

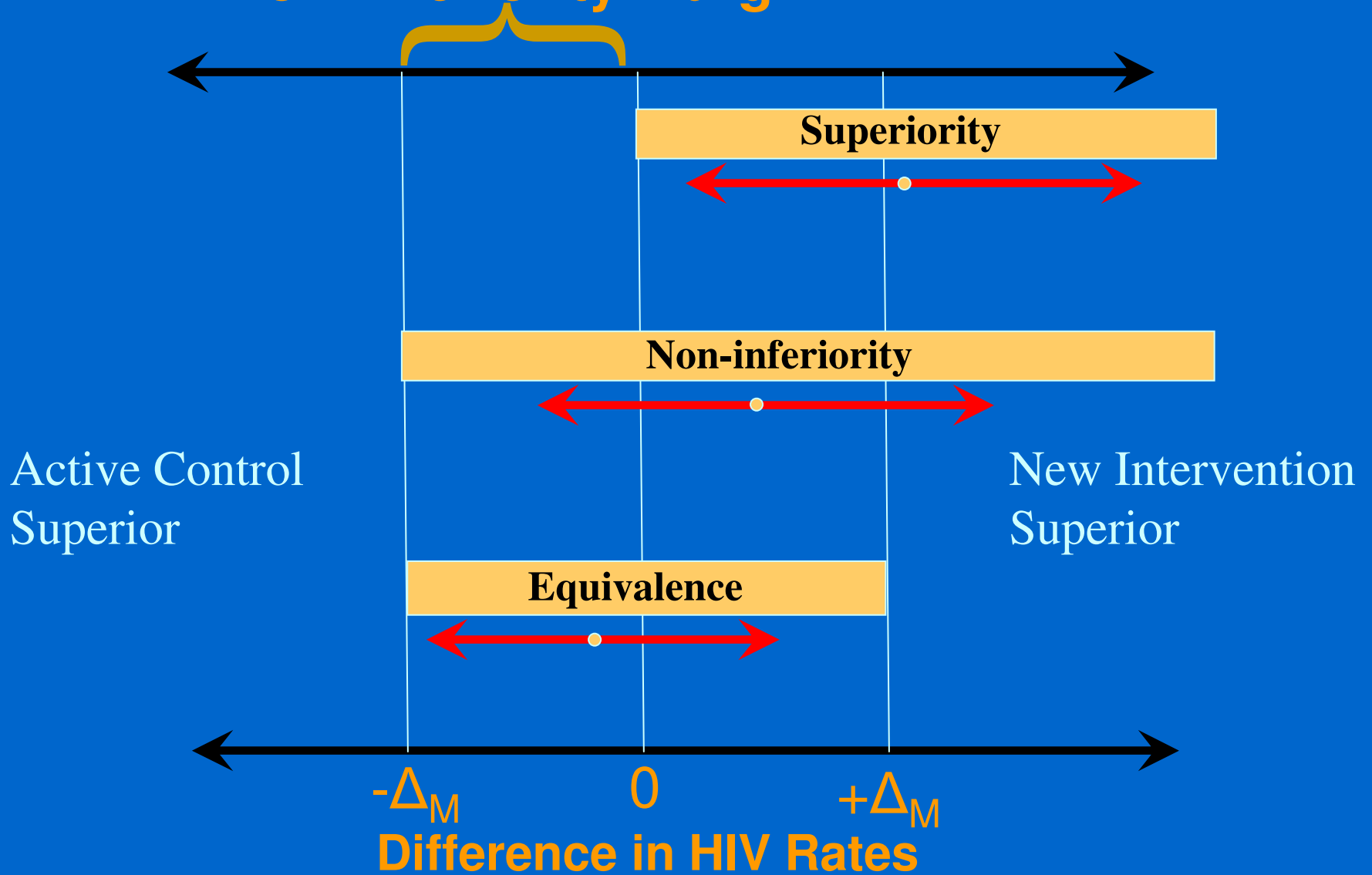
# Testing Superiority, Equivalence, and Non-Inferiority

Benoît Mâsse

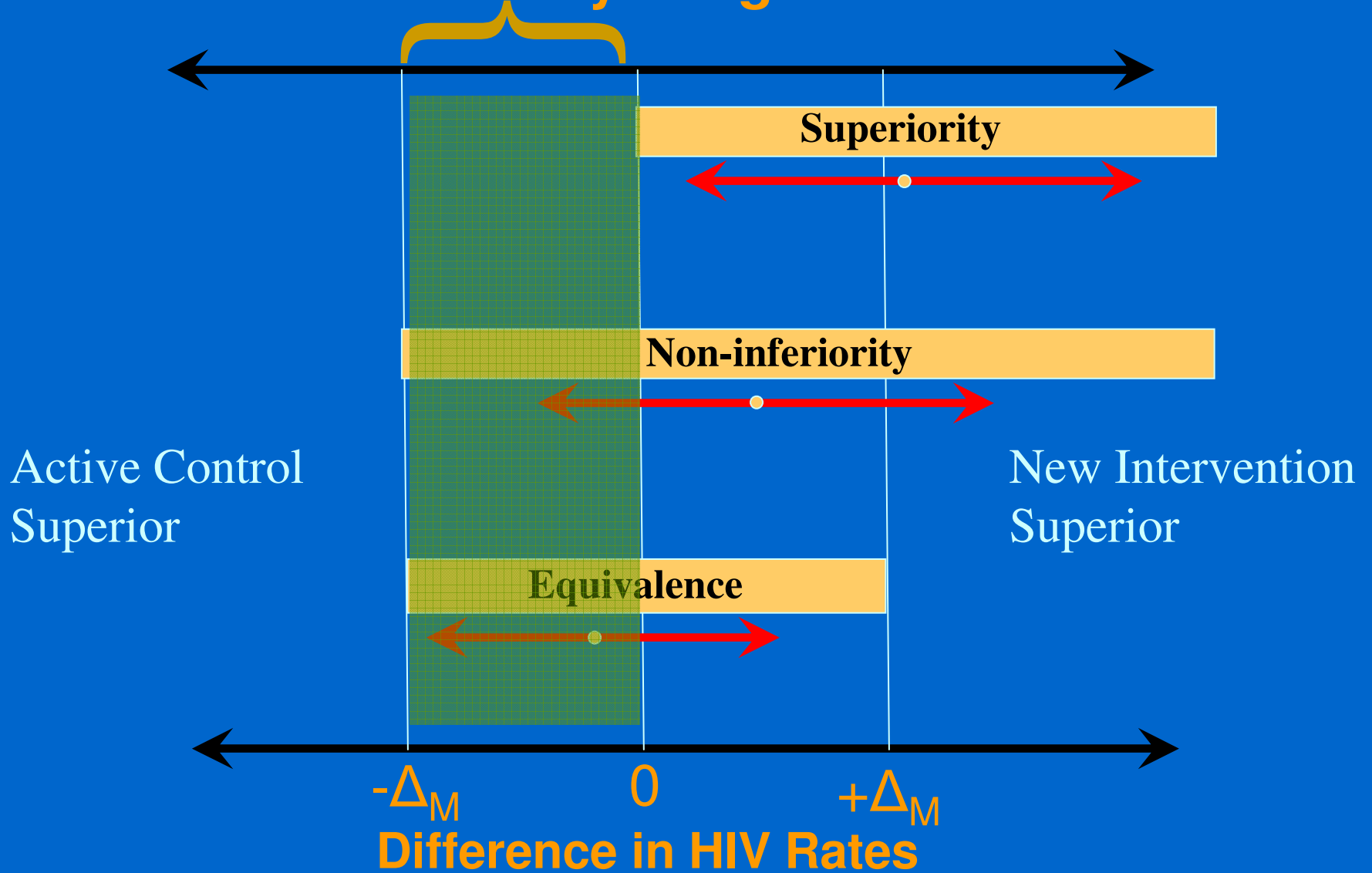
Statistical Center for HIV/AIDS Research & Prevention  
Seattle, WA USA

Consultation on Standards of Prevention in HIV Prevention Trials  
Speke Resort Munyonyo, Kampala, Uganda  
March 26-28, 2009

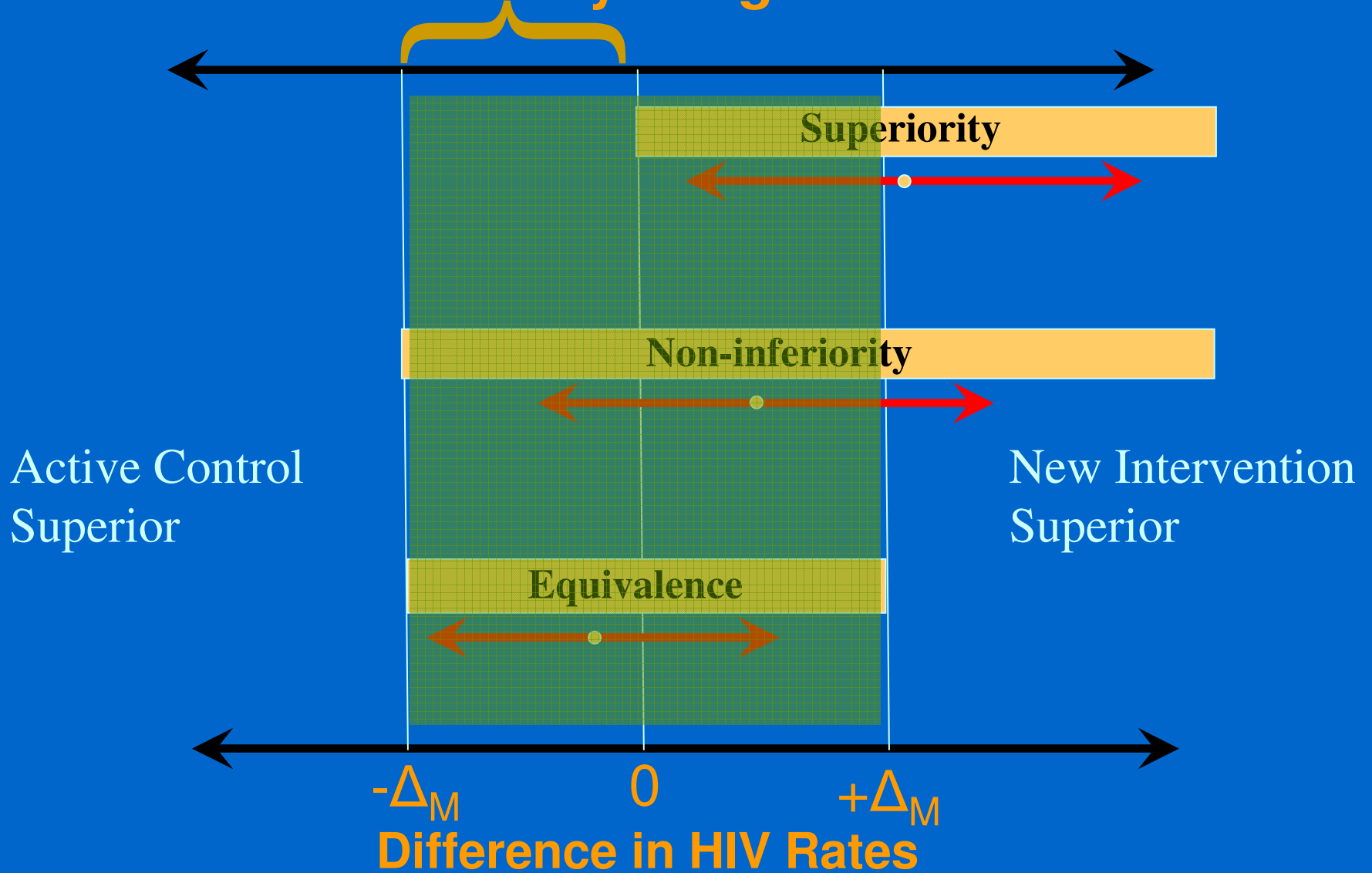
# Non-Inferiority Margin

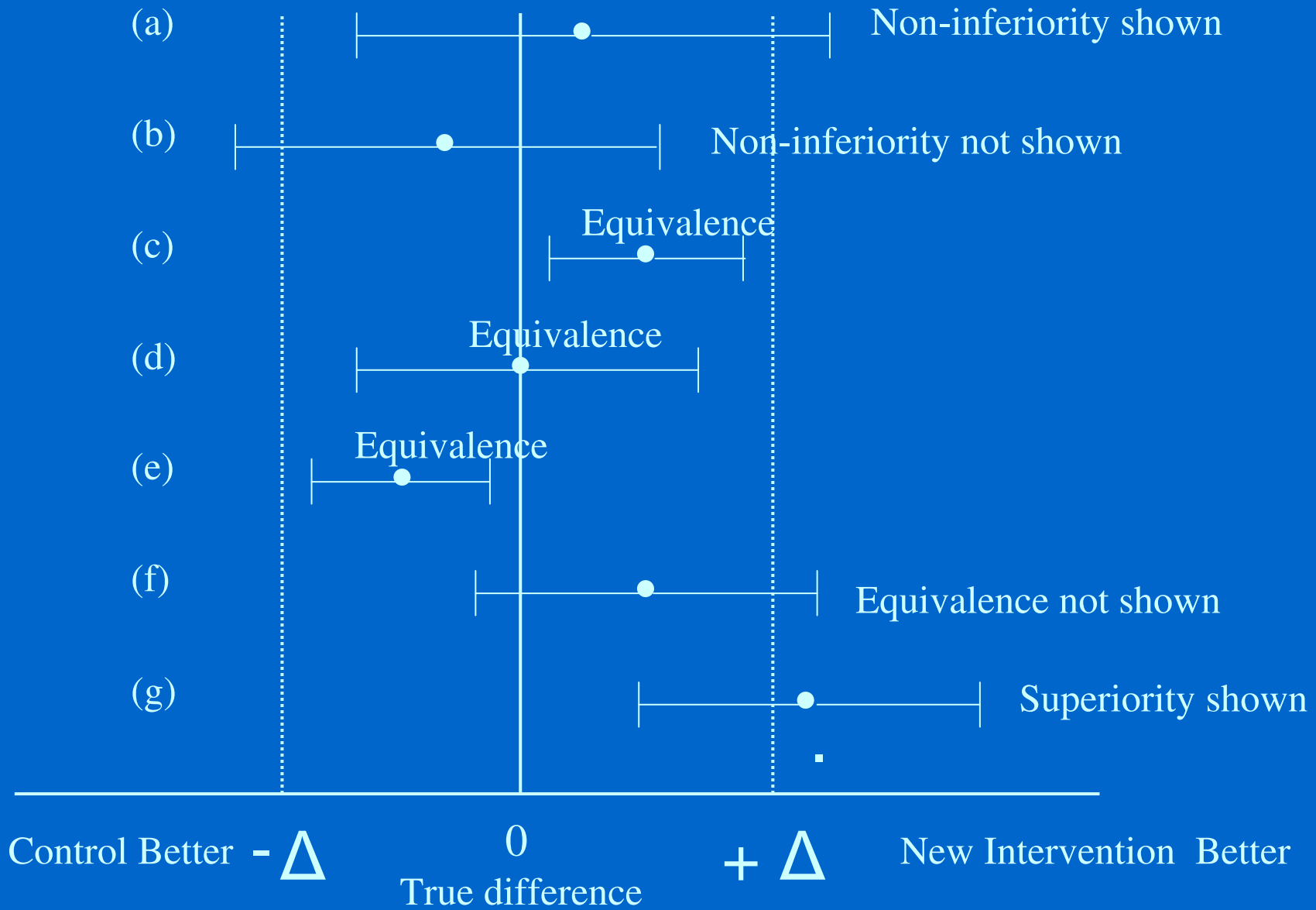


# Non-Inferiority Margin



# Non-Inferiority Margin





# ICH E10: Choice of Control Groups & Related Issues in Clinical Trials

	Type of Control			
Trial Objective	Placebo	Active Control Non-Inferiority	Active Control Superiority	Placebo + Active Control
Measure effectiveness	YES	NO	NO	YES
Show existence of effect	YES	Possible	YES	YES
Compare active interventions	NO	Possible	YES	YES

**Possible:** If there is historical evidence of sensitivity to intervention effect

# Are Non-Inferiority Trials Feasible?

Feasibility in terms of **Sample Size**

Sample size primarily driven by:

- 1) The anticipated effectiveness of the new intervention
- 2) The size of the non-inferiority margin:  
small margin requires large sample size

# Anticipated Effectiveness of New Intervention?

- Difficult to Determine
  - Phase II HIV prevention trials typically do not provide 'early' estimates of effectiveness
  - In this case, for sample size calculations, we typically assume that the new intervention has the **same** effectiveness as the active control
- Unfortunately, this leads to larger sample sizes

# Size of Non-Inferiority Margin (**M**)

No agreed way of determining **M**

- But always done conservatively
- For licensure, **M** typically need to be negotiated with regulators

# Size of Non-Inferiority Margin (**M**)

However, if the effectiveness of the active control is small to moderate (i.e. 30%-50%) **M will have to be quite small!**

# EFFECTIVENESS

Active Control

60%



Non-Inferiority  
Margin (**M**)

60% - M

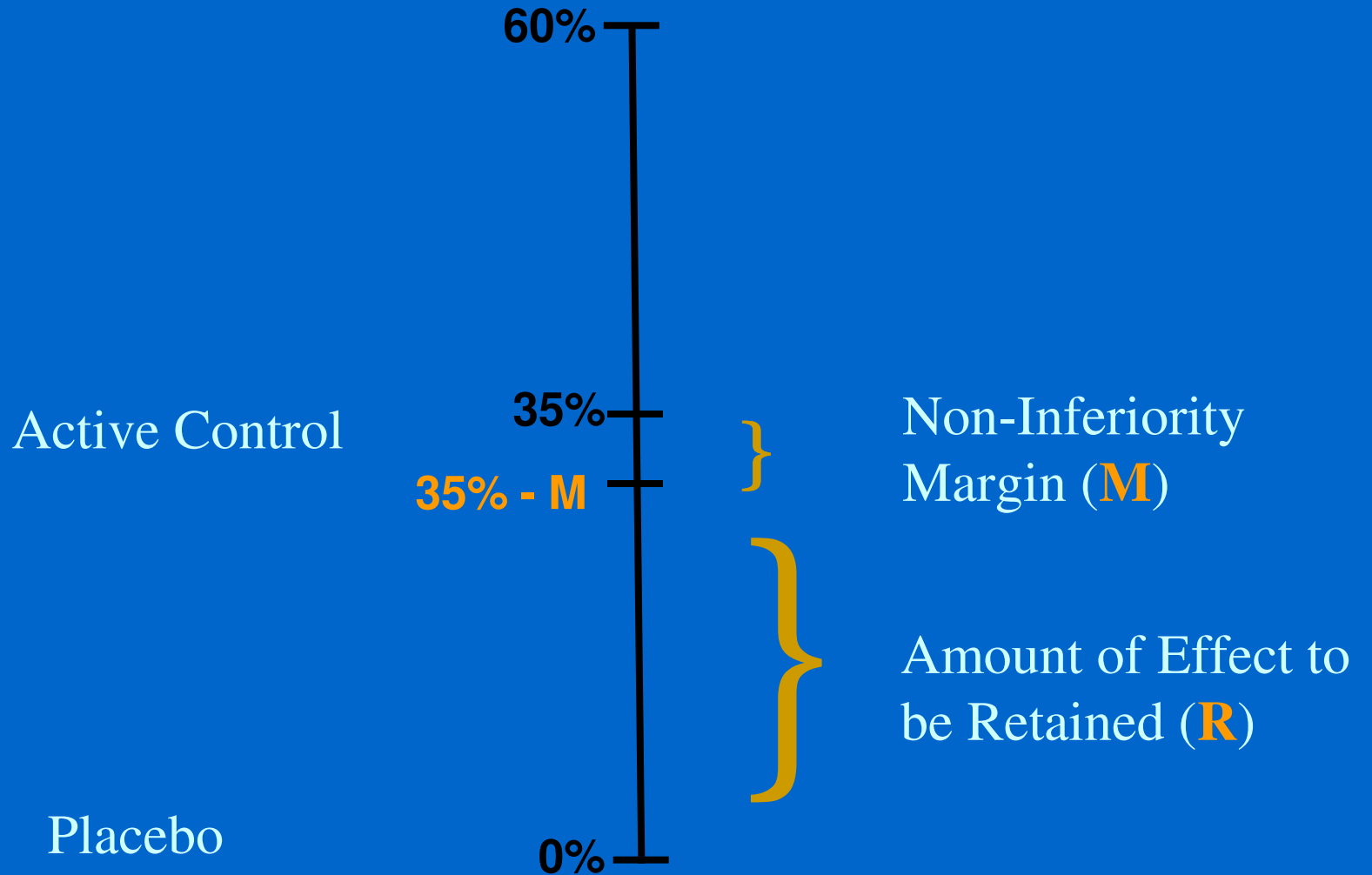


Amount of Effect to  
be Retained (**R**)

Placebo

0%

# EFFECTIVENESS



# Non-Inferiority Trial Examples

Active Control Effectiveness	Amount of Effect to be Retained	Number of HIV endpoints required*	Required resources
60%	25%	~80	~Average size of current trials
35%	25%	~1500	~5-7 times the size of current large trials
30%	25%	~6500	~20 times the size of current large trials

# Non-Inferiority Trial Examples

Active Control Effectiveness	Amount of Effect to be Retained	Number of HIV endpoints required*	Required resources
60%	40%	~190	~Average size of current large trials

# Size of Non-Inferiority Margin (**M**)

- 30-60 person-years per HIV endpoint
  - 1500 endpoints will require 45 000 to 90 000 person-years
  - 190 endpoints will require 6000 to 12000 p-y
- Small **M** leads to sample sizes in the range of +100 000 women !!!

# What about the impact of the standard prevention package?

- If the prevention package is indeed effective then this will increase the sample size further more

=> If baseline incidence is 2% instead of 4%, the # of HIV endpoints remains the same but the # of person-years will double

# Concluding Remarks

- Placebo or Active Controls?
  - Is 'effective' intervention accepted uniformly as standard treatment?
  - Will it 'work' in every populations?
  - Will past results be still valid?
- Placebo Controls: in un-tested populations
  - or where doubts exist

# Concluding Remarks

- Active Control Trials:
  - Non-inferiority trials are more challenging
  - Non-inferiority trials likely to be not feasible if effectiveness of active control is in the 20%-50% range.
- Superiority trials: ‘Beat’ the active control
  - Could aimed at superiority first then settle for non-inferiority ... that’s OK but need to define the non-inferiority margin a-priori.

# A Superiority Trial Example

Active Control Effectiveness	Effectiveness of New Intervention to be Detected	Number of HIV endpoints required*	Required resources
30%	55%	~160	~Average size of current large trials

\*Assuming a 2-arm superiority trial with 80% power and false-positive error rate of 2.5%