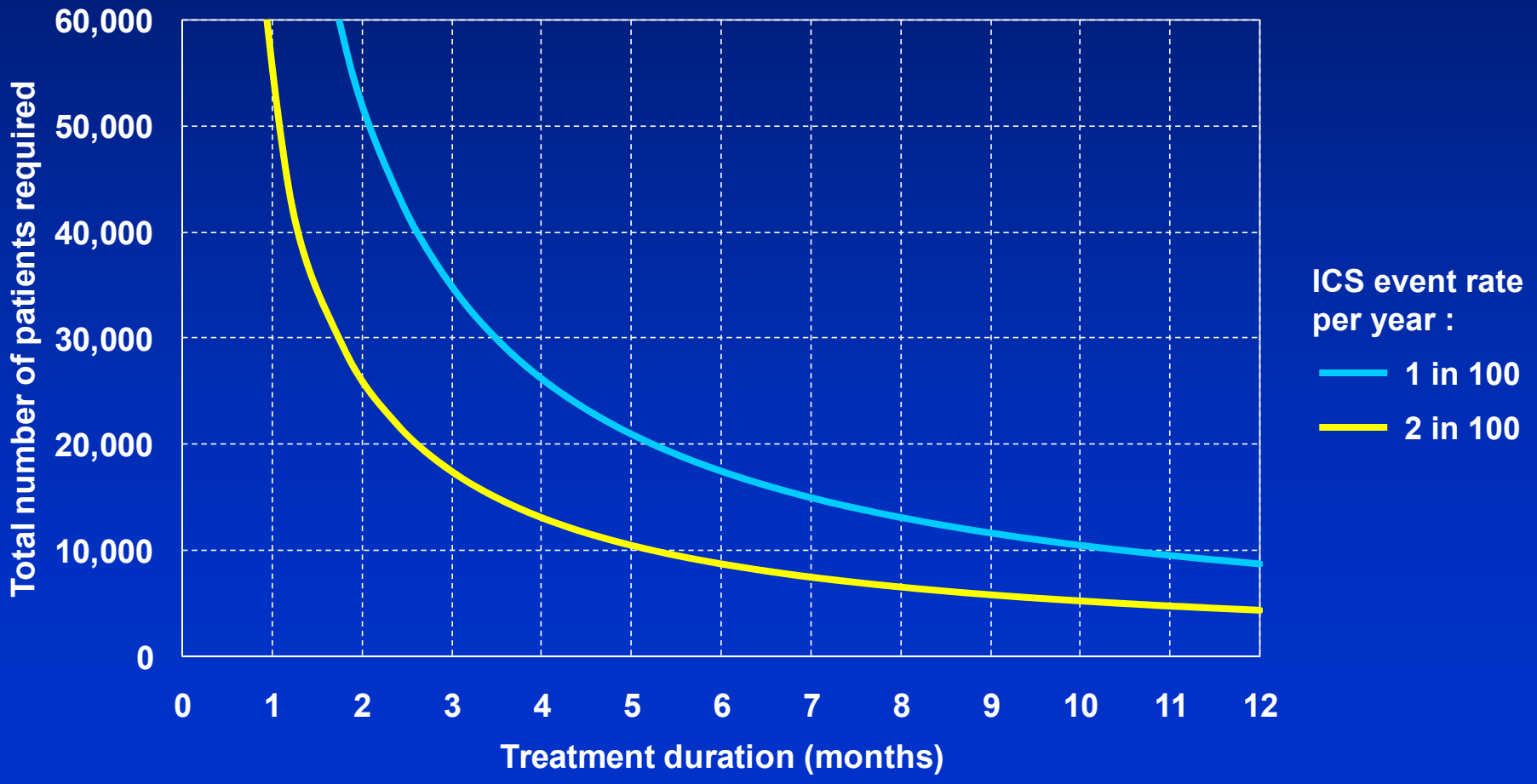
Trial Size Determinants and Sensitivities

- Trial size depends on
  - the significance level α (0.025) and power (90%)
  - the yearly event rate on ICS (p)
  - the relative risk (RR) to be ruled out
  - Number of Patients = $4p^{-1}(z_{\alpha}+z_{1\text{-power}})^{2} / \log(RR)^{2}$
- For an ICS annual event rate in the region of
  - 1 in 10,000, $N=420{,}000 / \log(RR)^{2}$, so if RR=2 $\Rightarrow$ N=874,000
  - 1 in 100, $N=4{,}200 / \log(RR)^{2}$, so if RR=2 $\Rightarrow$ N=8,740
- As the event rate decreases by a factor of 10, N increases by a factor of 10
- As the log RR to be ruled out decreases by half, N increases by a factor of 4

Treatment Duration Is Another Important Determinant of Trial Size



Expected Event Rates In Asthmatic Patients Receiving ICS Therapy

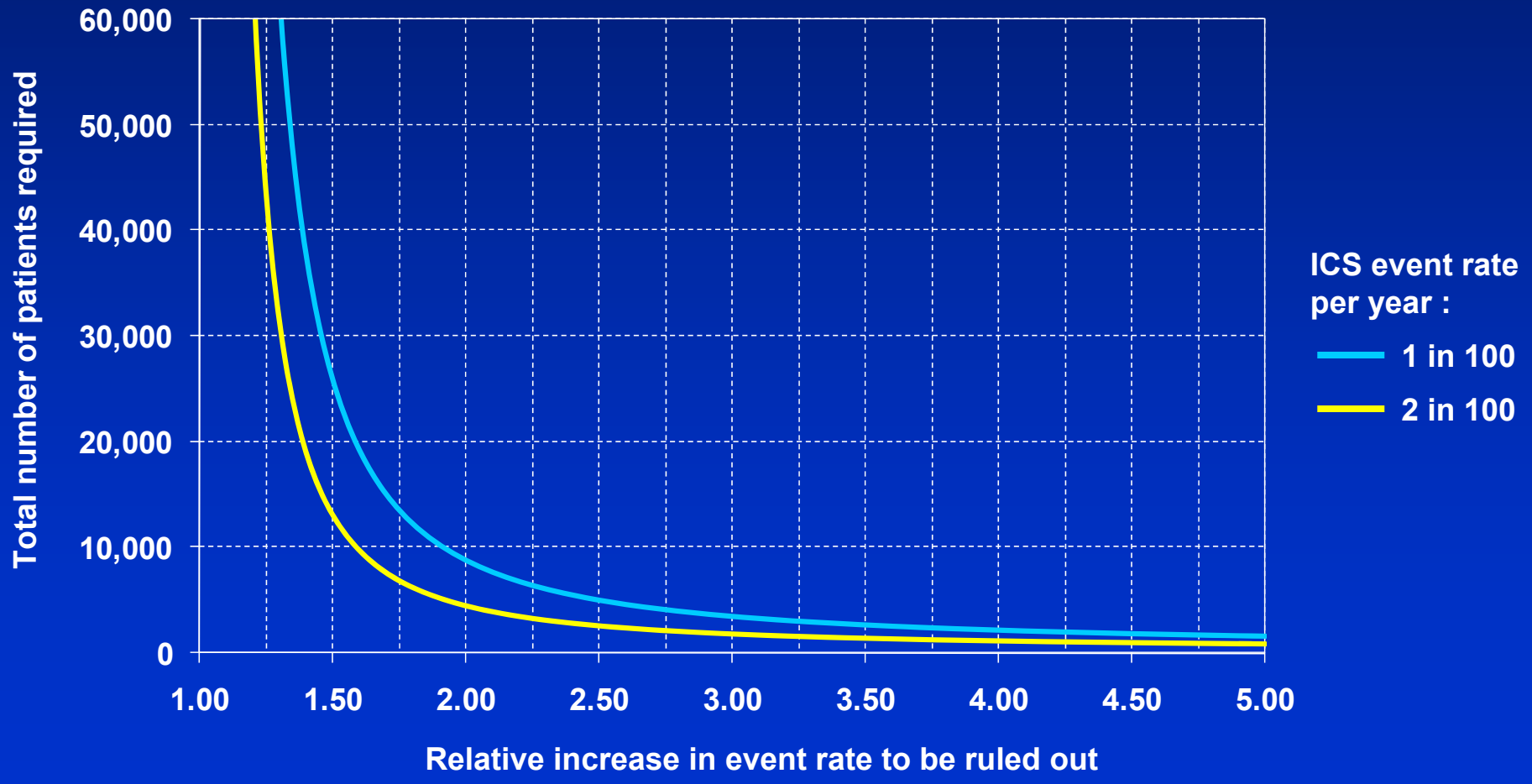
- Asthma related deaths[a]
  - 95% CI (0 to 0.08%) per year
  - Sears et al (2009) reports 0.02% per year
- Intubations[a]
  - 95% CI (0 to 0.08%) per year
- Hospitalizations[a]
  - 1.5% per year, 95% CI (1.1% to 2.0%)
- ED visits and hospitalizations[b]
  - 2.8% per year, 95% CI (2.1% to 3.8%)

[a] Based on 6,489 patients exposed to ICS for 3,543 patient-years across 27 randomized, controlled Symbicort trials.
[b] Rabe et al 2006; Scicchitano et al 2004; O'Byrne et al 2005: Composite endpoint of ED visits and hospitalizations used as efficacy endpoint. 28 events observed in 2,102 patients treated with ICS.

Trials for Very Rare Events, Like Asthma Related Death, Occurring in 1 In 10,000 Patients Per Year Require Over 800,000 Patients to Rule Out a 2-Fold Increase in Risk

Relative risk to exclude on comparator	Required number of events	Required number of patients	Comparator event rate per year (%)	Absolute difference in event rates (%)	Anticipated 95% CI width for absolute risk difference
Control event rate per year: 1 in 10,000 (0.01%)					
1.3	611	6,106,165	0.013	0.003	±0.002
1.5	256	2,566,648	0.015	0.005	±0.003
2.0	87	874,837	0.020	0.010	±0.005
5.0	16	162,267	0.050	0.040	±0.017
Control event rate per year: 1 in 1,000 (0.1%)					
1.3	611	610,891	0.13	0.03	±0.017
1.5	256	255,780	0.15	0.05	±0.027
2.0	87	87,523	0.20	0.10	±0.051
5.0	16	16,234	0.50	0.40	±0.169
Control event rate per year: 1 in 100 (1.0%)					
1.3	611	61,364	1.3	0.30	±0.170
1.5	256	25,693	1.5	0.50	±0.275
2.0	87	8,792	2.0	1.00	±0.515
5.0	16	1,631	5.0	4.00	±1.714

For Annual Event Rates in the Region of 1 or 2 in 100, Trial Size Increases Dramatically as the RR to be Ruled Out Drops Below 2

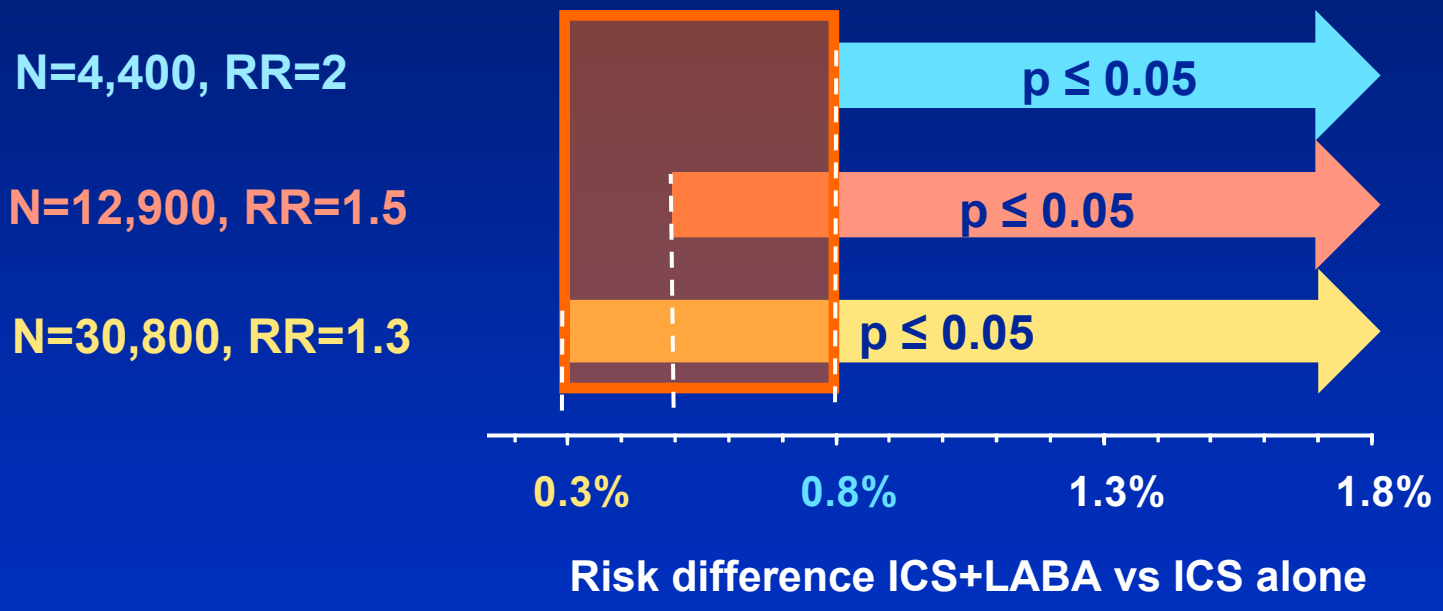


There Is Relatively Little to be Gained in Practical Terms in Sizing to Rule Out a RR Lower Than 2

Annual occurrence rate	RR to be ruled out	Number of events required	Total N required	Upper 95% CL for absolute increase in risk
2%	1.3	611	30,800	+0.5% CL
	1.5	256	12,900	+0.8% CL
	2.0	87	4,400	+1.3% CL

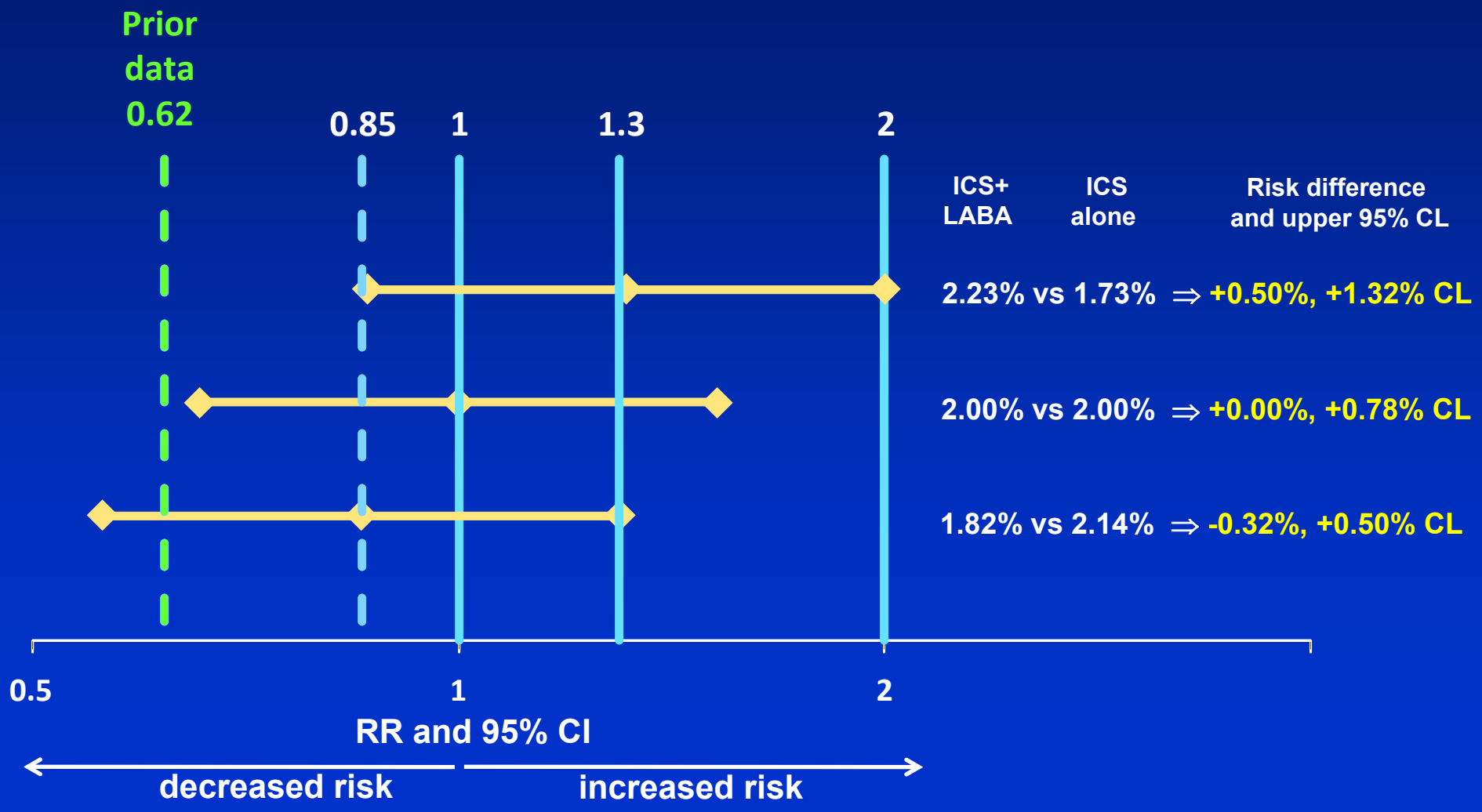
- **Ruling out a RR of 1.3 rules out a +0.5% increase in absolute risk**
- **Ruling out RR of 2 rules out a +1.3% increase in absolute risk**
- **Therefore, to rule out a 2 in 100 vs 2.5 in 100 increase in risk as opposed to a 2 in 100 vs 3 in 100 increase in risk requires a 7-fold increase in trial size**

For a 2 in 100 Annual Event Rate, Large Increases in Trial Size Result in Little Additional Gain In Terms of the Increase in Risk That Can Be Detected Statistically



- The large increase in trial size buys the orange box – it buys the ability to statistically detect a slightly smaller absolute risk difference of 0.3% as compared to 0.8%

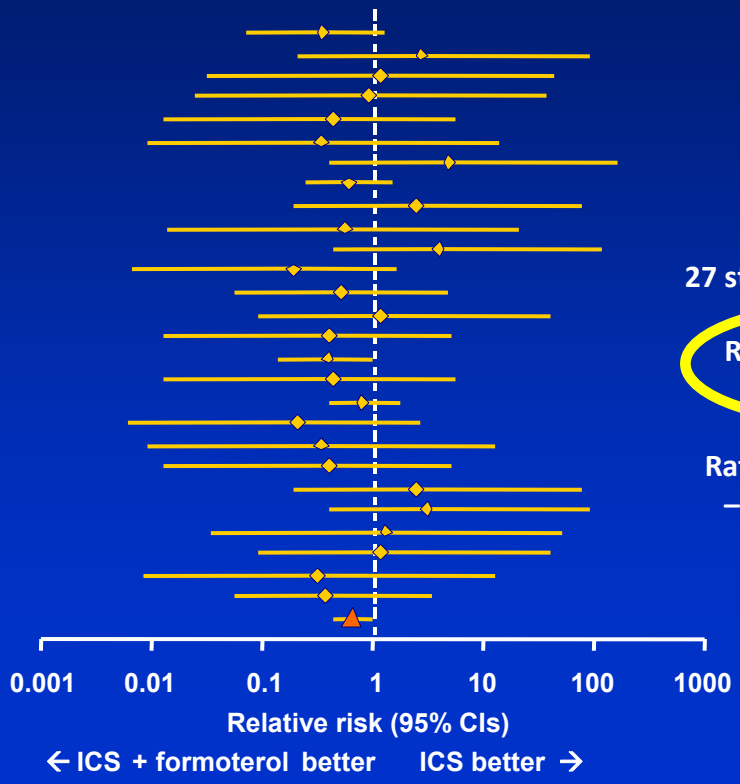
What Can We Rule Out in a 4,400 Patient Trial?



Power of a 4,400 Patient Trial to Rule Out a RR of 1.3 Is 93% Given Prior Data

Relative Risk Estimates of Hospitalizations by Trial and Overall

ICS + Formoterol vs ICS, Patients ≥ 12 Years



Statistical Considerations: Summary

- The event rate is the key determinant of study size.
- For events such as asthma death or intubations with rates in the region of 1 in 10,000 or 1 in 1,000, typically require at least 80,000 patients and are hence considered infeasible.
- For composite events with a rate in the region of 1 or 2 in 100, study size is lower but increases dramatically as the RR to be ruled out drops below 2.
- Reducing treatment duration from 12 to 3 months quadruples study size
- Large increases in trial size result in little additional gain in terms of increased risk that can be ruled out.