



# **What Makes a Good Cardiovascular Trial—DMEP Biometrics Perspective**

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# Diabetes CV Guidance <sup>1</sup>

- Compute point estimate of risk ratio or hazard ratio (drug vs control) for CV events and corresponding 95% confidence interval (CI)
- Compare upper bound of the 95% CI to 1.8 (i.e., 80% increase in risk) and 1.3 (30% increase in risk) -- ***non-inferiority setting***
- Upper bound of CI
  - > 1.8                      Non-approval
  - > 1.3 and < 1.8            Approval with requirement for additional post-marketing CV data. CI must exclude 1.3 subsequently to remain on the market
  - < 1.3                        Approval, post-marketing trials generally will not be required

<sup>1</sup> Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

# Data sources for CV events

- Data could come from various sources
  - Phases 2/3
  - Dedicated outcome study
    - Most of the data?
  - Combination of the above
- Complicated statistically to combine data from different sources, particularly short-term and longer-term trials that may have interim analyses

# Need adequate statistical power

- Power to rule out harm in a non-inferiority (NI) trial determined by type 1 error, margin (1.8 or 1.3) and expected number of primary CV events <sup>1</sup>
- Type 1 error (1-sided 2.5%) and margins (1.8, 1.3) fixed so

power ↔ # primary CV events

- ***Therefore critical to precisely define clinically relevant events to be used in analysis***

<sup>1</sup> logrank statistic, 1:1 randomization, true HR equals 1

# # primary CV events

Non-inferiority margin	Power		
	80%	85%	90%
1.8	<b>90</b>	<b>105</b>	<b>125</b>
1.3	<b>455</b>	<b>525</b>	<b>615</b>

# Good study quality

- Especially important in NI trials – deficiencies can bias towards the alternative (no-difference) hypothesis, the goal of the trial. Sloppiness in general obscures true treatment differences
- In general, conduct the study in a way that allows treatment differences, if they exist, to emerge
- **Standardized data** is one step towards improving quality of CV clinical trials

# Additional desirable design or data attributes

- *Adjust type 1 error for any repeated looks at the data for both NI margins, 1.8 and 1.3.* Guidance document specifies only nominal 95% CI w/o mentioning possible multiple looks over time. To date, many sponsors have submitted plans for repeated testing without adjusting for multiplicity.
- Collect follow-up primary endpoint data for all patients including after discontinuation
  - Intent-to-treat
  - Seems anti-conservative --- not always the case
  - Better to have the data than not