Implementation of ICH E17
-PMDA's perspective-

7th Joint Conference of Taiwan and Japan
on Medical Products Regulation

October 1st, 2019

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Disclaimers

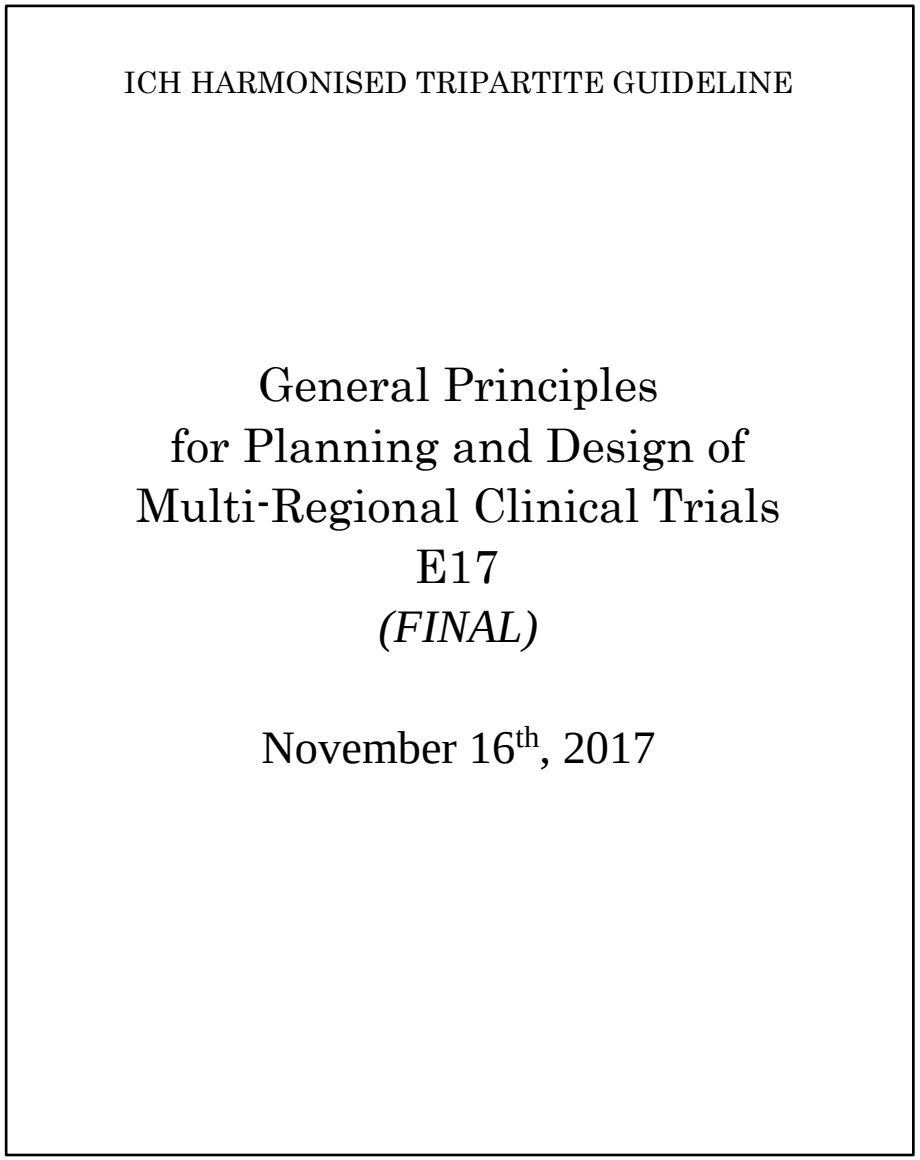
The views expressed in this presentation are those of the presenter and do not necessarily reflect the official views of Pharmaceuticals and Medical Devices Agency (PMDA).

Guidelines on MRCTs in Japan

Guideline	Issued year	Contents
Basic principles on Global Clinical Trials	2007	➢ Basic requirements to conduct a MRCT ➢ Basic points to consider in designing a MRCT
Basic principles on Global Clinical Trials (Reference Cases)	2012	➢ Points to consider for MRCTs in East Asia ➢ General points to consider for MRCTs
Basic principles for Conducting Phase1 Trials in the Japanese Population Prior to Global Clinical Trials	2014	➢ Reference cases regarding the necessity of conducting a phase1 trial in the Japanese population

https://www.pmda.go.jp/english/rs-sb-std/standards-development/cross-sectional-project/0010.html

ICH E17 guideline

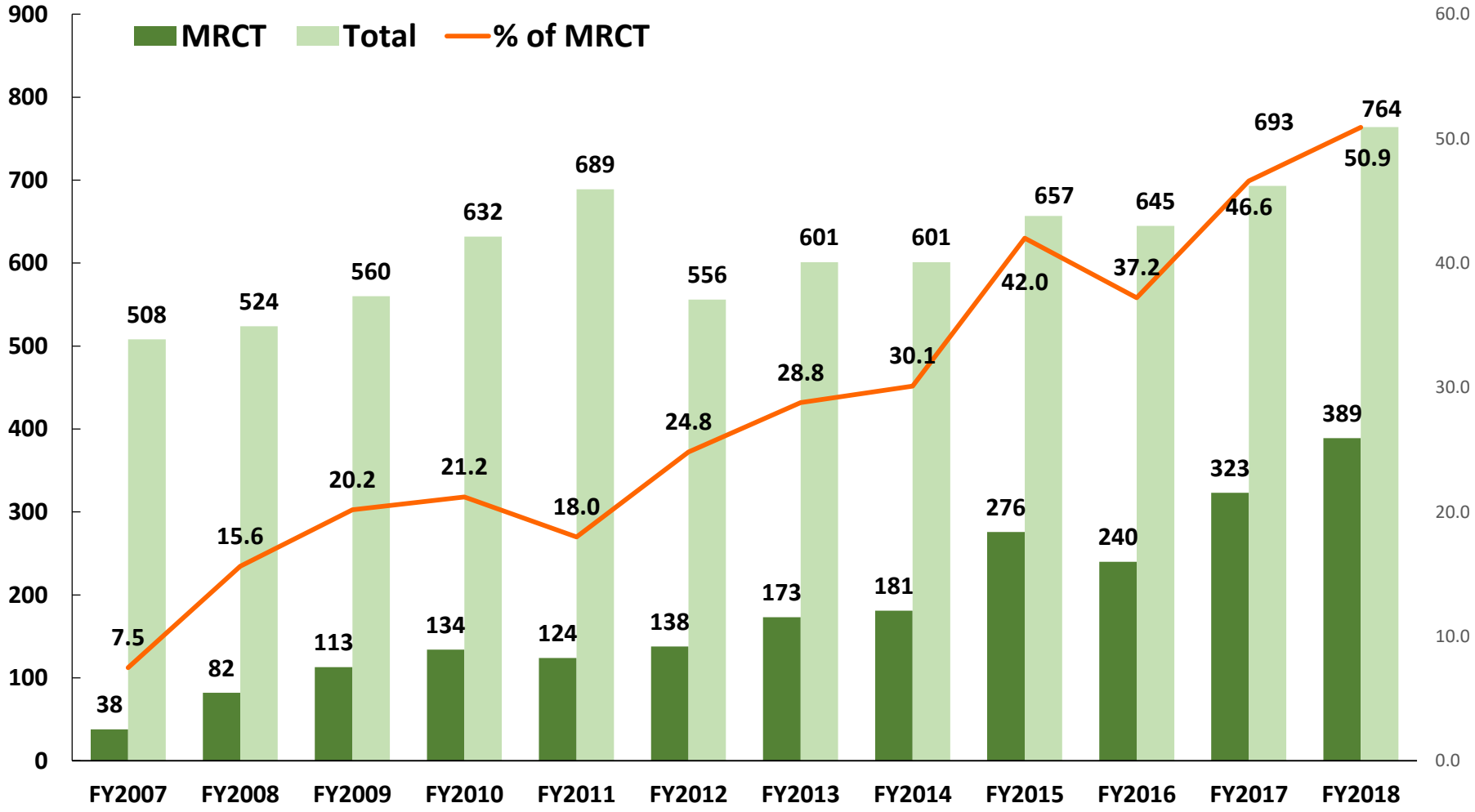

ICH HARMONISED TRIPARTITE GUIDELINE

General Principles
for Planning and Design of
Multi-Regional Clinical Trials
E17
(FINAL)

November 16th, 2017

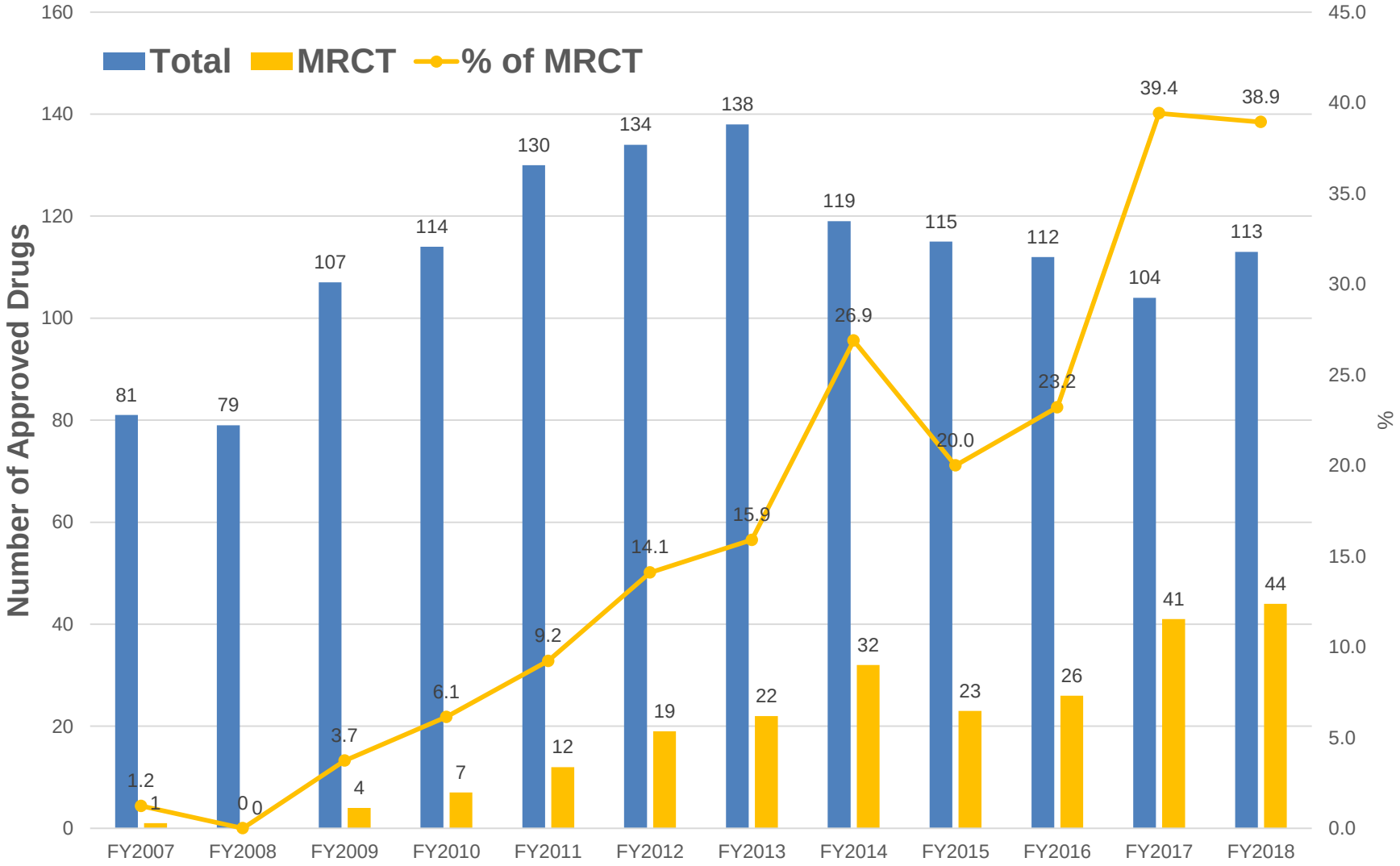
- Started in June 2014
- Draft in June 2016
- Finalized in November 2017
- Implemented (reached step 5) in June 2018 in Japan

Trends of MRCT-related Clinical Trial Notifications in Japan



MRCT : Multi-Regional Clinical Trial

Trends of new drug application based on MRCTs in Japan



ICH E17 training materials

- An extensive set of training materials has been developed to promote the efficient and consistent implementation of the E17 in the context of an evolving drug development environment.

ICH E17 training materials

- **Training material intended to provide clarity on key aspects of the guideline in order to facilitate a harmonized interpretation and implementation by industry and regulators in the ICH and non-ICH regions**
- **Training material does not provide additional guidance beyond E17**

Overview of Training material

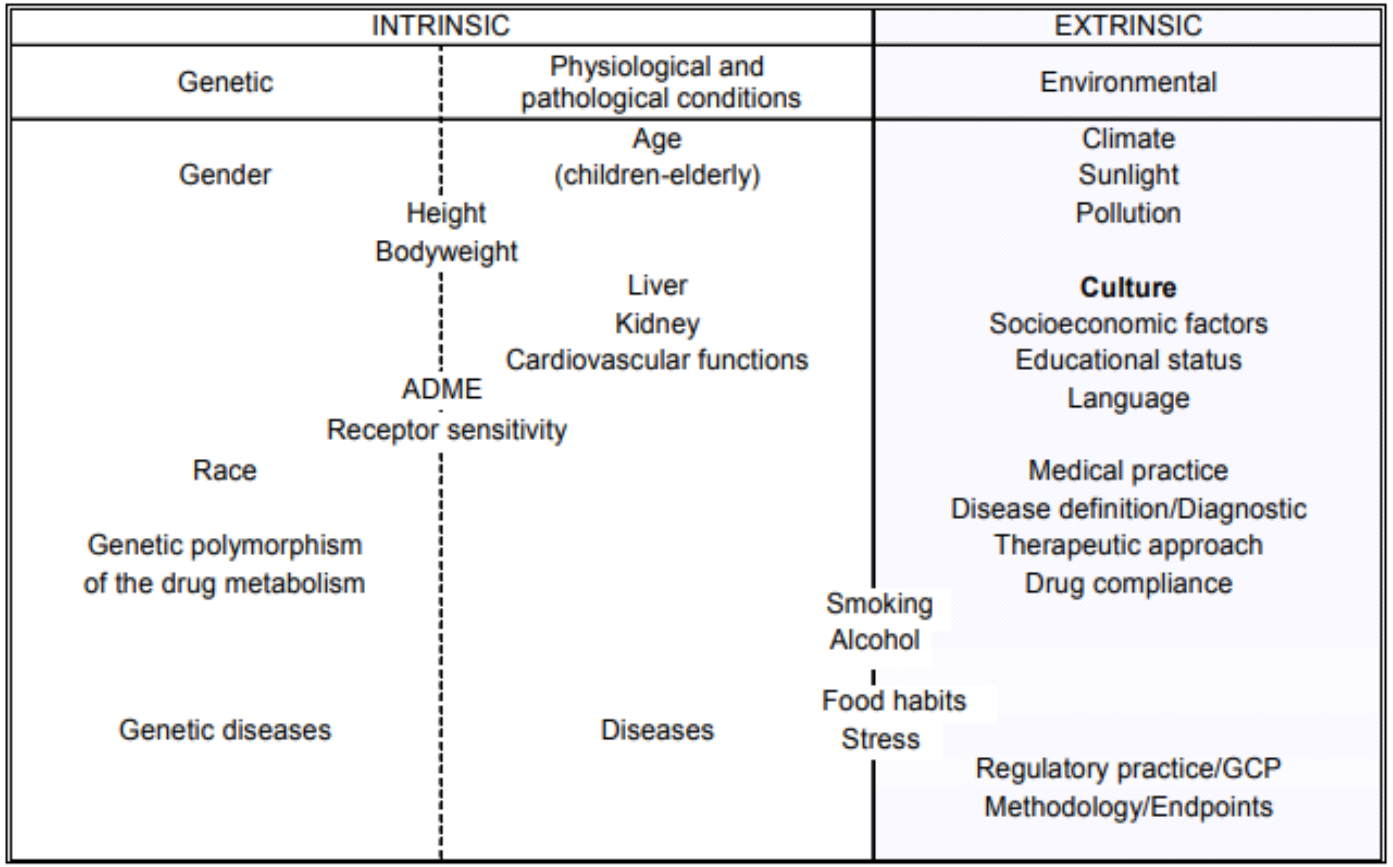
General modules

- Animated video; Main message of MRCTs
- Module 1; Overview of training material/Basic principles

Technical modules

- Module 2; Preconsideration of regional variability when recruiting diverse populations in global drug development
- Module 3; Selection of doses
- Module 4; Sample size allocation
- Module 5; Pooling strategies
- Module 6; Evaluation of Consistency
- Module 7; Selection of Comparators

Major intrinsic and extrinsic factors



(From Appendix A of ICH E5)

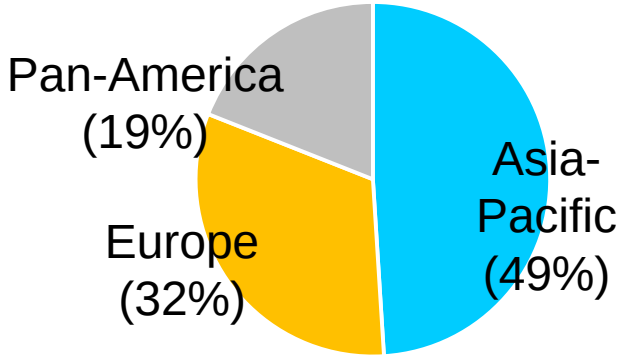
Not only intrinsic factors but also extrinsic factors may have a potential to affect the treatment effect

Example : AVAGAST Trial

Phase III trial assessing the clinical efficacy and safety of bevacizumab added to chemotherapy for first-line treatment of advanced gastric cancer

J Clin Oncol. 2011: 29: 3968-76

AVAGAST was a prospective, random-assignment, double-blind, placebo-controlled global phase III clinical trial.



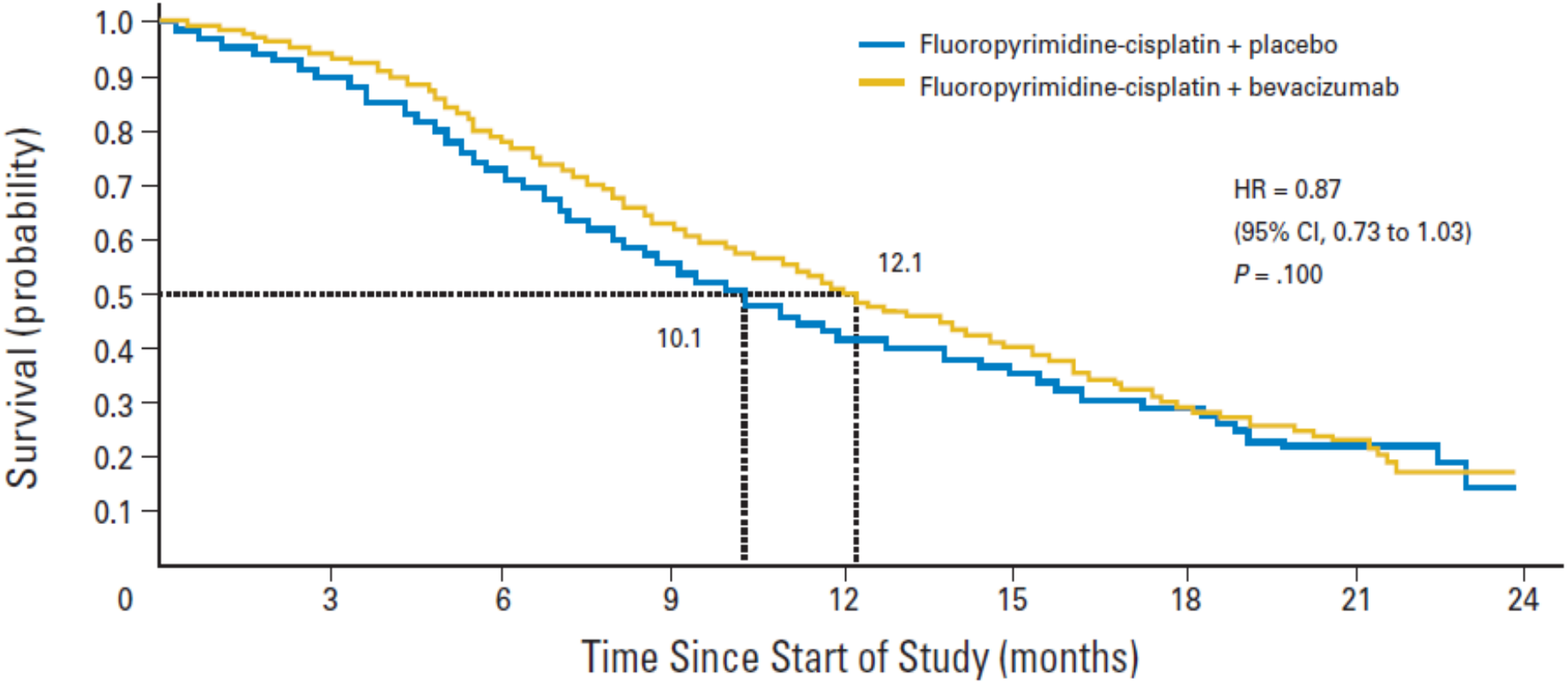
774 patients with previously untreated advanced gastric cancer

→ R → 1:1

- Bevacizumab + Standard Chemotherapy
- Placebo + Standard Chemotherapy

- Primary endpoint: Overall survival

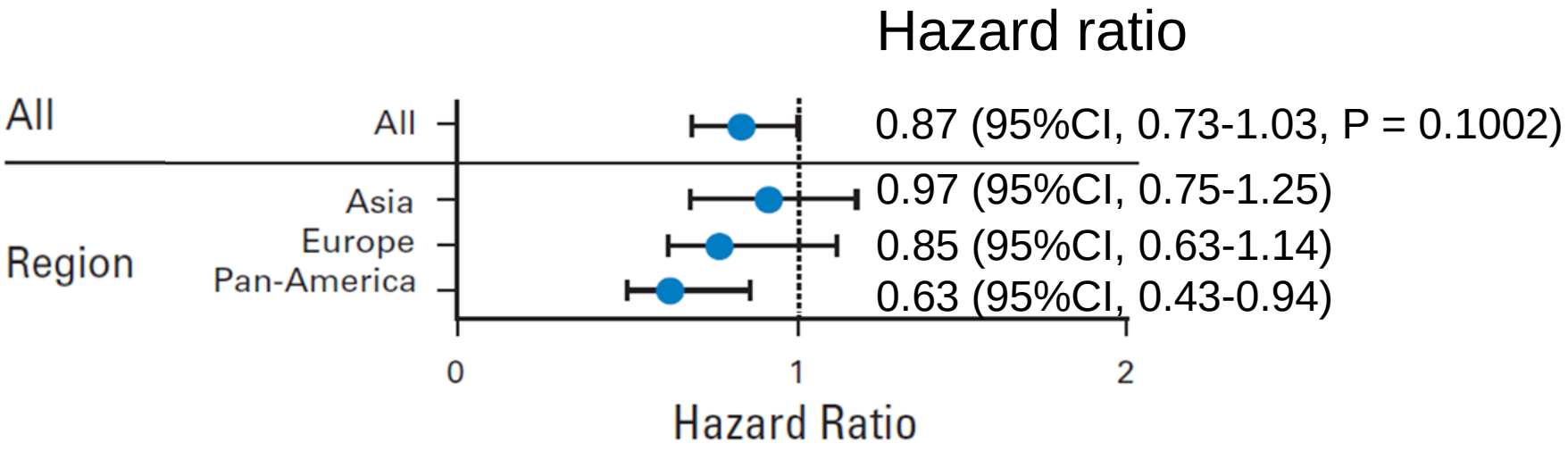
Example : AVAGAST Trial



Bevacizumab did not significantly prolong OS in the overall population.

Example : AVAGAST Trial

Subgroup analysis according to region



Bevacizumab seems to be effective in Pan-American patients, but not in Asian patients.

Example : AVAGAST Trial

Baseline characteristics by region (intention-to-treat population)

Characteristic	Asia (%)		Europe (%)		Pan-America (%)	
	bevacizumab n=188	placebo n=188	bevacizumab n=125	placebo n=124	bevacizumab n=74	placebo n=75
Liver metastases	29	26	35	38	42	41
Prior gastrectomy	32	31	22	25	31	23
Poststudy therapies:						
Patients with at least one treatment	59	67	24	29	24	15
Primary tumor site:						
Stomach	93	95	77	78	85	83
Gastroesophageal junction	7	5	23	22	15	17

Example : AVAGAST Trial

Author's explanation about the inconsistent result on overall survival among populations

(J Clin Oncol. 2011: 29: 3968-76)

- Although gastric cancer is a global disease, it is not uniform. There are differences in the presentation and management of gastric cancer patients in different countries and regions.

Example : AVAGAST Trial

Author's explanation about the inconsistent result on overall survival among populations

(J Clin Oncol. 2011: 29: 3968-76)

- Asian patients
  - more commonly receive second and further lines of therapy
  - more frequently have a prior history of gastrectomy
  - less frequently have liver metastases or proximal or gastroesophageal junction tumors

Example : AVAGAST Trial

These differences in ethnic factors might have caused the inconsistent result.

So, can you conclude these factors affected the treatment effect?

Example : Conclusion

- Exactly, there are some differences in the distribution of intrinsic and extrinsic factors among regions in AVAGAST Trial.
- However, it is difficult to conclude that those factors affect the treatment effect of bevacizumab with confidence.
- It is necessary to carefully examine the impact of those factors based on available data.

Process of identifying ethnic factors

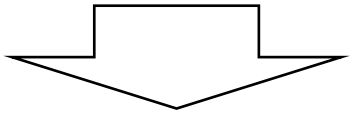
How to identify intrinsic and extrinsic factors which may affect the treatment effect and mitigation strategies

Step 1 “Collect”	Step 2 “Examine”	Step 3 “Reflect”
Collect available information about intrinsic and extrinsic factors which may affect the treatment effect	**Examine** the impact of these intrinsic and extrinsic factors for the drug development based on collected information	**Decide** which intrinsic and extrinsic factors may affect the treatment effect and should be **reflected** in the study design

(From E17 training material module2)

Current Challenges

- How to identify intrinsic and extrinsic factors important to the drug development programme?
- How to define pooled regions?
- How to determine the adequate number of specific local (e.g., Japanese) patients in MRCT and total clinical data package to meet the regulatory requirements of the region?
- How to consider when different results may be seen among regions?



Accumulation of examples is necessary

Thank You!