# Decision Criteria for IDMCs – Perspectives on current challenges

Adam Crisp, GSK

EFSPI/PSDM Meeting on
"Statistical Aspects of Safety Data in Clinical Trials"
23rd June, 2017

# Background

- Personal experience in the design and conduct of several cardiovascular outcomes trials
- Complex issues can arise in terms of sponsor, IDMC and regulatory interaction (both for efficacy and safety)
- Increasing sponsor attention to robustness of futility criteria
- Controversial recent examples in literature regarding use of interims and firewalling sponsors and regulators

# Topics for discussion

- Increasing focus on futility – how to set boundaries and create insight?
- Reacting to early trends – use of simulation before trial start
- Case studies
  - LATITUDE: two-stage design, sponsor access to first stage
  - LIGHT: sponsor access to interim results of safety trial with problematic consequences
  - ATMOSPHERE: BfArM request to discontinue treatment arm in spite of IDMC reassurance
- Concluding remarks

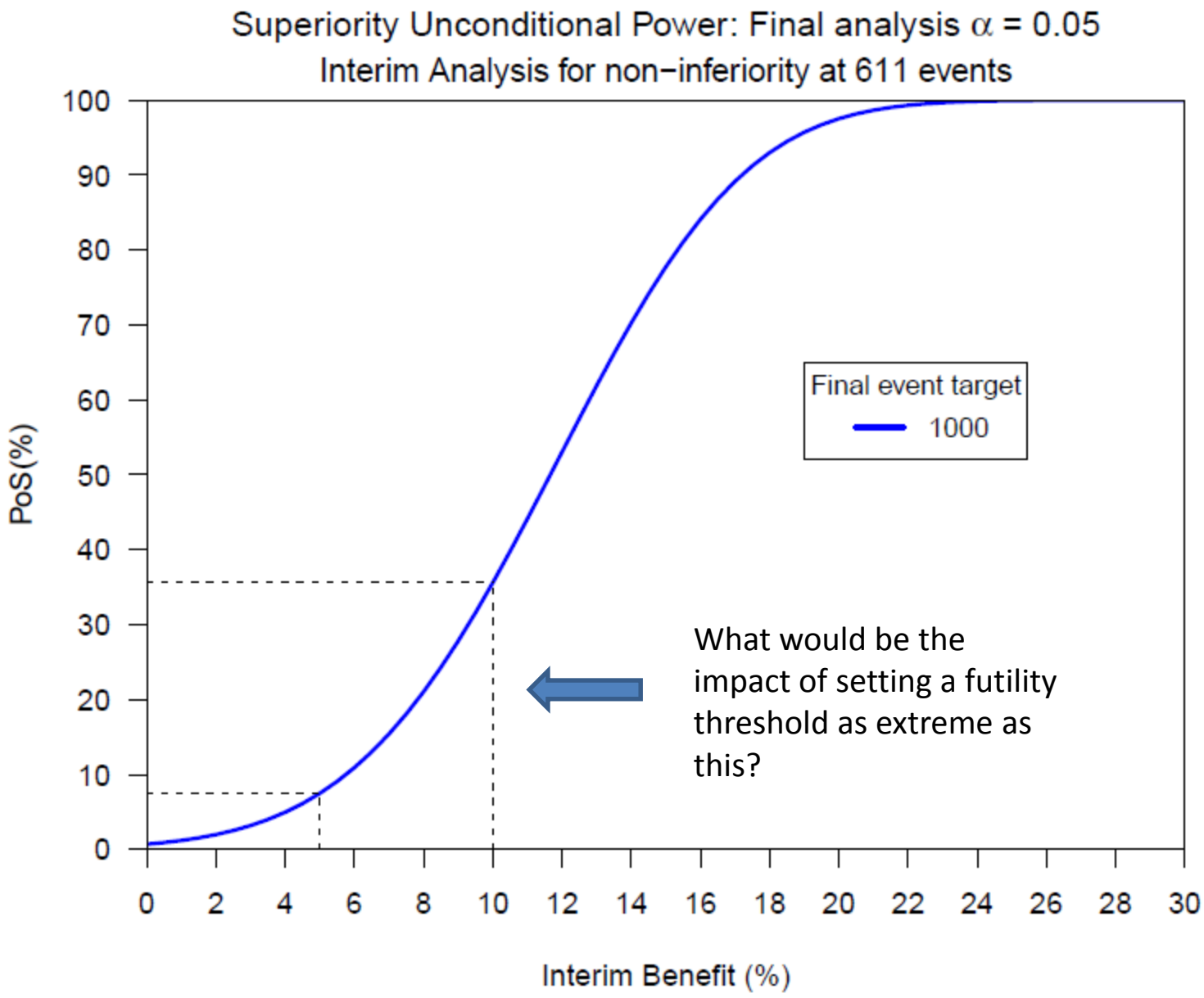
# A bit of supporting theory

- $E_i$ events at each analysis
- $\theta_{True}$ : true log Hazard Ratio (HR), $\hat{\theta}_i$ estimated log HR at each analysis
- Let $Z_i = \hat{\theta}_i / \sqrt{4/E_i}$
- Joint distribution of $\boldsymbol{Z} = (Z_1, Z_2, \ldots)$ is multivariate normal
- For given stopping rule, integrals of interest straightforward to calculate in R conditional on a true treatment effect
  - P(continue to success)
  - P(continue to failure)
  - P(incorrect stop)
  - P(correct stop)
- Bayesian extensions also possible, e.g. with data-driven or elicited priors

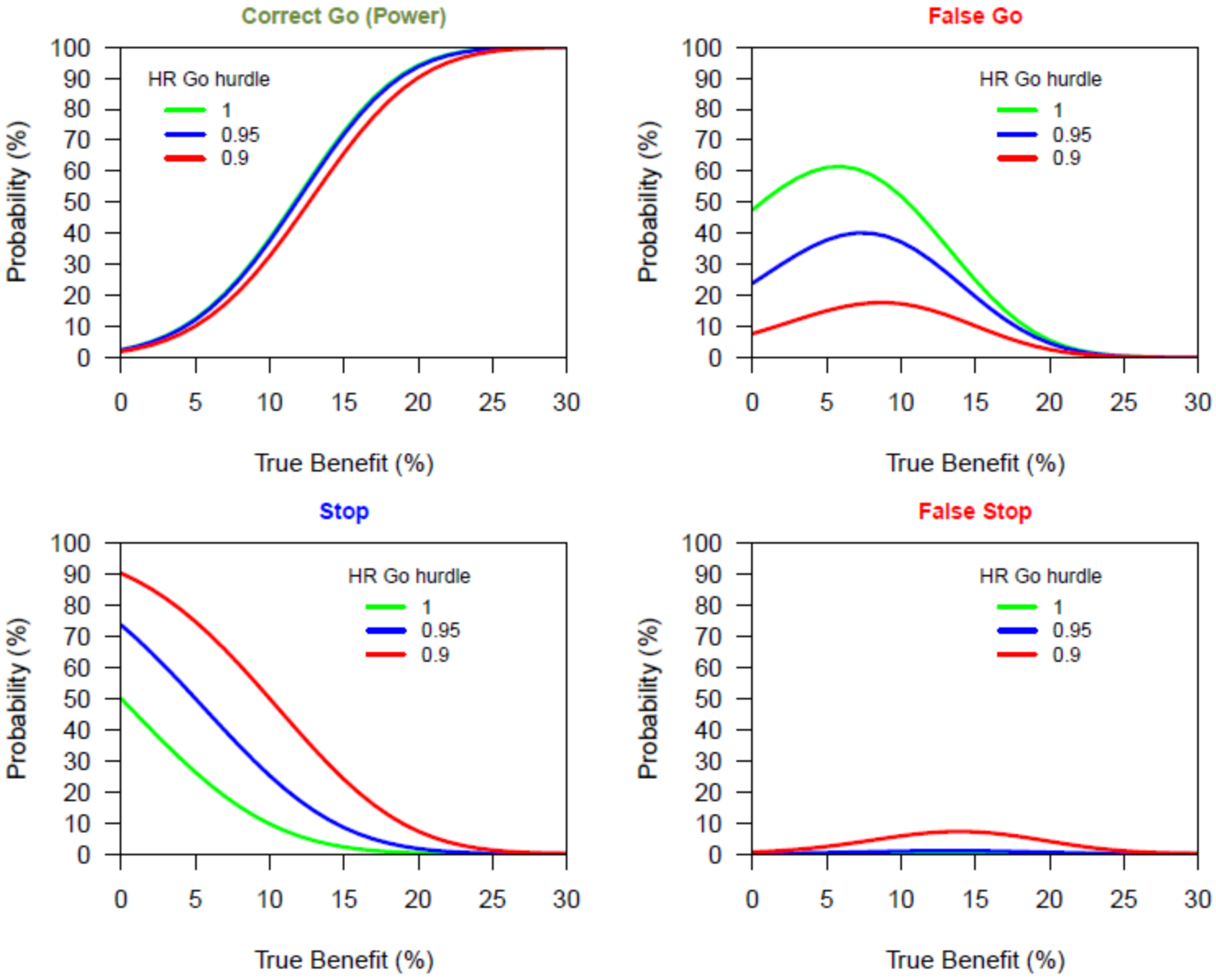
# Evaluating futility rules[#]

- Common approach: evaluate conditional/unconditional power as a function of interim effect size
- Identify a threshold based on low power
- Historical norm has been conservative (in sense of maintaining overall power)
- Problem: does not tell us how the rule will *perform*
  - Need operating characteristics

[#] "Rules" are in fact guidance for the IDMC, but we need to start somewhere


Superiority Unconditional Power: Final analysis α = 0.05
Interim Analysis for non−inferiority at 611 events
PoS(%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
Interim Benefit (%)
Final event target
1000
What would be the impact of setting a futility threshold as extreme as this?

Futility profiles, target P < 0.05. 611 / 1000 interim/final−analysis event split

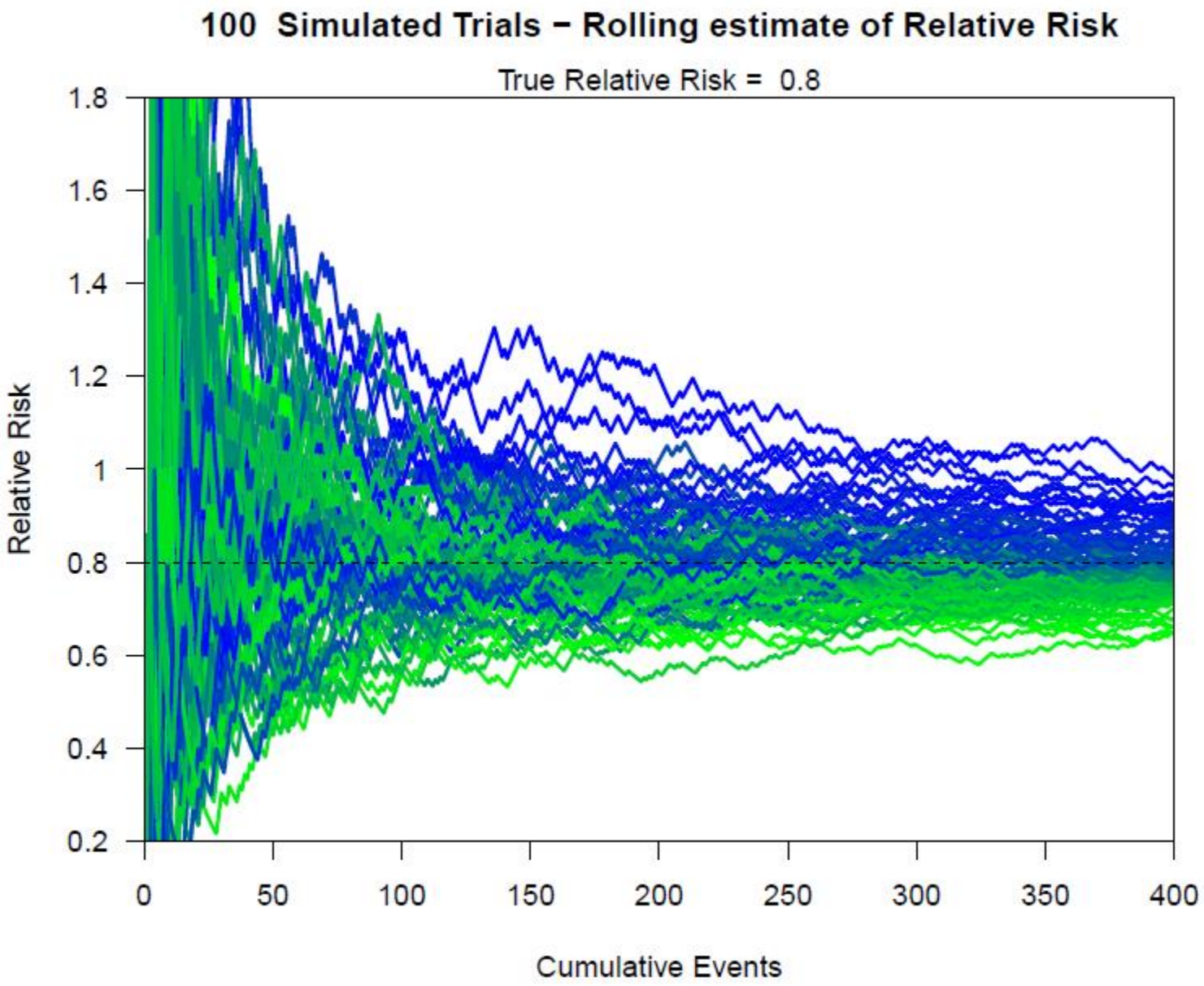


# Pre-trial simulation – understanding volatility

- Volatility in effect size is more obvious if we simulate pre trial
  - Plot rolling estimate of effect size vs #events
  - Illustrate how early trends can reverse, inform debate of interim-analysis timing and avoiding premature action

- Simple method: ignore time-to component, focus on rel-risk
  - For true rel-risk R, derive probability next event is on Treatment A or B, e.g. $p_A = R / (R + 1)$ for trial with two groups in 1:1 ratio
  - Run a “biased coin” simulation to generate an event stream and rolling estimates of relative risk

# Simulated rolling estimates of effect size



# Case Studies

# LATITUDE[#]

## Losmapimod for Acute Coronary Syndrome

Scenario

- Phase 3 outcomes trial
- Primary Endpoint: MACE, N > 20,000 for powered trial
- Phase 2: +ve biomarker results, but substantial undischarged risk

Context

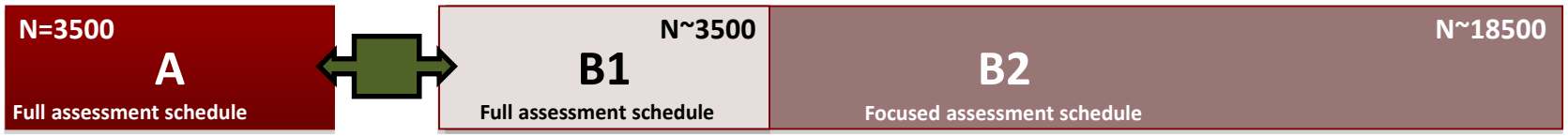
- Concern that historical futility analyses had lacked “bite” (e.g. stop if conditional power < 1%)
- Sponsor planned to review interim data while preserving trial integrity

[#] **O’Donoghue ML et al.** Rationale and design of the LosmApimod To Inhibit p38 MAP kinase as a TherapeUtic target and modify outcomes after an acute coronary syndrome trial. ***American Heart Journal*** **2015; 169 (5): 622 – 630.**

# LATITUDE Study Design

**A: Leading Cohort**
N=3500
~ 200 MACE events

**B: Main Cohort**
N ~22,000
1400 MACE events
1000-1200 CV death or MI events (Principal 2º EP)




*Seamless transition*

**Efficacy & Safety Assessment**
- Sponsor
- Executive Cmte
- IDMC

**Safety Assessment**
- IDMC review

[Combined safety data from Part A + Part B1 (~7000 subjects)]

**Part B futility interims**
- IDMC reviews at 700 and 1050 events

Full assessment schedule

Focused assessment schedule

**MACE: CV Death, MI, Severe Recurrent Ischemia req. Urgent Revasc**

# LATITUDE discussion

- Advantages
  - Embedding Part A in an outcomes trial allows Part A to be much larger than a stand-alone 2b trial
  - Operationally seamless to the extent possible
  - Full unblinding of Part A supports sponsor engagement in decision-making while preserving integrity of Part B
- Disadvantages
  - MACE events in Part A not included in primary analysis
  - Part A needs to be relatively small to support early futility assessment, risk of wrong decision
- Outcome: terminated at end of Part A

# LIGHT[#]

## Effect of naltrexone-bupropion on MACE in obesity

Design

- Pbo-controlled MACE non-inferiority study
  - 25% events (~87): HR margin = 2.0
  - 50% and 75% events, pre-specified alpha-spending for superiority
  - 378 events: HR margin = 1.4 (final analysis)

- All interims overseen by an IDMC

- 87-event interim shared with sponsor to enable regulatory file
- FDA and sponsor agreed to keep confidential, similar to model used in assessment of new diabetes therapies

[#] **Nissen, SE et al.** Effect of naltrexone-bupropion on Major Adverse Cardiovascular Events in Overweight and Obese Patients with with Cardiovascular Risk Factors: a randomized clinical trial. ***JAMA* 2016:315(10):990-1004.**

# LIGHT - outcome
## (based on JAMA editorial[#] and results paper)

- First interim: HR=0.59 (95% CI: 0.39 – 0.90)
- Interim submission: “more than 100 people” had access to results
- Co-development partner files patent for cardiovascular benefit (results in effect public), no pre-specified superiority boundary for 25% analysis
- Investigator and regulatory concerns re compromised trial integrity
- Trial’s academic leadership recommend terminate the study, by this point 50% planned events available, trial closed at 64% events
  - 50% events: HR=0.88 (99.7% CI: 0.57 – 1.34)
  - 64% events: HR=0.95 (99.7% CI: 0.65 – 1.38)
- New outcomes trial required, further commentary in JAMA editorial

[#] **Sharfstein and Psaty.** Evaluation of the cardiovascular risk of naltrexone-bupropion: a study interrupted. ***JAMA* 2016:315(10):984-986.**

# ATMOSPHERE[#]

## Aliskiren in Patients with Heart Failure

- Renin inhibitor aliskiren approved for patients with hypertension
- Common IDMC for ASTRONAUT trial (acute heart failure) and ATMOSPHERE (comparing different regimens to ASTRONAUT in chronic heart failure)
- Third trial, ALTITUDE, terminated for safety while ASTRONAUT and ATMOSPHERE ongoing, raising concerns about diabetics
- BfArM asked IDMC about effects of aliskiren in diabetics
- IDMC reassured BfArM that ALTITUDE results taken into consideration, but would not release ASTRONAUT or ATMOSPHERE data
- ASTRONAUT completes, nominal subgroup finding in diabetics, no IDMC action re ATMOSPHERE
- Without access to unblinded data, BfArM requests discontinuation of aliskiren in the ATMOSPHERE diabetic subgroup, sponsor agrees
- Final results of ATMOSPHERE report no differential effect in patients with/without diabetes
- IDMC publish letter in NEJM criticising BfArM for not respecting their independence (replies from BfArM and sponsor also published).

[#] **Swedberg K et al.** Challenges to Data Monitoring Committees when regulatory authorities intervene. ***NEJM*** **doi**: 10.1056/NEJMsb1601674

# Planning for necessary unblinding

- IDMC / sponsor interaction may require limited unblinding in special cases, need mechanisms to allow for this
  - E.g. sponsor CMO and Chief Statistician designated points of contact
  - However, organisational “distance” from study team depends on size of the sponsor

- Scenario: safety signal emerges (internal or external to trial), benefit/risk balance may still be positive, but actions are indicated for well-being of patients
  - Additional expert to join IDMC
  - Dear HCP letter
  - Plan research to understand finding (e.g. design mechanistic study to run in parallel)

# Closing remarks

- Sponsor statisticians play lead role in developing IDMC charters
- Charter principles integral to overall trial design
- Evaluate options thoroughly at design stage, allow time to agree principles with IDMC
- Ask “what if?” questions up front for robust scenario planning
- Futility: sponsor attitudes to risk depend on prior opinion and utility – can impact the design itself or plans for sponsor unblinding
- It’s not just sponsors that may have an interest in accessing IDMC data

# References

**O'Donoghue ML et al.** Rationale and design of the LosmApimod To Inhibit p38 MAP kinase as a TherapeUtic target and modify outcomes after an acute coronary syndrome trial. ***American Heart Journal*** **2015; 169 (5): 622 – 630.**

**O'Donoghue ML et al.** Effect of Losmapimod on Cardiovascular Outcomes in Patients Hospitalized With Acute Myocardial Infarction: A Randomized Clinical Trial. ***JAMA*** **2016;315(15):1591-1599*.***

**Nissen, SE et al.** Effect of naltrexone-bupropion on Major Adverse Cardiovascular Events in Overweight and Obese Patients with with Cardiovascular Risk Factors: a randomized clinical trial. ***JAMA*** **2016:315(10):990-1004.**

**Sharfstein and Psaty.** Evaluation of the cardiovascular risk of naltrexone-bupropion: a study interrupted. ***JAMA*** **2016:315(10):984-986.**

**McMurray JJV et al.** Aliskiren, enalapril, or aliskiren and enalapril in heart failure. ***NEJM*** **10.1056/NEJMoa1514859**

**Swedberg K et al.** Challenges to Data Monitoring Committees when regulator authorities intervene. ***NEJM*** **10.1056/NEJMsb1601674**

**Fleming et al 2017.** Data Monitoring Committees: Promoting best practices to address emerging challenges. ***Clinical Trials*** **14(2) 115 – 123**.