



# MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER of  
BRIGHAM AND WOMEN'S HOSPITAL  
and HARVARD

## Multi-Regional Clinical Trials (MRCTs): Practice and Issues of Multi-Regional Clinical Trials' Global Acceptance

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With thanks to:  
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Mila Owen

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# Our Mission

Engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.



# Agenda MRCTs: Science, and Regulations

- Why MRCTs?
- MRCT expectations, benefits and challenges
- International and regulatory considerations
- Rationale for acceptance of foreign country data
- Bridging study requirements

# Agenda MRCTs: Science, and Regulations

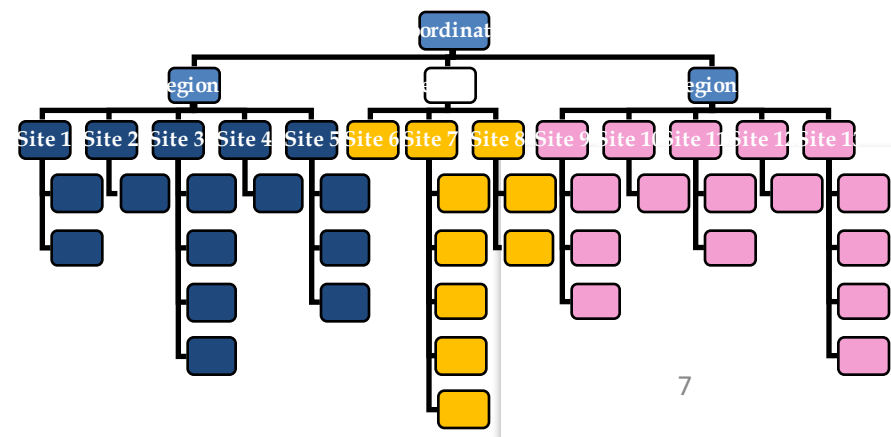
- **Why MRCTs?**
- MRCT expectations, benefits and challenges
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# Stages of Drug Development

1. Learning stage (phase 1 and phase 2 trials):
  - Safety, Dosing selection, Patient population selection
  - Efficacy screening using surrogate endpoint
2. Confirming stage (phase 3 trials, e.g., MRCT):
  - Efficacy (consistency across subgroups),
  - Safety, dosing,
  - Benefit/risk ratio

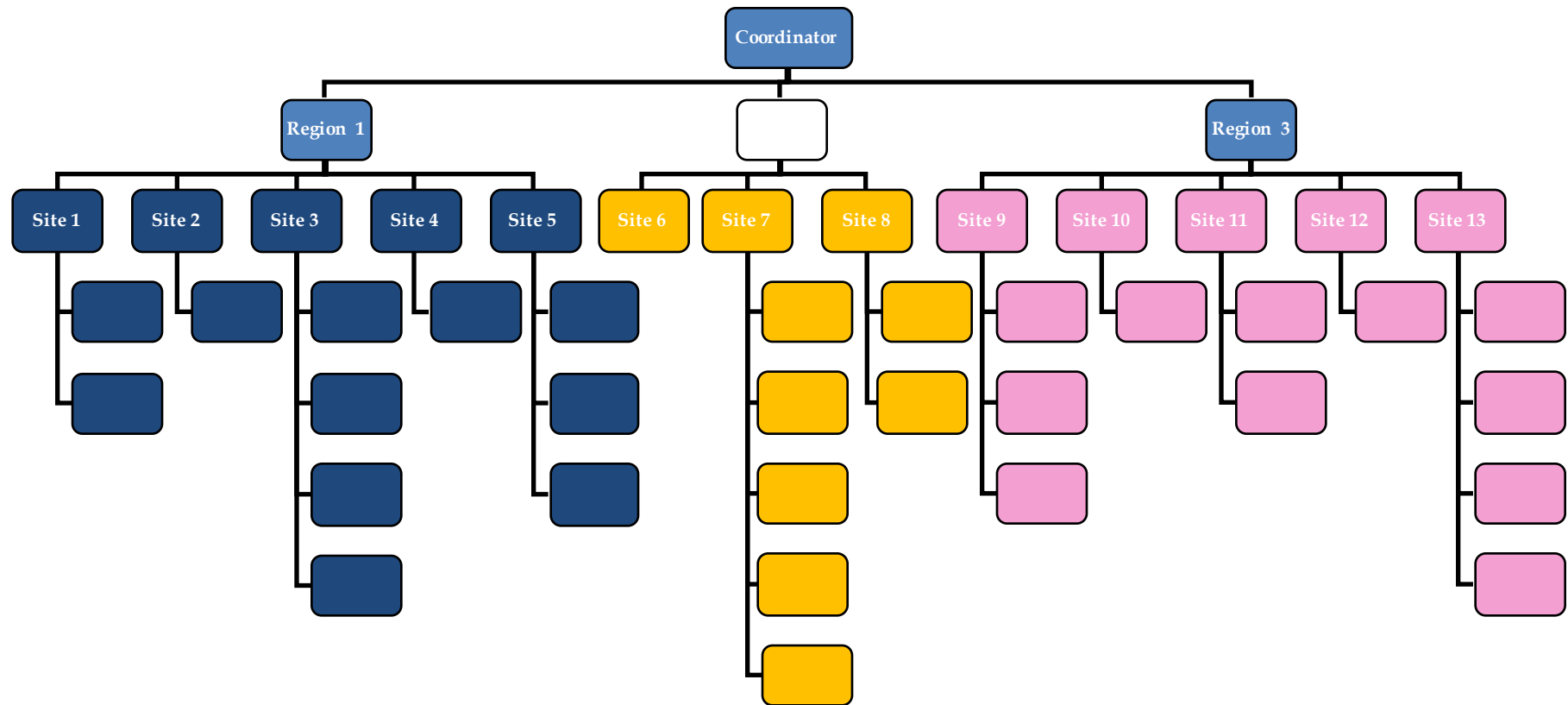
# MRCTs: Principles and Logic

- MRCTs rarely employed in Phase 1 and 2 trials
- MRCTs in Phase 3 clinical trials:
  - Expedite drug development and risk/benefit analysis
  - Better basis for subsequent generalization of the findings
  - Maintain same standards for multiple regulatory submissions
  - Reduce unnecessary cost and delay
- Assumption of consistency: that regions are equivalent and no significant differences exist
  - Understanding of and statistical assessment of consistency
  - Impact of intrinsic/extrinsic factors on outcome



# MRCT: Definition

A clinical trial with a common protocol, involving different centers and participants enrolled from different regions (countries), where the data collected is anticipated to be analyzed as a whole.\*

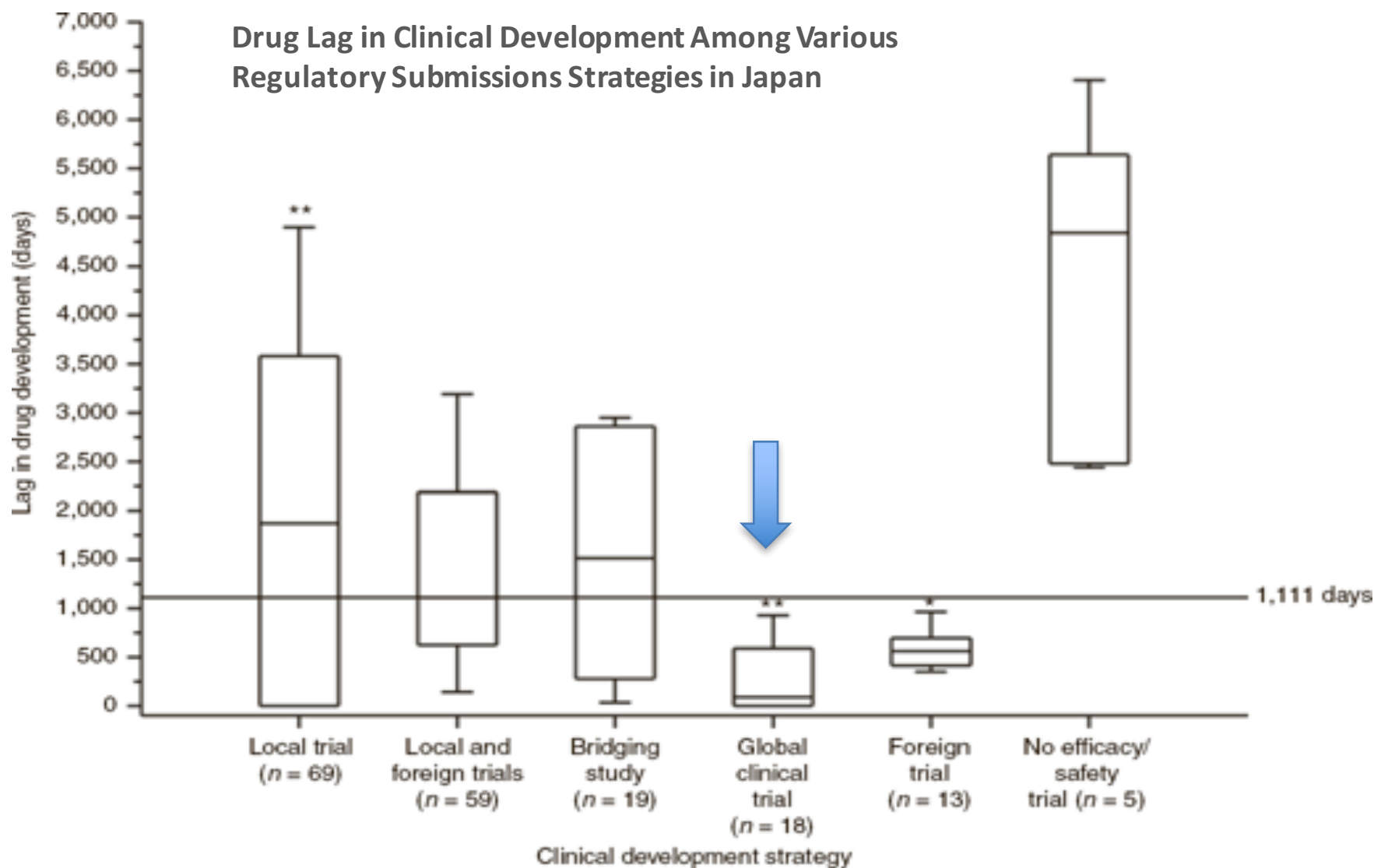




## Why MRCTs?

- More patient populations available for study
- Potentially treatment naïve individuals
- May be only practical way of accruing sufficient numbers of participants within a given time frame
- More rapid enrollment from wider population and differing clinical situations
- Potential important internal comparisons and data to defend generalization of the findings
- Simultaneous rather than sequential submissions for registration

# MRCTs Increase Efficiency and Reduce Drug Lag



# Your role as regulator is becoming increasingly complex

## MAXIMIZE BENEFIT

Bring beneficial drugs to patients  
as quickly as possible

Maintain incentives for  
companies & researchers to  
innovate

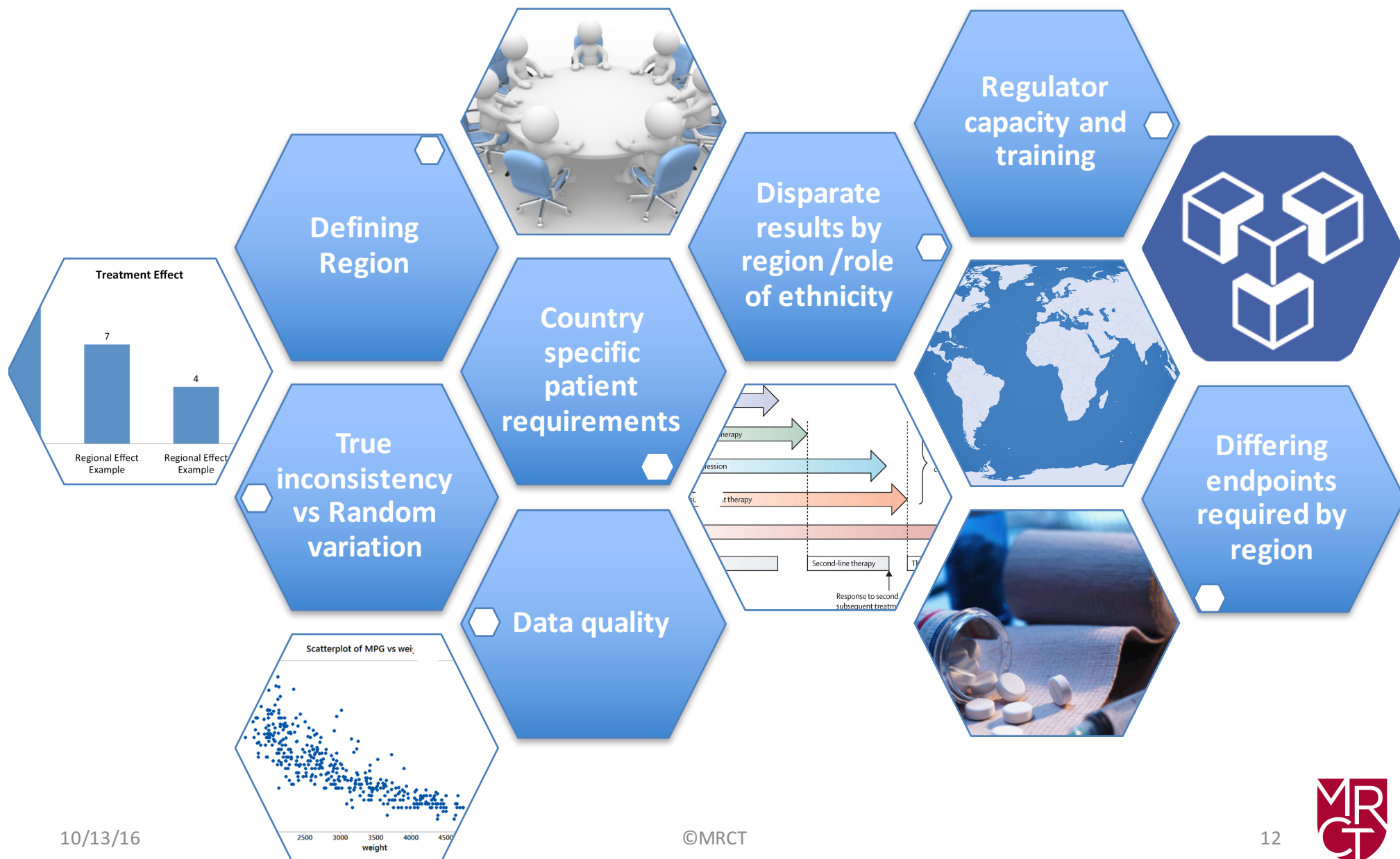
How do MRCTs fit in?

## DECREASE RISK

Ensure safety of  
patients by keeping  
ineffective/unsafe  
drugs out of the  
market

# Focus on MRCTs

## Examining the Key Issues



# MRCTs: not without precedent or guidance

- ICH-E5 Ethnic Factors in Acceptability of Foreign Clinical Data

- Bridging studies:

- Allows extrapolation of data from one region to another
    - Expedites drug development program
    - For multi-regional clinical trial to serve as a bridging study for a particular region, should be “persuasive”
    - Therefore, MRCT should be planned with sufficient numbers of subjects to have adequate power to have a reasonable likelihood of showing an effect in each region of interest
    - If to serve as bridging study, provide efficacy and safety by region, and examine consistency of effects across regions (and if dose-response relationship then efficacy and safety within and across regions.

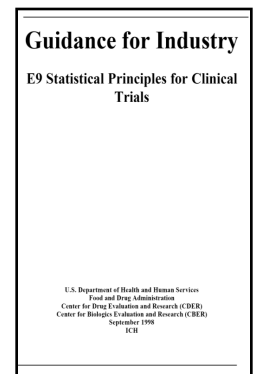
Guidance for Industry  
E5 – Ethnic Factors  
in the Acceptability of  
Foreign Clinical Data  

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Questions and Answers

# MRCTs: Precedent and Guidance

- ICH-E3 Structure and Content of Clinical Study Report
  - Individual center results should be presented when appropriate (sufficient #, etc.)
  - Treatment-by-center (country) analysis should be explored
  - “...Any extreme or opposite results among centers should be noted and discussed, considering such possibilities as differences in study conduct, patient characteristics, or clinical settings.”
- ICH-E9 Statistical Principles for Clinical Trials
  - Protocol implementation should be clear and similar at all sites
  - Procedures standardized, variation reduced
  - “...the usual sample size and power calculations depend upon the assumption that the differences between the compared treatments in the centers are unbiased estimates of the same quantity.”



# MRCT Design

- Implications for
  - Study design
  - Choice of endpoint(s)
- Particularly problematic if regulatory guidance differs as to what is acceptable study design or endpoint

If results of an MRCT are positive with acceptable benefit/risk ratio for a new drug, then further region subgroup analysis can be explored through different statistical methods depending on the level of “consistency” required.

How is “subgroup” defined?

How is consistency considered?



# Agenda MRCTs: Science, and Regulations

- Why MRCTs?
- MRCT expectations and design
- **MRCT challenges**
- International and regulatory considerations
- Rationale for acceptance of foreign country data
- Bridging study requirements



# Current Challenges Globally on the Status of MRCTs

- No clear global guidance on MRCTs
- Individual countries have published statements on topics related to MRCTs (including China)
- Use of foreign clinical data varies across countries
- Need for bridging studies or separate studies in the region's population
  - Ethnic factors and considerations (ICH 5)
  - Subgroup analysis

## MRCT: Ethnic variation vs. Random Variation (continued)

- Many of us make an *a priori* assumption of MRCTs that no or only minor regional variation exists
- No data now to predict which trials (or drugs, interventions, devices) are likely to demonstrate subgroup differences and no way to distinguish true consistency issues or ethnic variation from mere random variability.

# MRCT Challenges

- While the results of most multi-national trials do not demonstrate any internal inconsistency among regions or countries, on occasion **inconsistency between regions or countries** is observed and may be due to:
  - Inaccuracies in diagnoses or differences in natural history or stage of disease
  - Differences in medical or study practice(s) or concurrent medications
  - Differences in lifestyle, diet, or environmental influences
  - True genetic, racial, or ethnic differences among the regions
  - Random variation
  - Inconsistency at site, region or country level

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# Comparison Table for Foreign Data Acceptance

	Foreign Data	Local Participants	Data Analysis
<b>U.S.</b>	Foreign data allowed if relevant and applicable.	Not required but sometimes preferred	Recommends decreasing data variability
<b>China</b>	Accepted (except for biologics), but local data required.	Precise requirements for each phase. 100 pairs. Draft Provisions for Drug Registration issued.	Trend consistency across local and global population
<b>India</b>	Allowed except for phase I trials and vaccine trials.	Precise requirements for each phase.	No specific requirements
<b>E.U</b>	Accepted if in compliance with member and EU law.	Not required.	Intrinsic/Extrinsic factors considered when extrapolating data.
<b>Japan</b>	Accepted unless issues with local participant or data requirements.	15-20% required.	Data must be consistent across local and global population – specific methods
<b>Aus, Can, S. Africa, Brazil, Mex, Turkey, S. Korea</b>	No specific requirements	Not required	No specific requirements

# MRCTs: Asia Pacific Countries

- Simpler regulatory frameworks
  - Korea, Taiwan, Hong Kong, Singapore, Australia, New Zealand
- More rigorous requirements and procedures
  - Japan – requires specific participant numbers and consistency across global trial and locally
  - Impactful new legislation with short implementation window
    - China: IMCT application in China
    - India: Phase I allowed only if Indian company, bridging required and other regulations imposed over last 3 years

# Sample Size Requirement in New Drug Registration – China (May change with new draft legislation)

## Current China Regulatory Policies for the Registration - Interpretation

- 如果不考虑在中国注册上市: 样本量无要求  
(No requirement for sample size if not considering China registration)
- MRCT数据用于国内上市注册(首先在国外上市)  
(MRCT data and results for China registration, must be used for approval (and approved) in overseas)
  - 如果中国部分结果与总体结果一致, 则按照进口药品注册的临床试验要求  
(If China subgroup results are consistent with overall results, then China registration needs:)
    - 药代+至少100对受试者 (100 pairs + PK/PD)
  - 如果中国部分结果与总体结果不一致, 则按照适宜的桥接策略或重新进行针对中国人群的临床试验(要求具有统计显著性)  
(If China subgroup results are NOT consistent with overall results, then China registration needs a independent phase III trial with statistical significance)

# How the US FDA has evolved in Considering MRCTs

- Following ICH-E5<sup>1</sup>, FDA does not require studies that are conducted solely outside the U.S. to be performed under an Investigational New drug Application (IND) In the U.S., CFR 21.314.106 governs which foreign data are acceptable.
- local data is not needed if three criteria are met:
  - The foreign data must be “relevant and applicable” to the US population.
  - The foreign studies must be performed by competent investigators.
  - The FDA must have confidence in and the ability to validate or verify the data. <sup>3</sup>
  - An application based solely on foreign clinical data may be approved if data are applicable to the US population and medical practice.
  - The FDA may require a “bridging study” if it is concerned about the applicability of a study’s results to its population. <sup>4</sup>

1. Khin, et al. “Regulatory and Scientific Issues Regarding Use of Foreign Data in Support of New Drug Applications in the United States: An FDA Perspective,” *Nature Reviews Clinical Oncology* 2011.  
2. Food, Drugs and Cosmetics Act of 1938, most recently amended 2016  
3. 21 CFR 314.106. The acceptance of foreign data in a new drug application.  
4. Chin and Bairu, “Global Clinical Trials: Effective Implementation and Management”, Academic Press 2011



## United States FDA (Cont'd)

- Can ask for a “bridging study” if concerns about the applicability of a study’s results to its population
- In the case of clear evidence of an ethnic difference, separate trials are highly recommended so regional considerations can be incorporated into the design; the trial can be conducted to control extrinsic factors enter a study population with relatively homogenous intrinsic factors

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# FDA's review of MRCT's generally involves evaluation of study results (statistical analyses) according to region/country

- Evaluate the study data and the conduct and key metrics of quality
- Evaluate statistical displays of key sources of variation, bias and uncertainty
- Regional and site outcomes evaluated:
  - Dropouts, differences in response rates, outcomes, covariates, exposures, follow-up, concomitant drugs
- Individual patient profiles within sites - which sites and which patient records to evaluate in more detail - possible auditing strategies (usually relies on electronic records)
- Possibly intrinsic factors (markers, gender, ethnicity) or possibly extrinsic factors) recruitment patterns, medical support system, standards of care
- Align inspection with review of data and insights for audits



# What US FDA considers when encountering heterogeneity

- Interpretation of the global estimate and region and specific estimates is challenging
- Often the cause of heterogeneity (variability between regions) is unknown
- Differences in treatment effects are expected; however, too much heterogeneity is problematic
  - Are these treatment differences real and are they systematic in the sense that treatment effects are consistently better or worse in the U.S. and what are the reasons for it



# Study undertaken by FDA statisticians to evaluate possibility of systematic regional differences

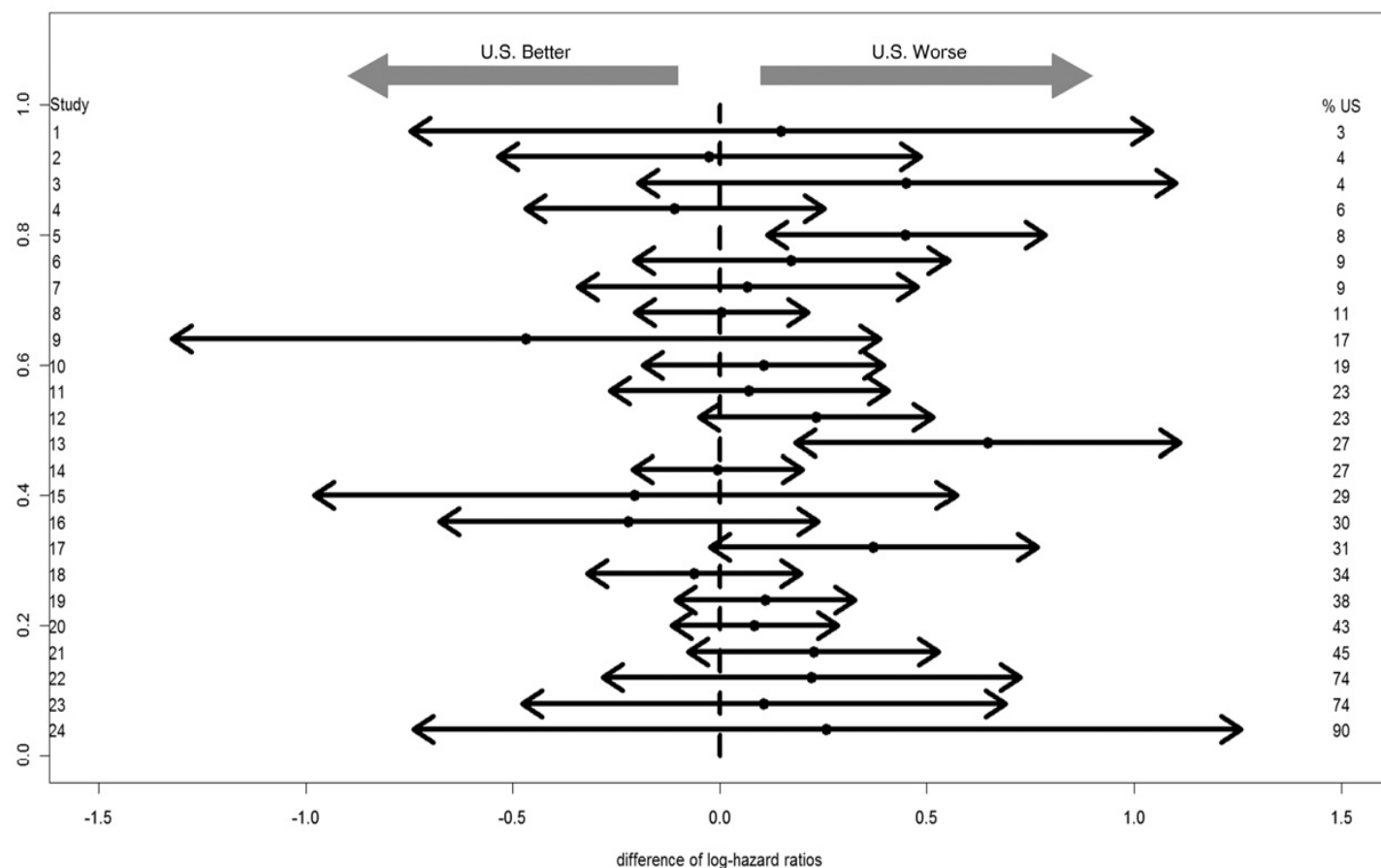
- Major cardiovascular outcome studies evaluated over the last 10 years
- Overall study result statistically positive, ie. demonstrated overall effect
- Region never pre-specified as a factor to be evaluated statistically
- 24 independent studies

CORRESPONDENCE

Research  
Correspondence

Regional Treatment Effects  
in Studies of Cardiorenal Drugs  
A Summary of Recent Clinical Trials

\*John Lawrence, PhD  
Steve Bai, PhD  
H. M. James Hung, PhD  
Robert O'Neill, PhD

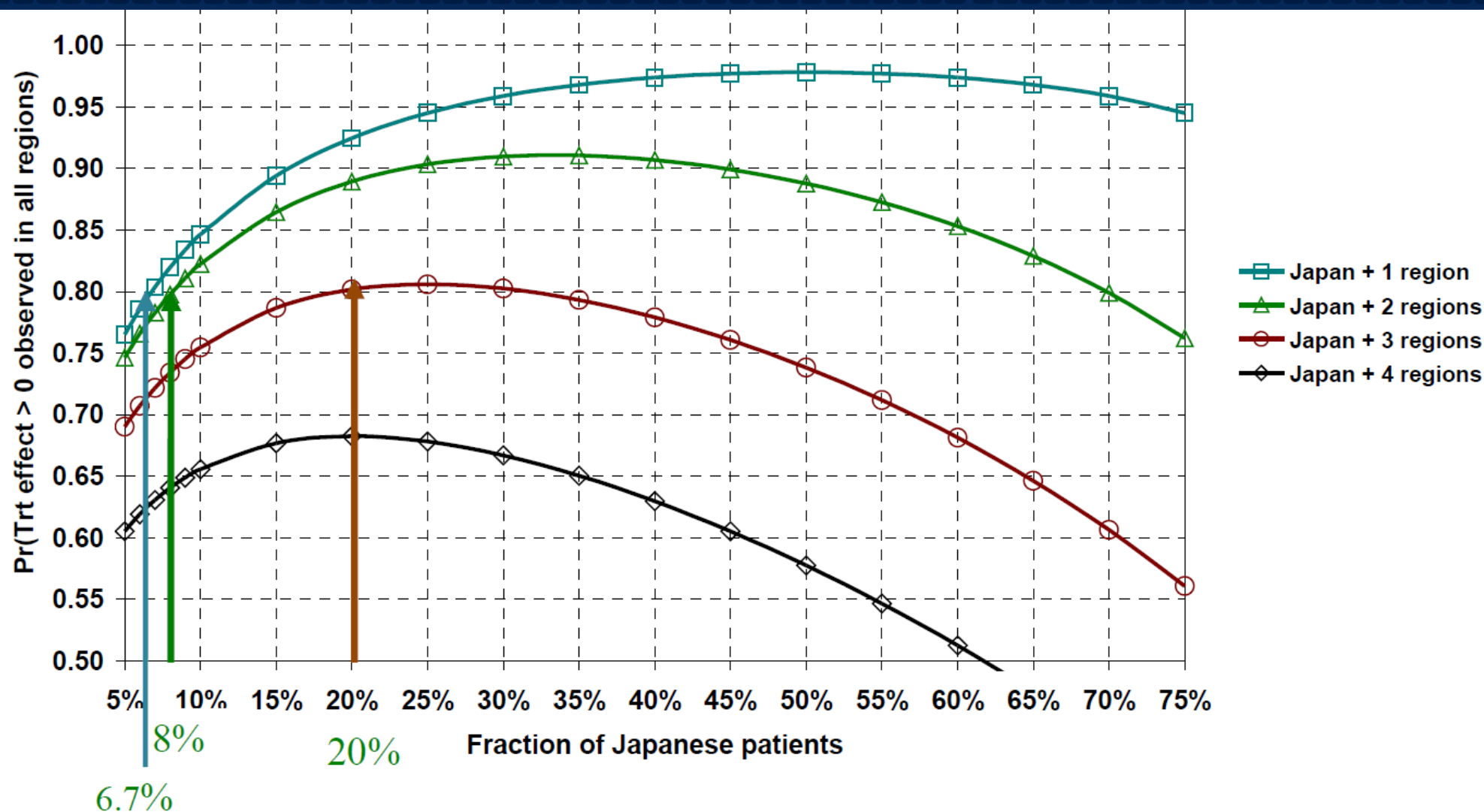


**Figure 1** Estimates and Confidence Intervals for Difference in Log-Hazard Ratio Between U.S. and Non-U.S. Treatment Effects for Each Study

Studies are listed in order from top to bottom by percent of U.S. enrollment (shown in the column on right). **Circles** indicate the point estimate of the difference between log-hazard ratios (U.S. compared with non-U.S.), and **arrows** represent the 95% confidence interval for this difference.



# “Heterogeneity” could be observed by chance



**When fraction of Japanese is 6.7%,  
negative treatment effect is observed in Japanese with probability of ~20% by chance**

Example: What should we do when difference is observed between Japanese & overall?

## Basic Principles on Global Clinical Trials (Reference Cases)

- *the reason for the difference should be considered by using data such as subgroup analysis*
  - not enough to conclude that difference is chance finding without any exploration
  - one approach could be to evaluate the difference in background characteristics between Japanese and overall population & to assess effect of the difference on efficacy results by using subgroup analysis in overall population



## An Example:

### Toprol –XL; the Current Drug Label ; “Clinical Trials”

**MERIT-HF was a double-blind, placebo-controlled study of Toprol-XL conducted in 14 countries including the US. It randomized 3991 patients (1990 to Toprol-XL) with ejection fraction  $\leq 0.40$  and NYHA Class II-IV heart failure attributable to ischemia, hypertension, or cardiomyopathy.**

**The protocol excluded patients with contraindications to beta-blocker use, those expected to undergo heart surgery, and those within 28 days of myocardial infarction or unstable angina.**

**The primary endpoints of the trial were (1) all-cause mortality plus all-cause hospitalization (time to first event), and (2) all-cause mortality.**





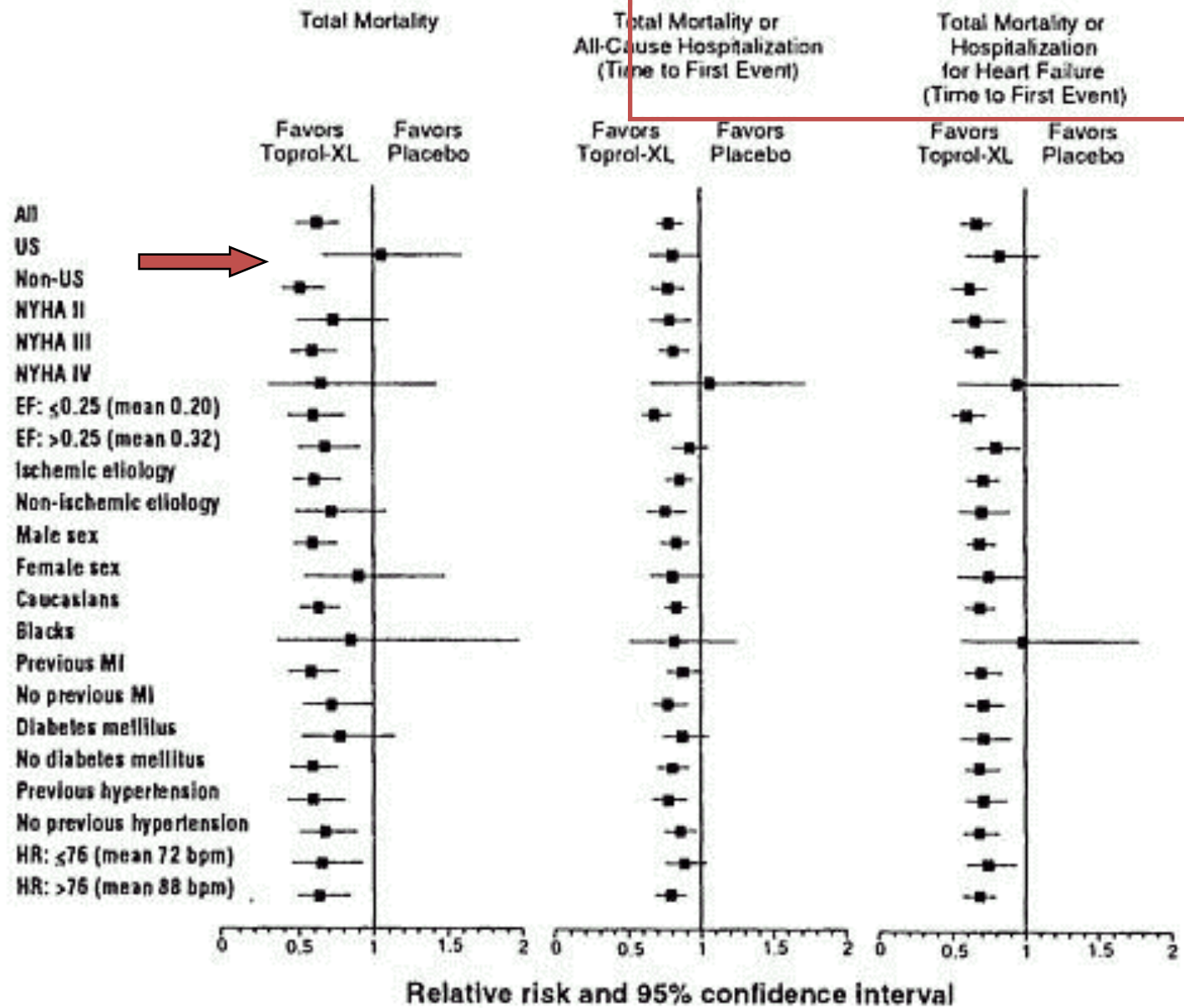
## MERIT-HF Results

*The trial was terminated early for a statistically significant reduction in all-cause mortality (34%, nominal  $p=0.00009$ ). ...*

The figure below illustrates principal results for a wide variety of subgroup comparisons, including US vs. non-US populations (the latter of which was not pre-specified). *The combined endpoints of all-cause mortality plus all-cause hospitalization and of mortality plus heart failure hospitalization showed consistent effects in the overall study population and the subgroups, including women and the US population. However, in the US subgroup and women, overall mortality and cardiovascular mortality appeared less affected. Analyses of female and US patients were carried out because they each represented about 25% of the overall population.* Nonetheless, subgroup analyses can be difficult to interpret and it is not known whether these represent true differences or chance effects.



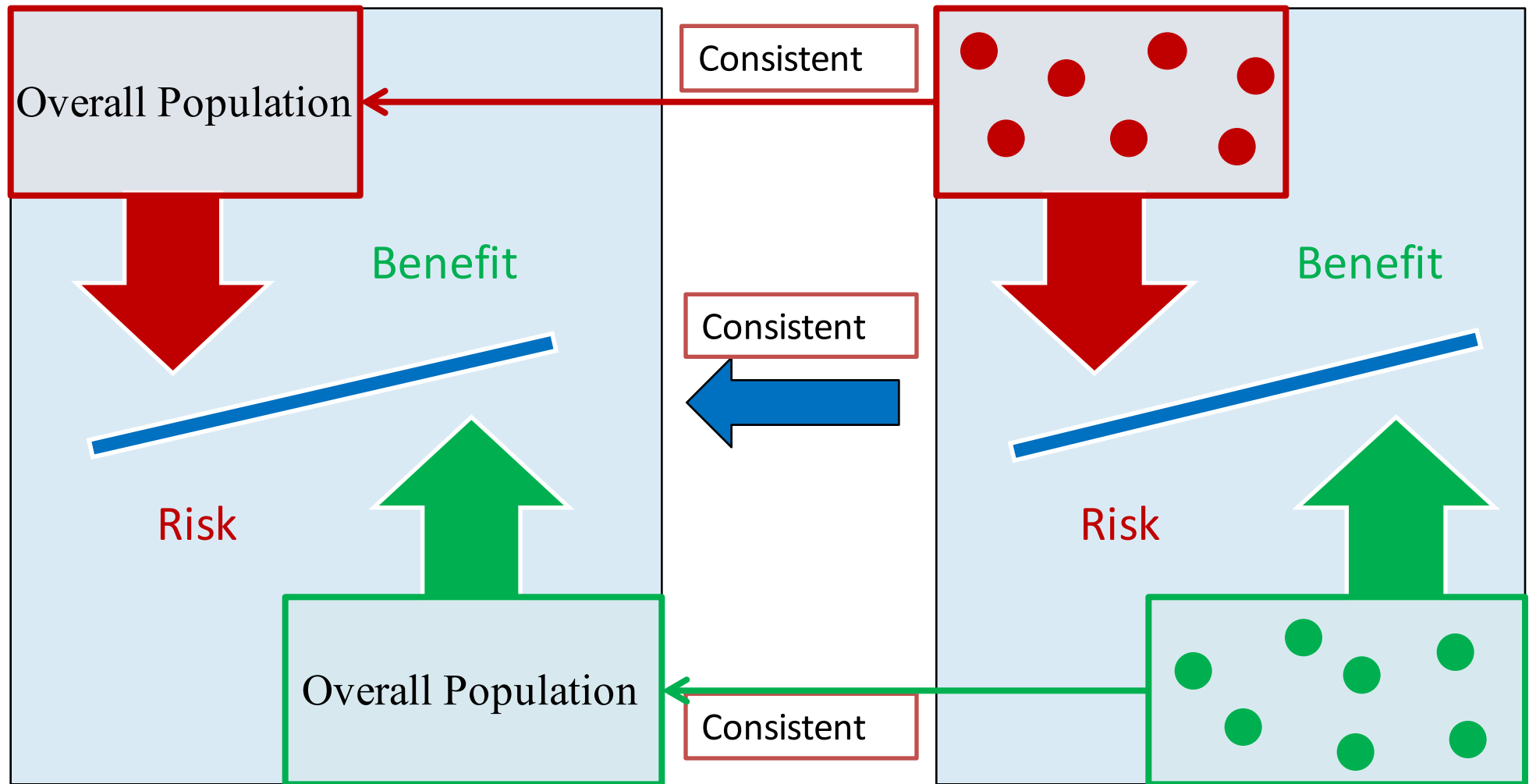
## Results for Subgroups in MERIT-HF



US = United States; NYHA = New York Heart Association; EF = ejection fraction; MI = myocardial infarction; HR = heart rate.

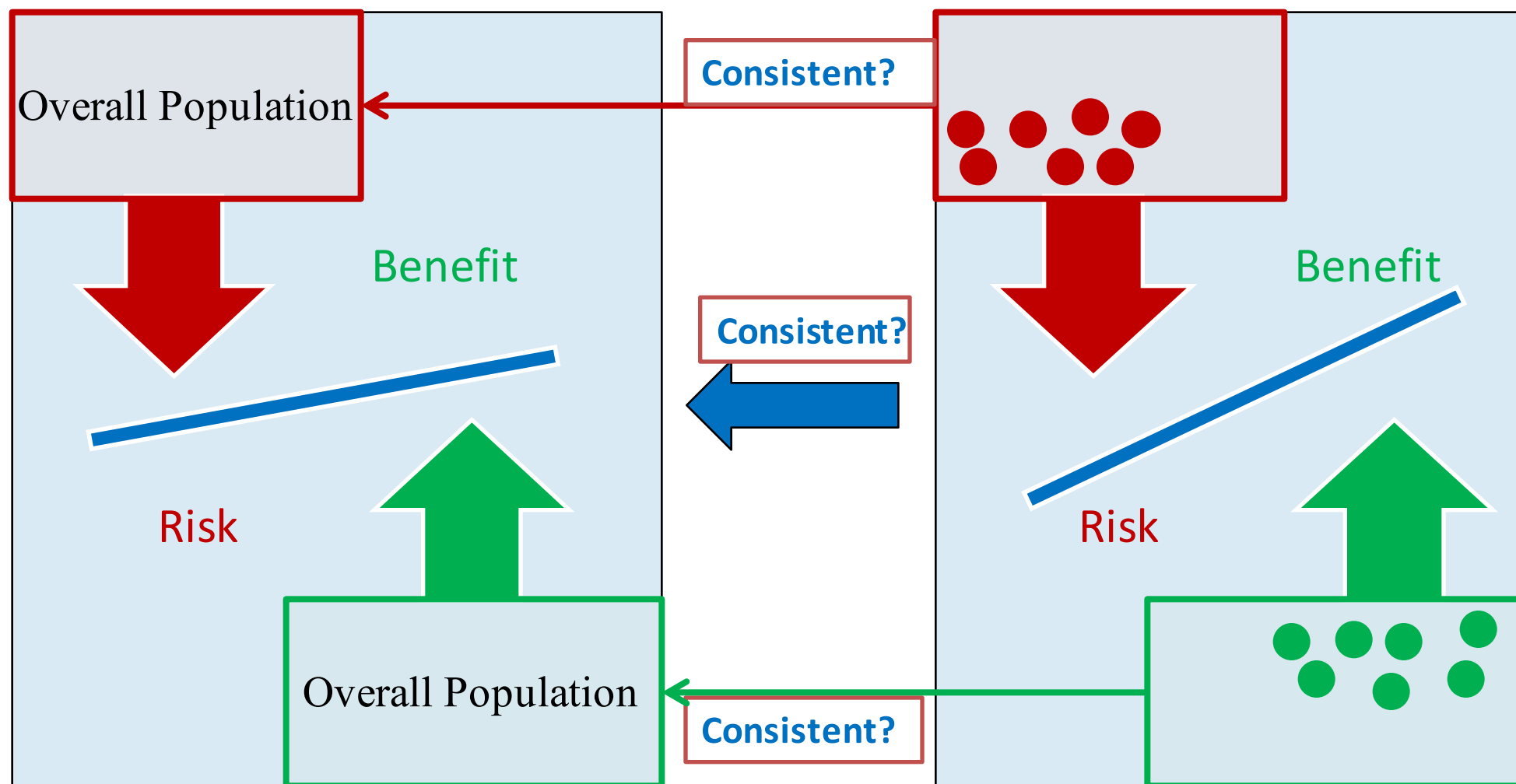
# How to Assess Consistency in an MRCT?

# “Trend” Analysis Linkage to Consistency



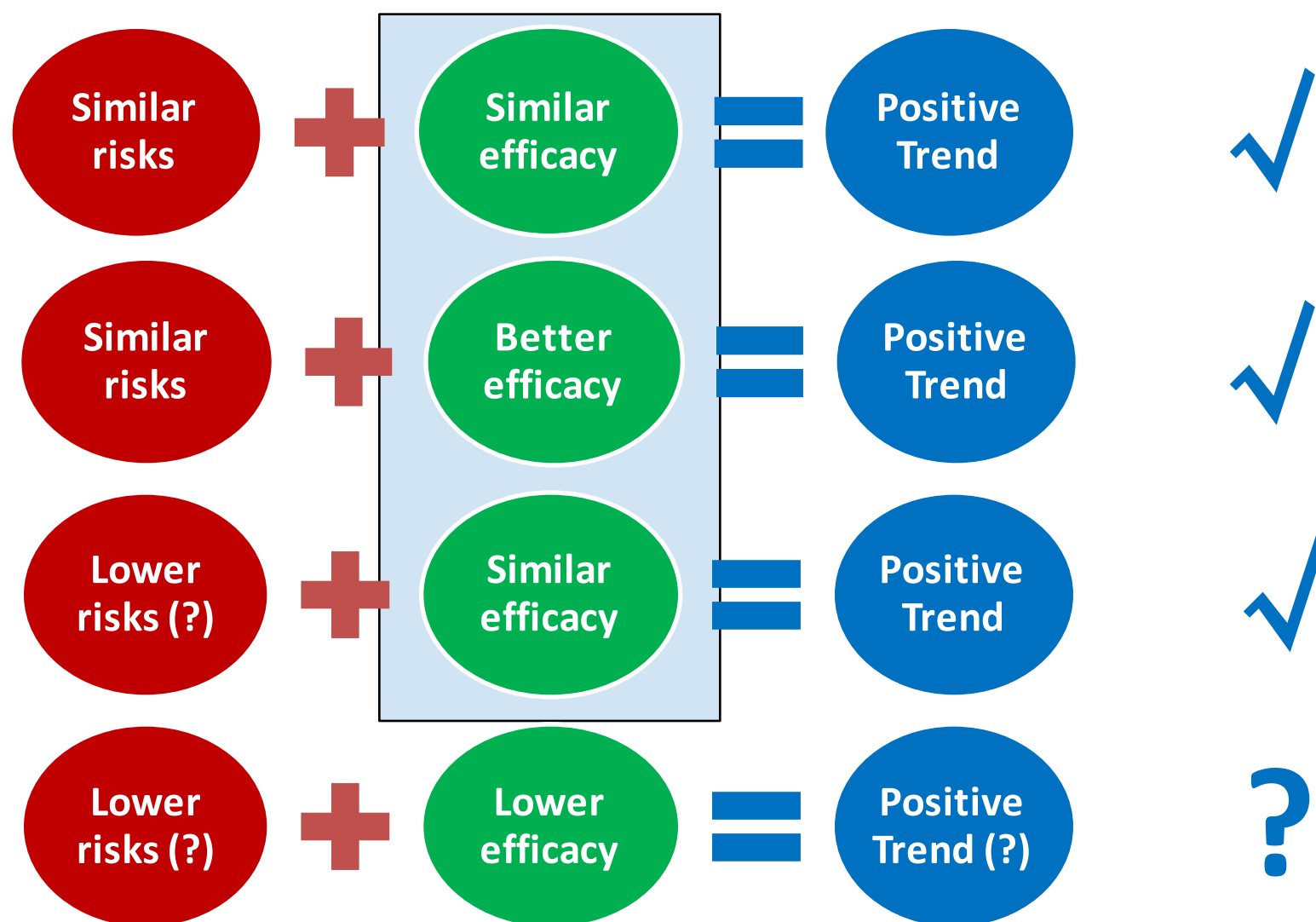
# “Trend” Analysis

## Interpretation & Elaboration - Linkage to Consistency



# “Trend” Analysis

## Interpretation & Elaboration - Linkage to Consistency



Chinese subpopulation vs. overall population in a positive trial

# Consistency Assessment in MRCT

## - Level of Consistency with Statistical Methods

# Consistency and Disease Categories

Consistency should be considered with different disease settings. Considering medical needs and potential impact of ethnic factors in clinical practice, three different disease categories may be considered:

**Category 1:** Unmet medical needs and/or rare disease

**Category 2:** Common disease without potential ethnic differences

**Category 3:** Common disease with potential ethnic differences



# Consistency and Disease Categories

Consistency should be considered with different disease settings. Considering medical needs and potential impact of ethnic factors in clinical practice, three different disease categories may be considered:

**Category 1:** Unmet medical needs and/or rare disease

—————→ Same trend required

**Category 2:** Common disease without potential ethnic differences

—————→ Treatment effect proportional

**Category 3:** Common disease with potential ethnic differences

—————→ Treatment effect in region demonstrates clinical significance with statistical rigor.

# Level of Consistency for Different Disease Categories

## Disease Category 1

- Level 1 consistency required: to assess regional treatment effect in disease with unmet medical needs, e.g., HIV/AIDS, some malignant tumor, rare disease, et al.

Equivalency

## Disease Category 2

- Level 2 consistency required: to assess regional treatment effect for common disease with no evidence of potential ethnic difference in treatment. In this setting, certain regional effect size is required

Proportionality

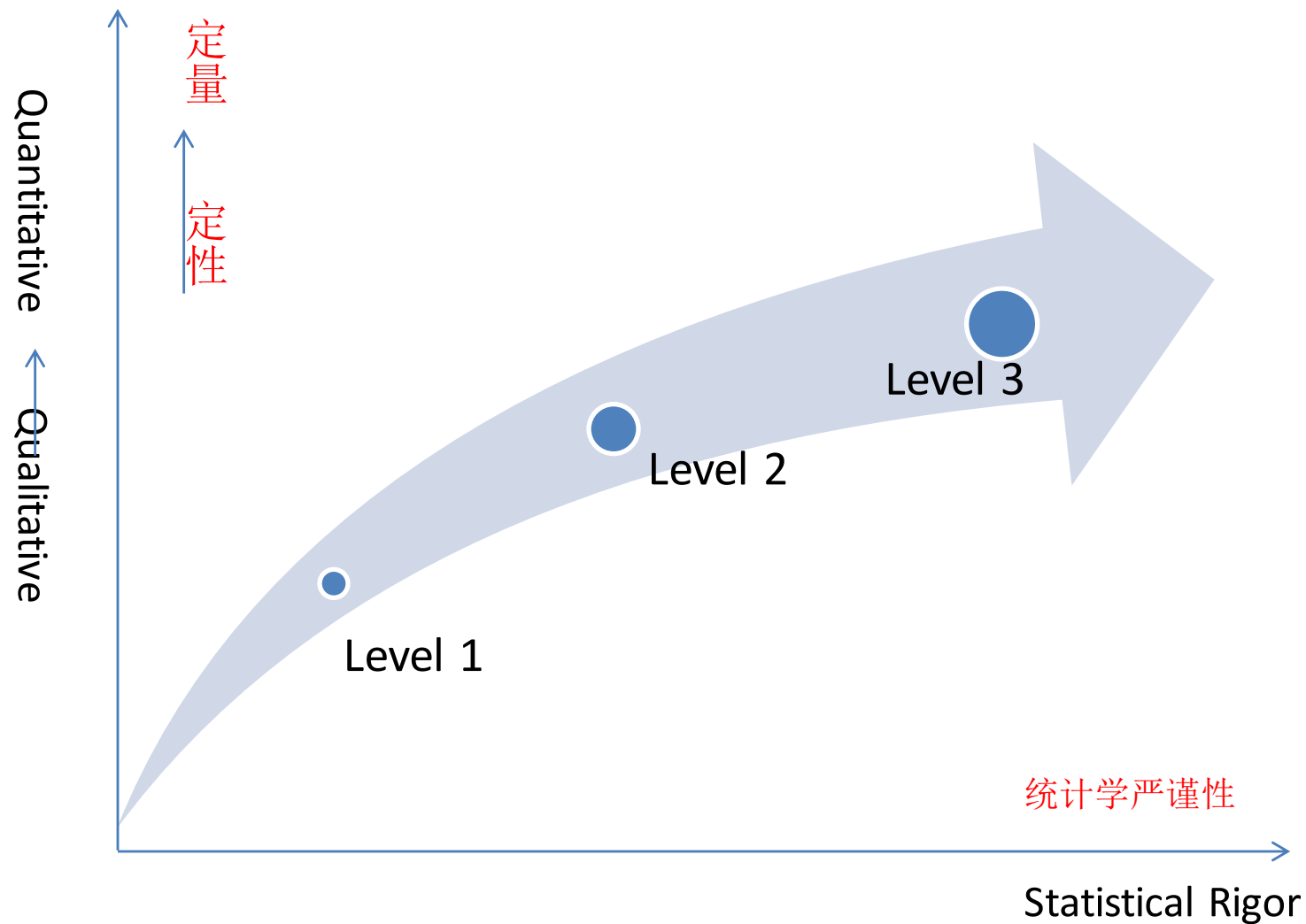
## Disease Category 3

- Level 3 consistency required: to assess regional treatment effect for common disease with evidence of potential ethnic difference in treatment. In this setting clinical significance with statistical rigor of regional treatment effect is required.

Clinical significance  
with statistical rigor

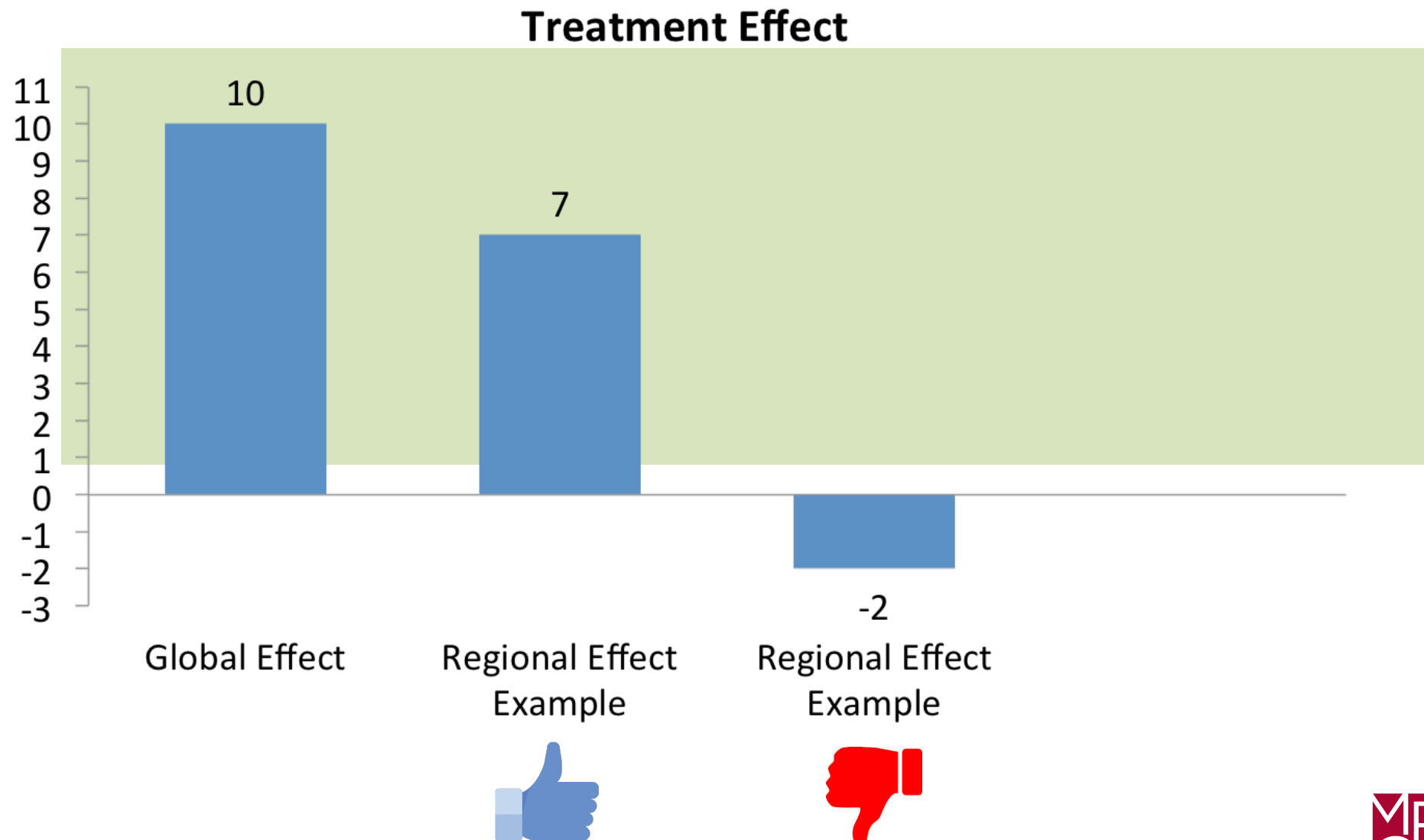


# Level of Consistency: from “weak” to “strong”

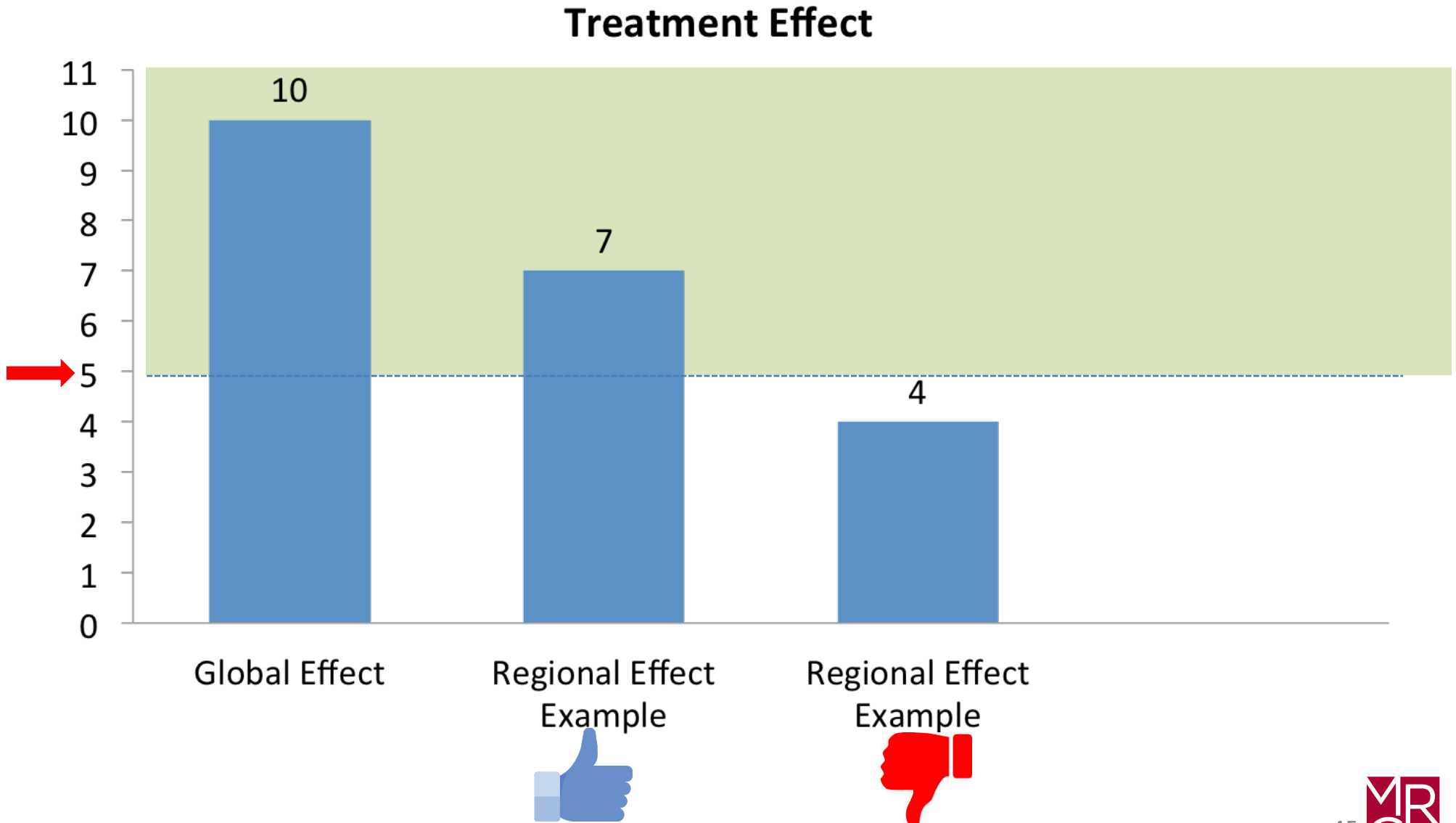


# Level 1 Consistency; Observational trend

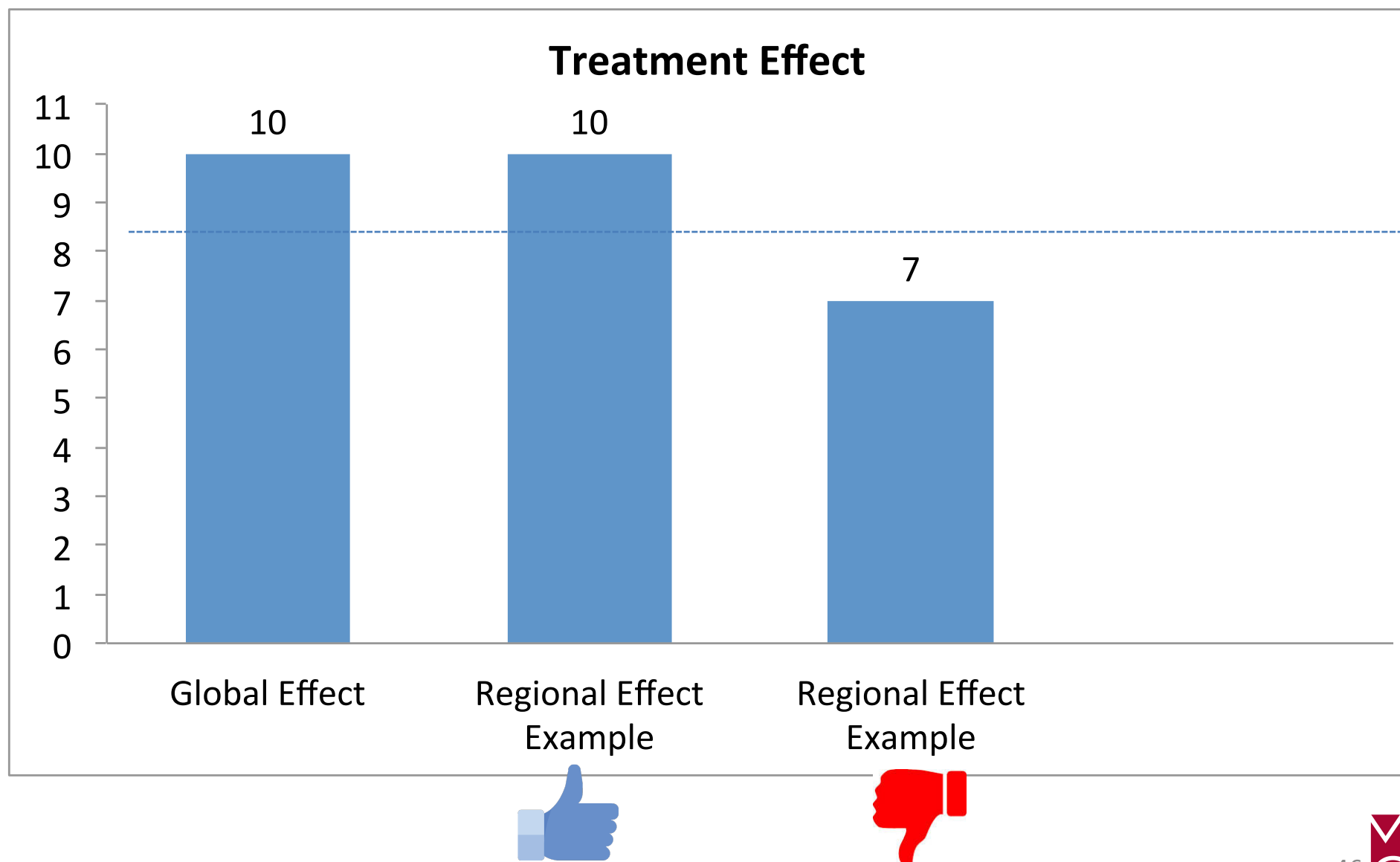
All treatment effects  $> 0$



## Level 2 Consistency, Treatment effects are proportional; At least 50% retention

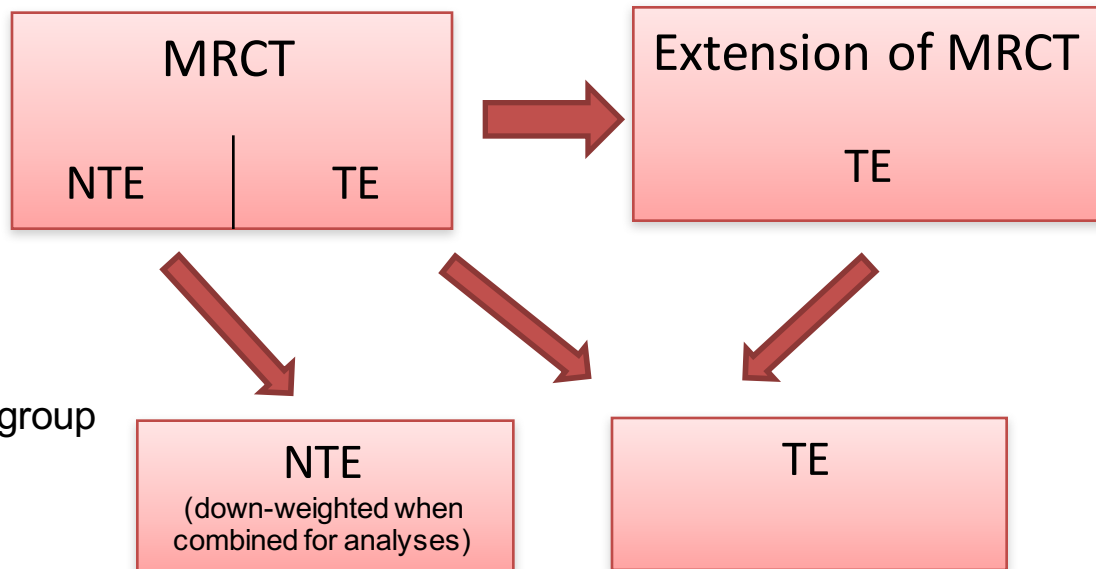


## Level 3 Consistency, Treatment effect in region demonstrates clinical significance with statistical rigor.



## Level 3 Consistency: Overall treatment effects and for region achieve clinical significance with statistical rigor

- To achieve statistical rigor for both overall and regional subgroup, use either **data within MRCT** **OR** **data from MRCT plus an extension trial**, if the sample size in the MRCT is not adequate to assess clinically meaningful treatment effect with statistical rigor.



Where:

TE: targeted ethnic group

NTE: non-targeted ethnic group

- To achieve statistical rigor for the regional results, information for the region analysis may combine both region information and the information borrowed from other regions. The information borrowed will be down-weighted

# Conclusions

## **Increasing use of MRCT design in worldwide drug development**

- To expedite simultaneous new drug development with greater patient populations
- To maintain the same level of scientific rigor in the trial design when the outcomes are presented to different regulatory agencies for evaluation
- Positive results and benefit / risk ratio of MRCT provide solid basis for the totality of evidence for a new drug registration globally

## **Opportunities**

- Continue refinement of consideration of requirements for “consistency”
- Enhance post-approval monitoring and pharmacovigilance globally
- Regulatory convergence surrounding country specific requirements for MRCTs





# MRCT – the Opportunity and Promise

- Advancing the practice of MRCTs globally will support simultaneous global submissions
  - Shifting focus from patient number requirements to a regional perspective of the total study population size driven by the study objective and overall hypothesis
  - Emphasis on regulatory decisions based on benefit-risk of disease state, patient population, unmet medical need in determination of Phase 3 requirements

# Questions for Discussion

- When conducting an MRCT with sequential participants enrolled,
  - What is the impact on the overall results?
  - Are the country/regional results alone interpretable ?
- When interpreting the regional results in MRCT
  - If variability exists, how to interpret and/or deal with it? Validity issue or Quality issue or both?
    - Extrapolation of treatment effects to China population with heterogeneity ( *Quantitative and Qualitative*) of treatment effects among regions/Countries.
    - Interpretation of treatment effects: which factor (s) most important to evaluate relationship of treatment effects: Site/center/clinic, Country , Region?

Thank you