ICH
harmonisation for better health

Module 6
Evaluation of consistency

ICH E17: General principles for planning and design of Multi-Regional Clinical Trials

International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

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Outline

- What is consistency?
- Why is a consistency evaluation necessary?
- How should a consistency evaluation be done in an MRCT?
- Examination of regional consistency
- Case study: the PLATO trial
- Concluding remarks

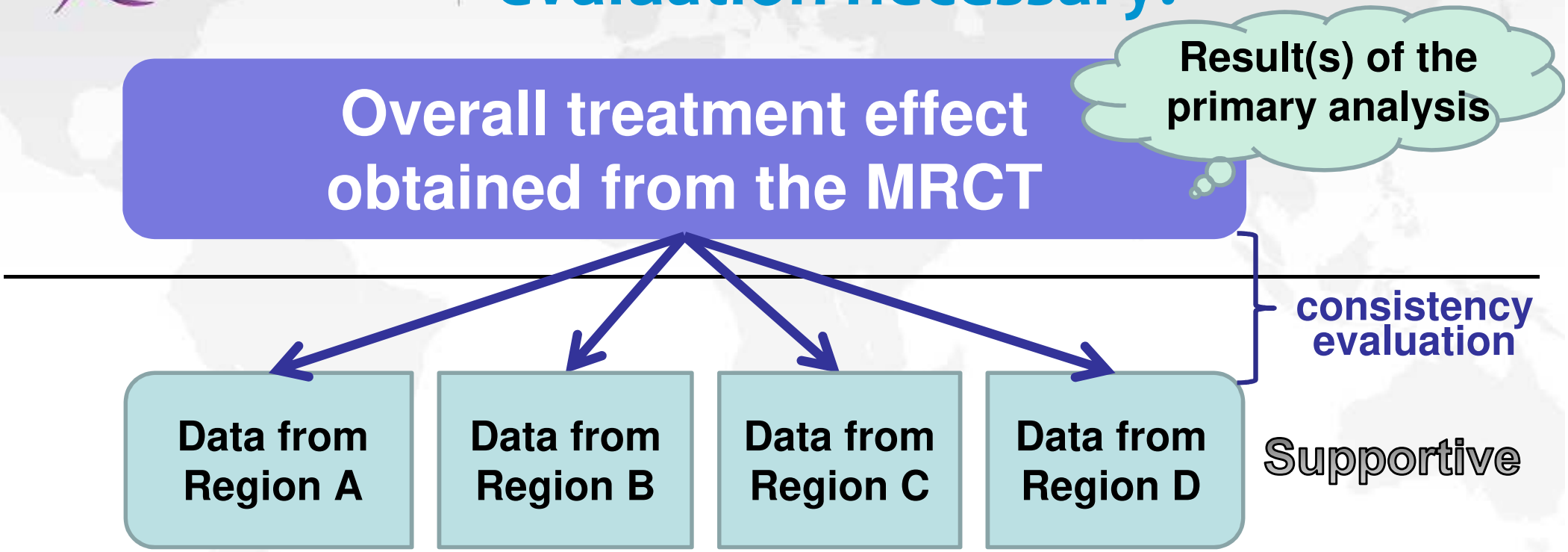
What is consistency?

Absence of clinically relevant differences between treatment effects in different regions or subpopulations of an MRCT

Clinically relevant difference should be considered depending on

- ✓ **Intended indication**
- ✓ **Endpoint**
- ✓ **Anticipated treatment effect**

Why is a consistency evaluation necessary?



- ✓ E17 guideline is intended to increase the acceptability of MRCTs in global regulatory submissions
- ✓ To achieve this objective, a consistency evaluation should be planned to assure that the treatment effect applies particularly to the regions included in the MRCT
- ✓ Planning of a consistency evaluation will impact many design factors including stratification, sample size allocation (see Module 4), and pooling strategies (see Module 5)

How should a consistency evaluation be done in an MRCT?

- **A structured exploration of regional differences should be planned**
  - Intrinsic and extrinsic factors which may affect the treatment effect (see Module 2) should be identified and evaluated by region
- **The potential eventualities of the trial results should be carefully considered at the planning stage**
  - These may include expected and/or unexpected potential differences across regions
  - This consideration is to ensure a comprehensive evaluation and to minimize unnecessary post-hoc analyses
- **Evidence for consistency of treatment effects across regions should be evaluated holistically**

Examination of regional consistency

A strategy for structured exploration of regional differences should be planned

Known Known

- Factors known a priori to be prognostic or predictive (i.e. intrinsic and extrinsic factors which may affect the treatment effect)
- Predefined in the protocol, focusing on pooled and/or stratified subpopulations

Known Unknown

- Unexpected differences with regard to known factors
- May be predefined in the protocol, including subgroup analyses defined by traditional demographic (e.g. race, age, gender) and baseline factors

Unknown Unknown

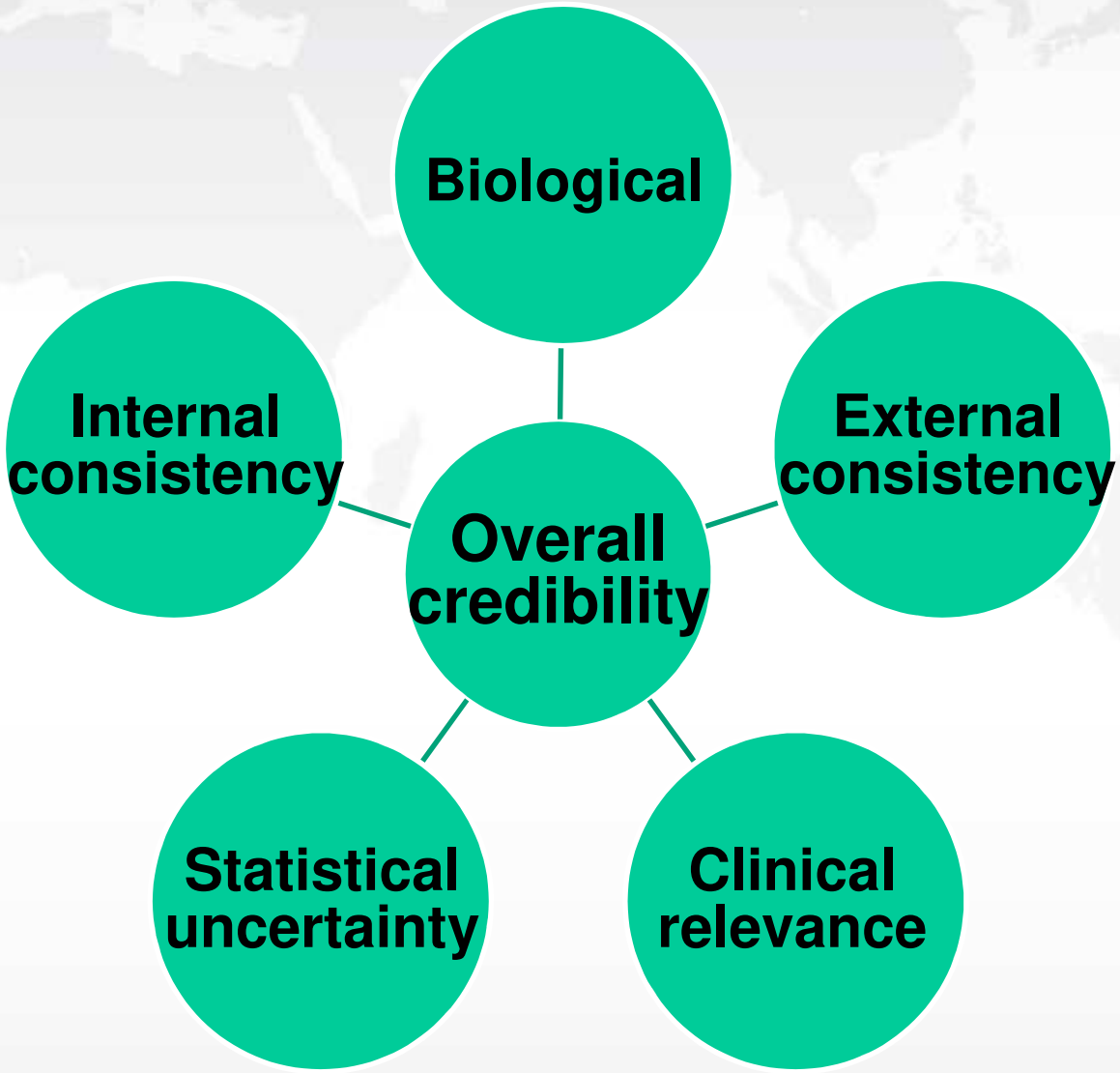
- Unexpected differences with regard to unknown factors
- Further post-hoc investigation
- May include additional data

Examination of regional consistency (continued)

Known Known
- Factors known *a priori* to be prognostic or predictive

Known Unknown
- Unexpected differences with regard to known factors

Unknown Unknown
- Unexpected differences with regard to unknown factors

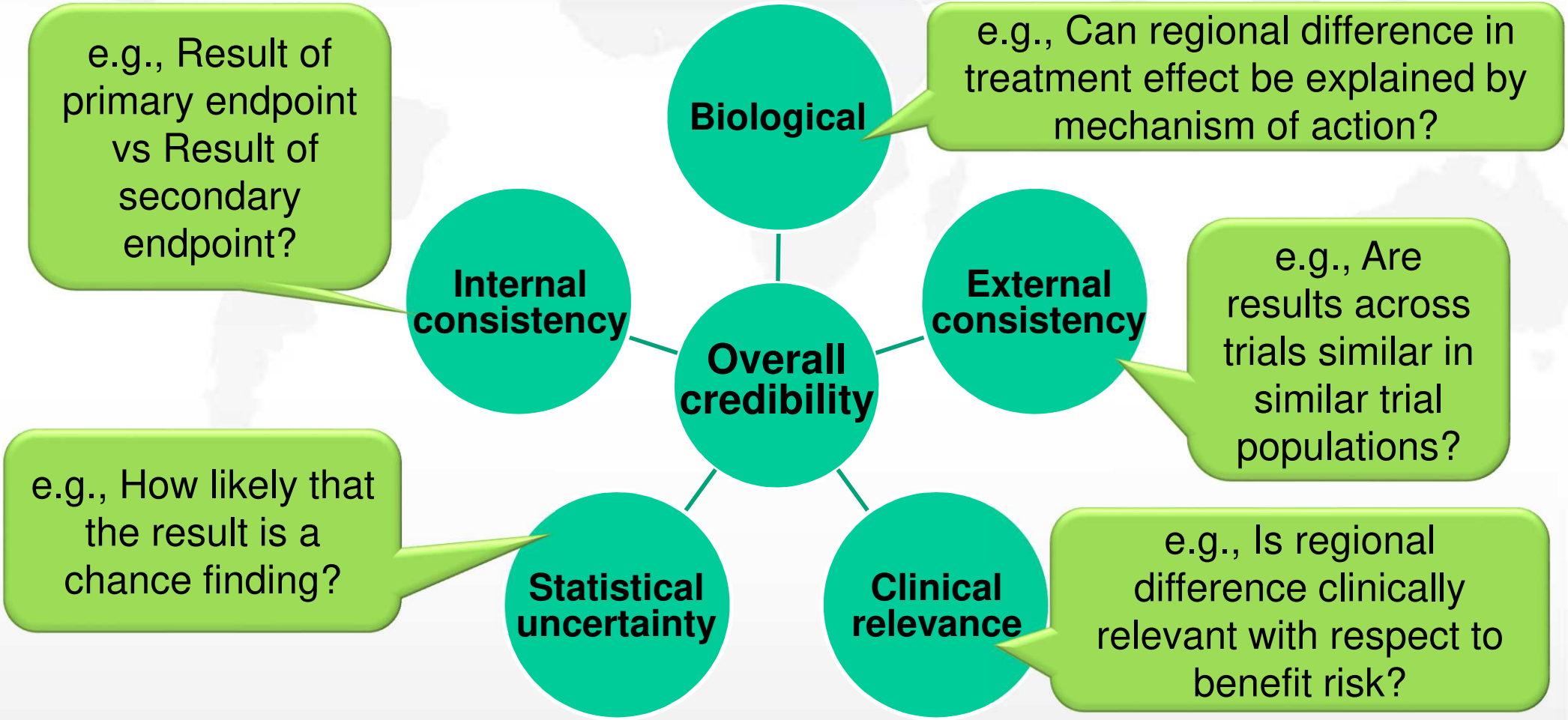


These eventualities should be carefully considered at the planning stage.

Consistency should be evaluated holistically

[Section 2.2.7 Statistical Analysis Planning]

The assessment of consistency of treatment effects should be done with diligence to inform regulatory decision-making.



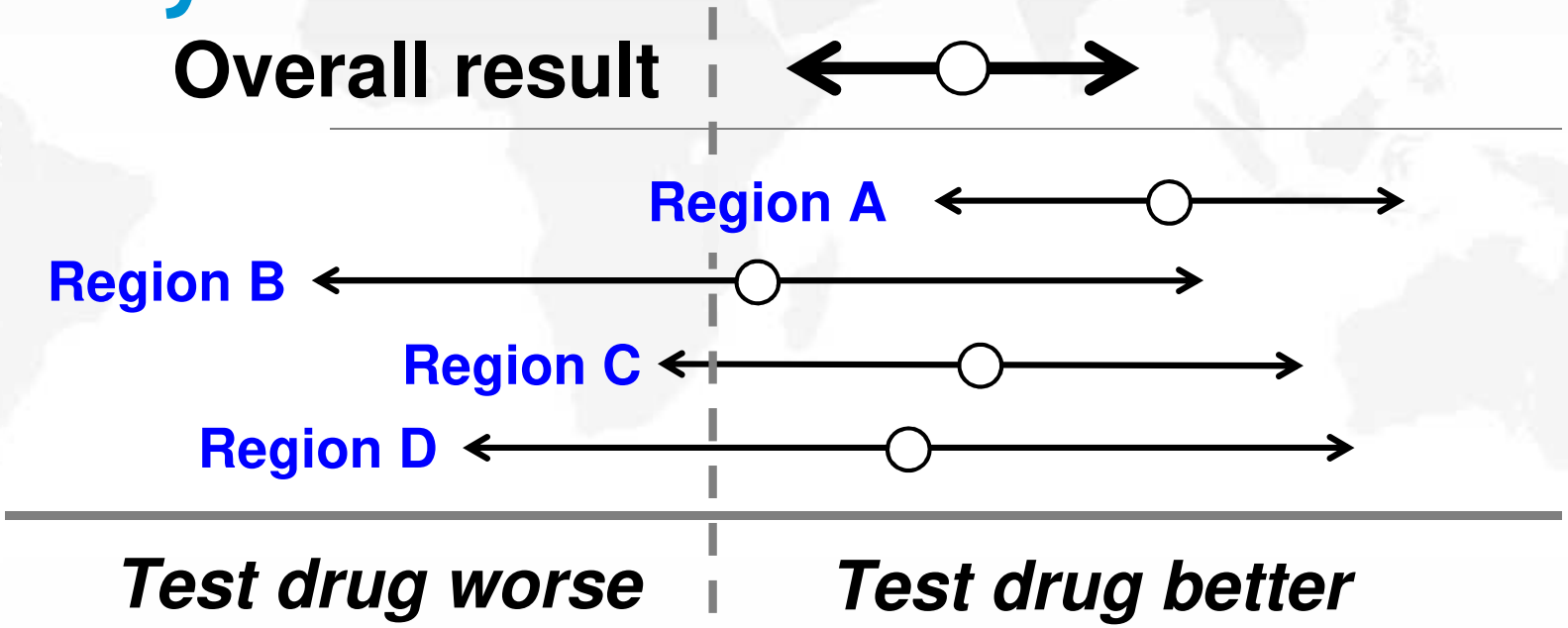
The more the aforementioned considerations support a potential finding, the greater the likelihood the finding is not false.

Examination of regional consistency

Evaluation of regional consistency is NOT hypothesis testing, but a supportive and/or descriptive investigation, whether prior assumptions hold true.

- Descriptive summaries
- Graphical displays (e.g., forest plots)
- Model-based estimation (including covariate-adjusted analysis)
- Test of treatment-by-region interaction as a method for signal generation

Graphical evaluation of regional consistency



After we achieve “significance“ of the overall result, an additional question is important:

Is there evidence that the overall result does not apply to all regions?

➔ Holistic evaluation is needed

Linking regional variability, sample size allocation, pooling and consistency evaluation

Proactively understand intrinsic and extrinsic factors which may affect the treatment effect, prioritize the importance of these factors for each specific drug development programme (Module 2)

Power the primary hypotheses with proper planning of overall sample size, accounting for variabilities across regions and subpopulations (Module 4)

Define pooled regions and subpopulations for design considerations regarding stratification and randomized allocation (Module 5)

Allocate sample size to the pooled regions and subpopulations based on the balanced approaches and priorities (Module 4)

Plan the consistency evaluation by pre-specified pooled regions and subpopulations, then, as needed, examine consistency holistically (Module 6)

Consistency evaluation in relation to regional variability, sample size allocation, and pooling

Consistency evaluation and Regional variability (Module 2)

- Identify and prioritize intrinsic and extrinsic factors, which may affect the treatment effect. This enables a structured evaluation of consistency
- The regional difference of treatment effect may be explained by difference in regional distribution of intrinsic and extrinsic factors

Consistency evaluation and Sample size allocation (Module 4)

- Proportional allocation to regions according to disease prevalence enables faster recruitment, while equal allocation optimizes the likelihood of detecting inconsistency; a balanced approach is needed
- Sample size allocation to a specific region based on preservation of effect or local significance may inflate overall sample size, and is not practical

Consistency evaluation and Pooling strategies (Module 5)

- The chance of inconsistent findings may increase with number of regions
- Pooling across regions based on intrinsic and extrinsic factors known to potentially affect the treatment effect may reduce the chance of such findings, but also reduces the chance of detecting true inconsistent findings
- It is important to balance these considerations

Case study: the PLATO trial

- **This case example is to illustrate:**
  - identification of intrinsic and extrinsic factors that could potentially explain regional differences: Slides #18, 19
  - structured approach to better understand the observed regional heterogeneity: Slides #17-20
  - various analytical approaches to evaluate consistency: Slides #17, 19, 20

PLATO trial

Design of The PLATO (Platelet Inhibition and Patient Outcomes) trial:

Phase Ⅲ multi-regional, randomized, double-blinded, double-dummy, parallel group

Superiority hypothesis:

Ticagrelor is superior to Clopidogrel in the prevention of cardiovascular events in patients with acute coronary syndrome (ACS)

Primary endpoint:

A composite of cardiovascular death, myocardial infarction (MI), and stroke

Clopidogrel	**Ticagrelor**
(+Placebo, matched to Ticagrelor) Loading Dose: 300 mg Maintenance Dose: 75 mg x1/day	(+Placebo, matched to Clopidogrel) Loading Dose: 180 mg Maintenance Dose: 90 mg x2/day
[Concomitant medication] Aspirin (ASA) Loading Dose: 160-500 mg (if applicable) Maintenance Dose: 75-100 mg/day; up to 325 mg/day after stent replacement	

Efficacy results, overall

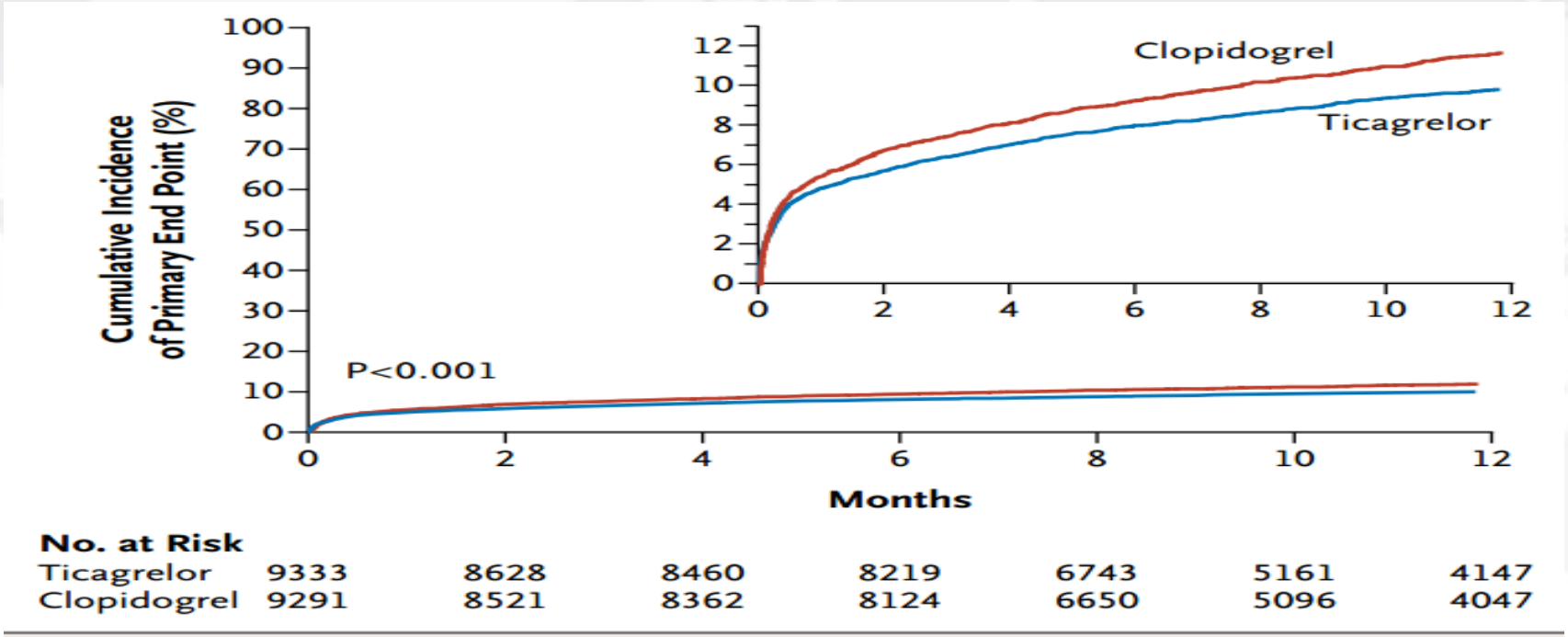


Figure 1. Cumulative Kaplan–Meier Estimates of the Time to the First Adjudicated Occurrence of the Primary Efficacy End Point.

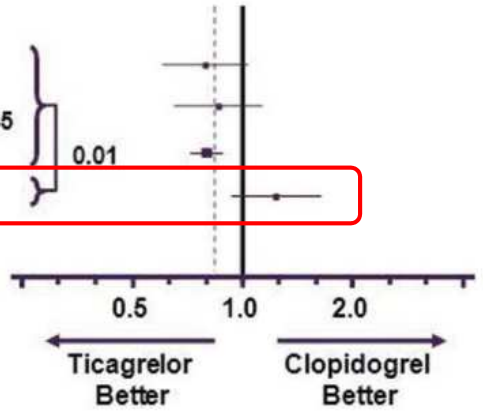
		Cumulative Incidence of Endpoint, Ticagrelor vs Clopidogrel (%)
Primary Endpoint Met?	Yes	9.8% vs 11.7% (H.R. 0.85; 95% CI 0.77-0.92; p<0.001)
Main Secondary Endpoint Met? (Patients with planned surgery)	Yes	8.9% vs 10.6% (p=0.003)

Superiority of Ticagrelor to Clopidogrel was demonstrated

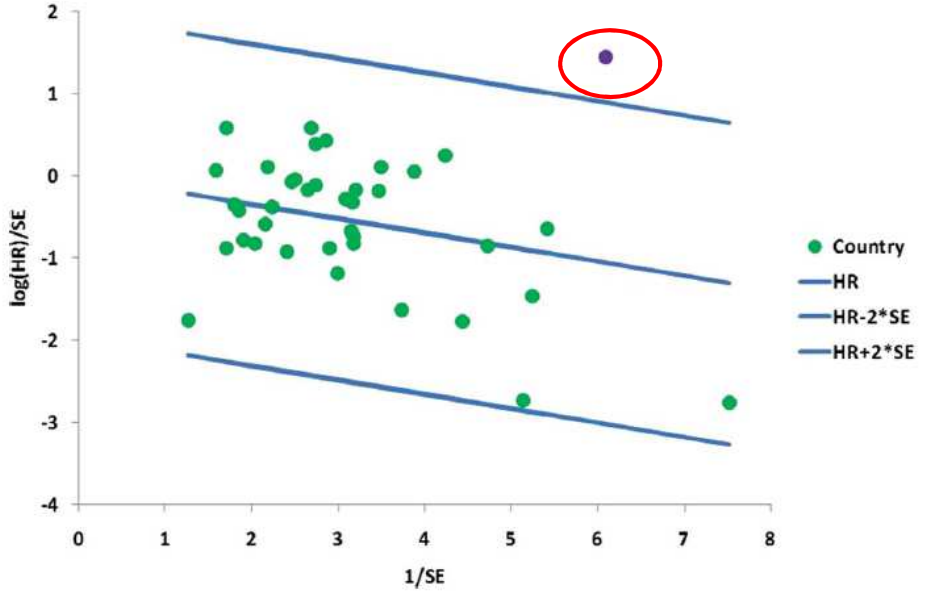
https://www.fda.gov/AdvisoryCommittees/Calendar/ucm214252.htm

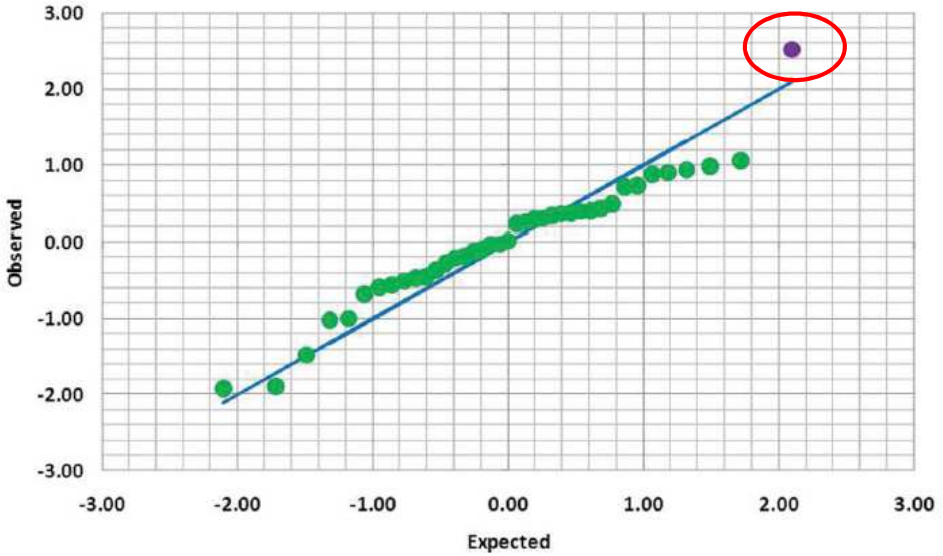
Efficacy results, by subgroup

Characteristic	Total Patients	KM at Month 12 Tic	KM at Month 12 Clop	HR (95% CI)	Interaction p-values
Geographic Region					
Asia / Australia	1714	11.4	14.8	0.80 (0.61, 1.04)	0.045
Cent / Sth America	1237	15.2	17.9	0.86 (0.65, 1.13)	
Euro / Md E / Afr	13859	8.8	11.0	0.80 (0.72, 0.90)	0.01
North America	1814	11.9	9.6	1.25 (0.93, 1.67)	



The results of the subgroup analyses show the inconsistency across pre-defined regions

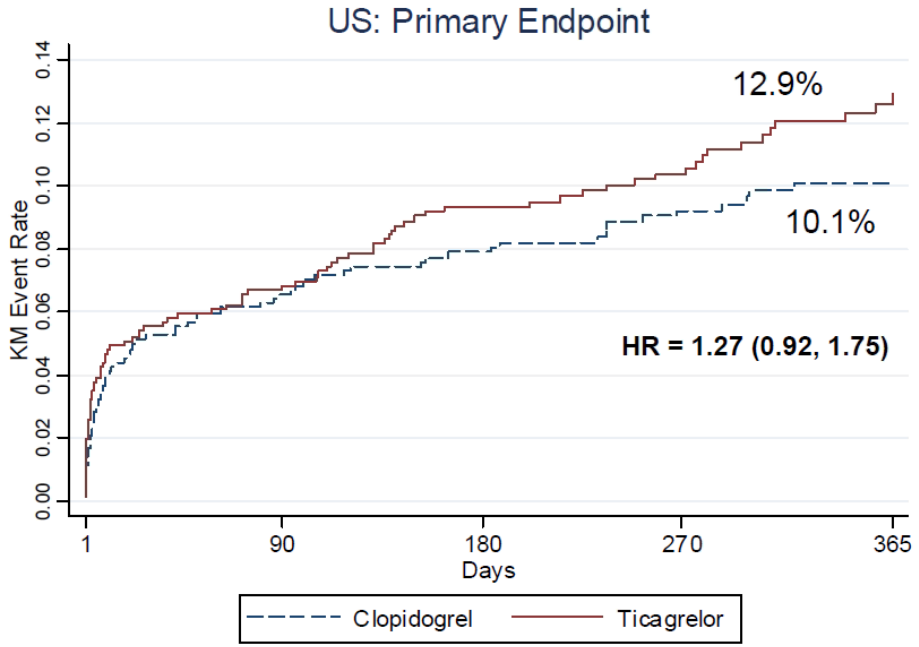




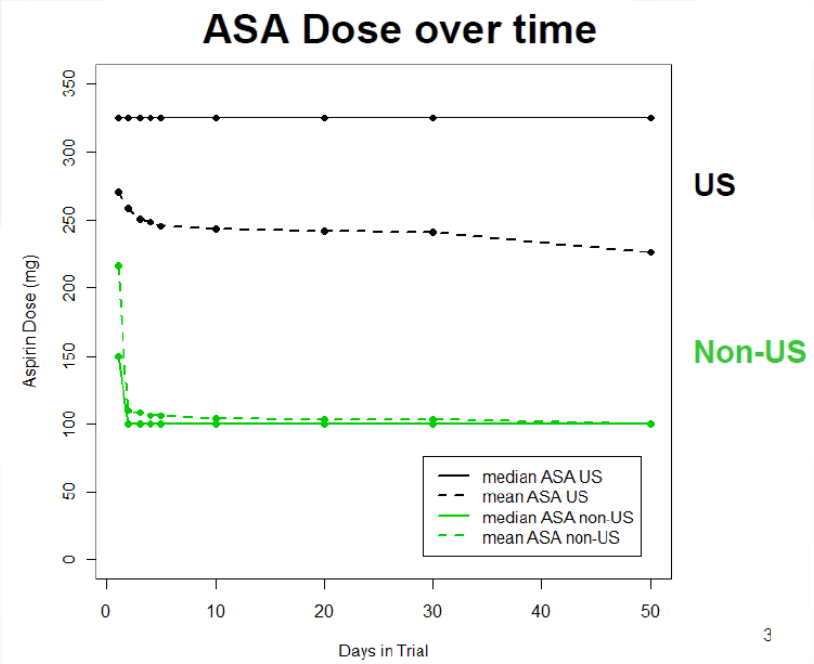
Kevin J. Carroll & Thomas R. Fleming (2013) Statistical Evaluation and Analysis of Regional Interactions: The PLATO Trial Case Study, Statistics in Biopharmaceutical Research, 5:2, 91-101.

Imbalances that might explain the US vs Non-US regional interaction

In the US, event rates in the Ticagrelor group start surpassing event rates in the Clopidogrel group by 150 days of treatment , the exact opposite of what is observed in the rest of the world.



The mean and median aspirin doses (ASA) throughout the trial were significantly higher in the US population than in the non-US populations.



https://wayback.archive-it.org/7993/20170405212359/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM221383.pdf

Internal consistency: impact of aspirin dose by regions

Region	ASA Dose (mg)	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
US						
	>=300	324	40	352	27	1.62 (0.99, 2.64)
	>100 – <300	22	2	16	2	
	<=100	284	19	263	24	0.73 (0.40, 1.33)
Non–US						
	>=300	140	28	140	23	1.23 (0.71, 2.14)
	>100 – <300	503	62	511	63	1.00 (0.71, 1.42)
	<=100	7449	546	7443	699	0.78 (0.69, 0.87)

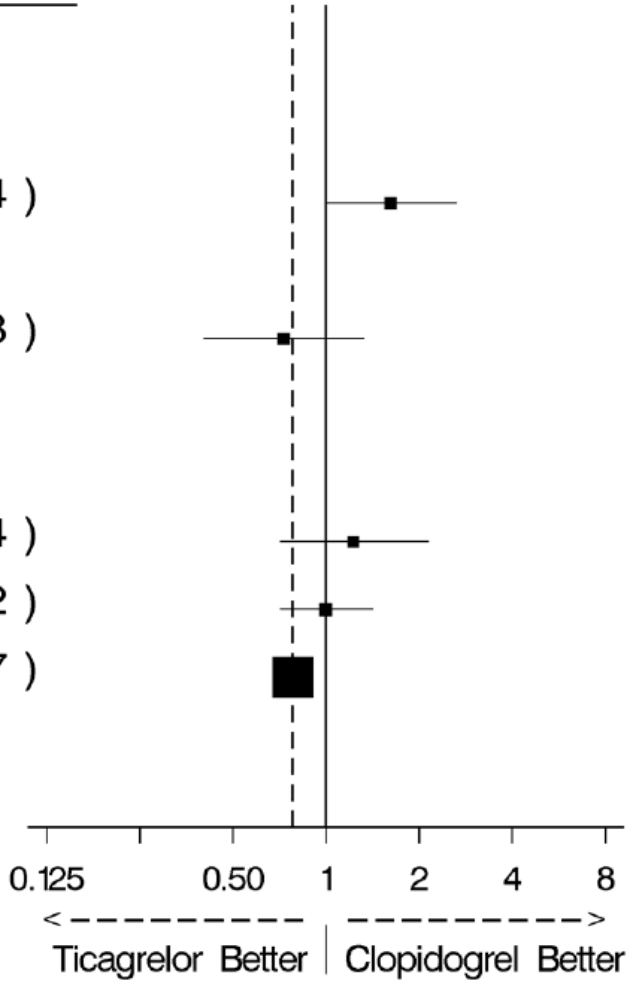
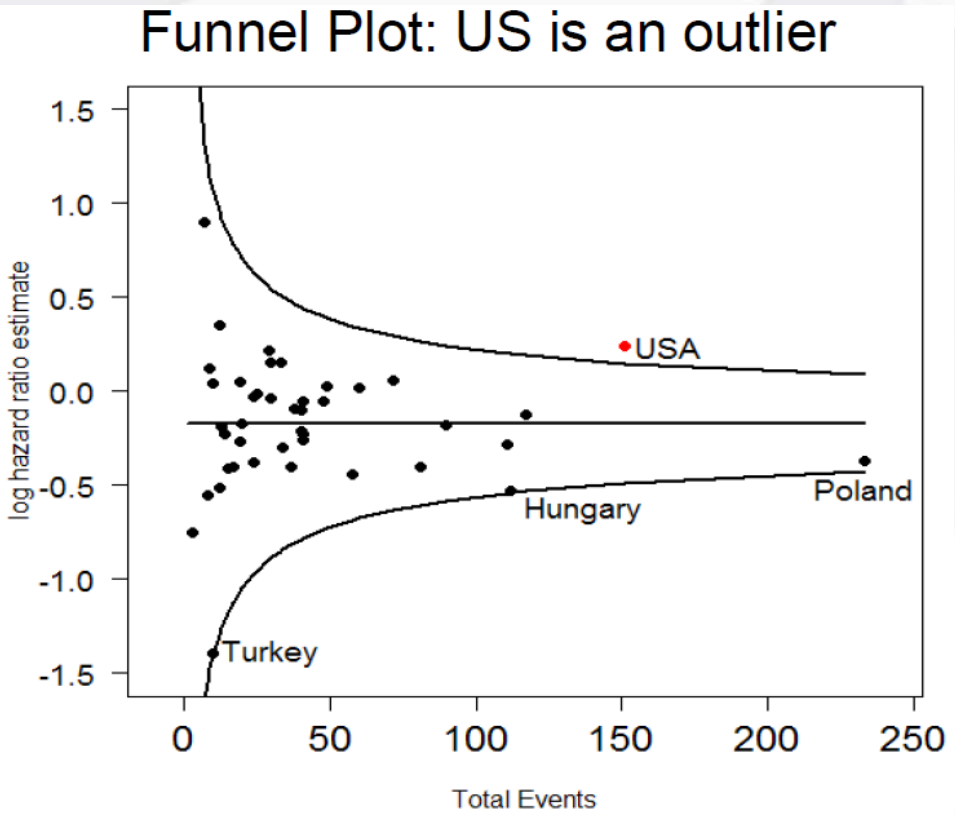


Figure 19 of the AZ briefing document

https://wayback.archive-it.org/7993/20170405212347/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM220197.pdf

Graphical evaluation of regional consistency: statistical uncertainty



A Play of Chance?

- Total primary events: 1878 (151 in US)
- Treatment-by-US interaction is significant (p=0.0095)
- 3 countries had estimated HR ≥ 1.27
  - Australia (N=92), Taiwan (N=83) and US (N=1413)
- P(HR≥1.27 in US | true HR=0.84) < 0.006

Although US is an outlier in the funnel plot, it is still possible that this observation could be due to play of chance.

https://wayback.archive-it.org/7993/20170405212359/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM221383.pdf (accessed May 19 2019)

Learning from the PLATO case study

- **Design:**
  - 4 geographical regions were pre-defined, pooling from 43 countries.
  - Sample size was somewhat balanced across regions, so that exploration of consistency was possible
  - Effect of Aspirin maintenance dose was not known *a priori*. If the use of Aspirin was known to be a potential predictive factor, stratification of the trial by the Aspirin dose or restriction to low dose Aspirin may have been considered.

Learning from the PLATO case study

- **Consistency assessment in the PLATO trial follows a structured approach described in the E17:**
  - 31 pre-specified subgroup analyses were performed by intrinsic and/or extrinsic factors and by regions. These analyses showed the treatment was largely consistent across these factors, except regions
  - Subgroup analyses by region utilized various approaches to evaluate consistency across regions:
    - Descriptive summaries
    - Graphical plots (e.g., Forest plots, QQ plots)
    - Treatment-by-region interaction

Learning from the PLATO case study

- **Unfortunately, pre-specified analyses didn't reveal plausible reasons for the regional differences.**
- **A holistic evaluation was performed to better understand the observed regional heterogeneity**
  - Study Conduct
  - Internal Consistency: Impact of ASA dose, across US and non-US regions
  - Statistical Uncertainty (i.e., Play of chance)
  - Biological Plausibility

Epilogue of the PLATO trial

- **Special warning on Aspirin dose was described in the Ticagrelor label in various regions**
- **A subsequent PEGASUS trial demonstrated a similar treatment effect in the low dose aspirin maintenance group**
  - In patients who had prior MI 1-3 years earlier, ticagrelor (90 mg or 60 mg, twice daily) in combination with Aspirin (75-150 mg daily) significantly reduced the risk of CV death, MI, or stroke

Ticagrelor 90 mg vs. Placebo; % (HR, 95% CI; P-value)	Ticagrelor 60 mg. vs. Placebo; % (HR, 95% CI; P-value)
7.85 vs 9.04 (0.85, 0.75-0.96, p=0.008)	7.77 vs 9.04 (0.84, 0.74-0.95, p=0.004)

Bonaca MP, et al. "Long-term use of ticagrelor in patients with prior myocardial infarction". *The New England Journal of Medicine*. 2015. 372(19):1791-1800.

Concluding remarks

- **Evaluation of regional consistency is not hypothesis testing, but a key supportive analysis**
- **Planning of a structured consistency evaluation will require careful design considerations, including stratification, sample size allocation (see Module 4), and pooling strategies (see Module 5)**
- **A holistic evaluation of expected and/or unexpected inconsistencies in an MRCT offers opportunities to understand the overall treatment effect and intrinsic and/or extrinsic factors that modify this treatment effect across regions**
- **PLATO case study brings forth several important points to consider on design and analysis of MRCTs**