Design Considerations for Dedicated CV Safety Outcome Trials - Therapeutic CV Safety Assessment

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Disclaimer

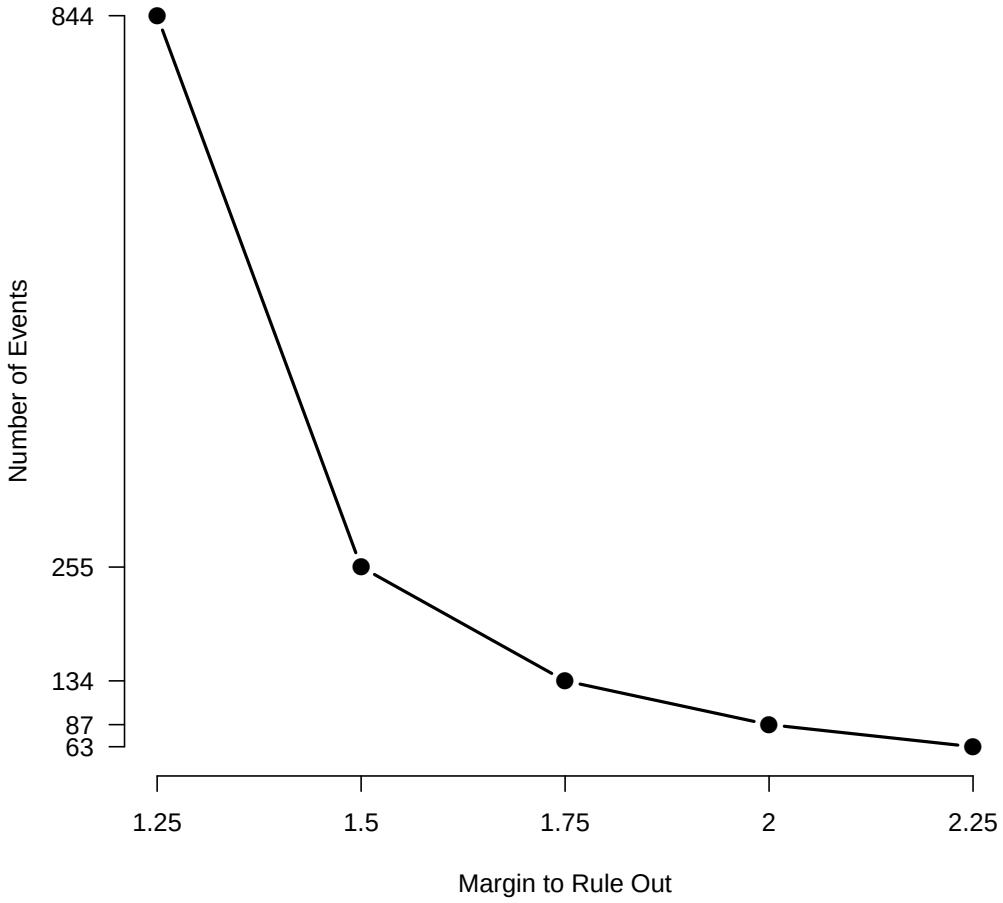
- The views expressed in this presentation are those of the presenter and must not be taken to represent policy or guidance on behalf of the Food and Drug Administration.

Intertwining of Statistical and Clinical Issues

Size of trial(s) depends on several factors (clinical and statistical) to ascertain the number of events needed to achieve the desired statistical power (i.e. event driven trials).

1. Definition of CV outcome (MACE?)
2. What level of $(1-\beta)$ should be used to power the study?
3. What degree of risk to rule out (upper bound of the 95% CI)?
   - Measure on absolute or relative scale?
4. What is the assumed true hazard ratio of investigative treatment relative to control?
5. What is the background event rate of the control group?
6. Does the study need to be powered for both the ITT and PP analysis populations?

Impact of Choice of Margin to Rule Out



Calculations based on 90% power, true HR $= 1$, and two-sided $\alpha = 0.05$.

Impact of the Background Rate

- The number of events that can be expected are related to the background event rate.
  - Formula: Person Years = No. Events / Background Rate
- To rule out a HR of 1.25 then the number of person years needed is:

Background Rate	0.5%	1.0%	1.5%	2.0%
Person Years	168,800	84,400	56,267	42,200

Reducing Pre-Approval Burdens

- For products that require dedicated CV outcome trials pre-approval it is possible to rule out a larger degree of risk at time of filing with post-marketing requirement to reach desired risk level.
- **Diabetes Guidance**: At time of filing, must rule out a risk of **1.8** and as a post-marketing commitment must rule out a risk of **1.3**.
  - To rule out a risk of **1.8** with a background rate of 2.0% this requires approximately 6,100 person years.
  - Similarly to rule out a risk of **1.3**, this requires approximately 30,550 person years.
- Is this the way of the future for dedicated CV outcome safety trials?