



Module 2

Pre-considerations of regional variability when recruiting diverse populations in global drug development

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

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Module 2: Introduction and objectives

- **Pre-consideration of regional variability and its mitigation could affect various design perspectives.**
- **Module 2 focuses on how to ensure that the population targeted in the MRCT is relevant to all regions to support a marketing authorisation.**
 - In particular, how to identify intrinsic and extrinsic factors which may affect the treatment effect.
 - Pre-considerations of regional variability in relation to other design factors (e.g., definition of endpoints, analysis planning, use of concomitant medications) are described in the E17 guideline.

Outline

- **Why pre-considerations of regional variability are important in the design of an MRCT**
- **How to identify intrinsic and extrinsic factors which may affect the treatment effect and mitigation strategies**
 - Collect
 - Examine
 - Reflect
- **Concluding Remarks**
- **Examples**

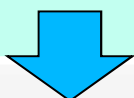
Why pre-considerations of regional variability are important

- **Intrinsic and/or extrinsic factors may impact the treatment effect**
- **Pre-consideration and mitigation of large differences across regions can support adequate interpretability of the results of an MRCT in different regions**
- **Pre-consideration of regional variability should be reflected in the trial design to lead to a successful MRCT**

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

Step 1 “Collect”

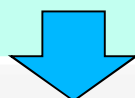
Collect available information about intrinsic and extrinsic factors which may affect the treatment effect



See slide 7-8

Step 2 “Examine”

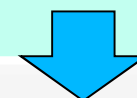
Examine the impact of these intrinsic and extrinsic factors for the drug development based on collected information



See slide 9

Step 3 “Reflect”

Decide which intrinsic and extrinsic factors may affect the treatment effect and should be **reflected** in the study design



See slide 10

Step1 “Collect” information

Major intrinsic and extrinsic factors are described in Appendix A of ICH E5

INTRINSIC		EXTRINSIC
Genetic	Physiological and pathological conditions	Environmental
Gender	Age (children-elderly)	Climate Sunlight Pollution
	Height Bodyweight	Culture Socioeconomic factors Educational status Language
	Liver Kidney Cardiovascular functions	Medical practice Disease definition/Diagnostic Therapeutic approach Drug compliance
	ADME Receptor sensitivity	Smoking Alcohol Food habits Stress
Race		Regulatory practice/GCP Methodology/Endpoints
Genetic polymorphism of the drug metabolism		
Genetic diseases	Diseases	



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

Step1 “Collect” information

- **Search medical and scientific literature, guidelines and other publicly available information**
 - disease information
 - genetic information
- **Search databases (e.g., WHO disease database, registries)**
 - epidemiological data
 - historical data
- **Consult local healthcare professionals**
 - clinical practice, therapeutic approach in their region

Step2 “Examine”

- Examine the impact of intrinsic and extrinsic factors based on collected information about the drug and from studies, literature, databases, local healthcare professionals
- If needed, collect more information by conducting studies or use modeling and extrapolations, e.g., PK-PD studies, exploratory studies
- Intrinsic and extrinsic factors which may affect the treatment effect can be identified based on the information above

PK: pharmacokinetics
PD: pharmacodynamics

Step3 “Reflect”

Some possible mitigation and design strategies include:

- **Define clear and specific inclusion and/or exclusion criteria**
- **Decide on stratification and/or pooling for the factors which may affect the treatment effect**
- **Consider study power and proper allocation of subjects to (pooled) regions and/or pooled subpopulations**

→ See Module 4, 5 and 6 for further consideration

Concluding remarks

- **Pre-considerations of regional variability are important in the design of an MRCT because intrinsic and extrinsic factors may affect the treatment effect and the interpretation of the trial.**
- **A stepwise approach to identify these factors as well as some mitigation and design strategies are proposed.**



Module 2: example 1

A new basal insulin development program with an examination of intrinsic and/or extrinsic factors for pooling of regions in an MRCT

Outline

The following slides show an example of a hypothetical MRCT of a basal insulin* using E17 principles to illustrate how intrinsic and/or extrinsic factors can influence the pooling of regions in an MRCT

* This new basal insulin is expected to be long acting, i.e. reducing number of injections

Indications for use of a new basal insulin and sensitivity to intrinsic and/or extrinsic factors

- **Type 1 diabetes,**
 - Intrinsic and extrinsic factors are not critical to the global development programme, i.e., the effect of insulin in subjects is not sensitive to these factors.
- **Type 2 diabetes, adults**
 - Some identified extrinsic factors may impact the effect of insulin in subjects and should be examined during the planning phase of the development programme.

Extrinsic factors relevant to type 2 diabetes

Regional differences in diet, lifestyle and medical practice can be important when planning and interpreting data from MRCTs

- Diet:
 - Some regions: High fat and/or low carbohydrate meals
 - Other regions: Low fat and/or high carbohydrate meals
- Lifestyle:
 - Differences in adherence to exercise regimen
 - Differences in body composition
- Medical practice
 - Differences in medical care (including concomitant medications)

Pooled regions based on diet for an MRCT in type 2 diabetic subjects

Example:

- 1. Asia: Japan, China, South Korea, Malaysia, Singapore, Thailand, Vietnam**
- 2. Americas: USA, Canada, Latin America**
- 3. Europe and EAEU*: Europe, Russia, Kazakhstan**

*** Eurasian Economic Union**

Example 1: Conclusion

- **For some drugs the response to treatment may be affected by extrinsic factors**
- **Therefore, it is important to understand:**
 - the extrinsic factors that may impact the treatment effect
 - the prevalence of these factors across geographic regions
- **Subjects with similar extrinsic factors can be pooled**
- **Differences in some factors may be mitigated, but the degree of mitigation should not impact the generalisability of study results**
- **Sufficient number of subjects from different regions should be enrolled to support the evaluation of the consistency of treatment effects among regions**



Module 2: example 2

**Treatment of non-small cell lung cancer with gefitinib;
an example where intrinsic factors
matter**

Outline

The following drug development example illustrates how intrinsic factors can impact the treatment effect and how this can be informative for identifying appropriate target populations.

Gefitinib

- **Small molecule inhibitor of EGFR tyrosine kinase**
- **Target population: patients with NSCLC**
- **During drug development, the science behind the potential predictive biomarker for EGFR TKIs in NSCLC was unclear**
- **Two phase II studies (IDEAL I & II) in advanced NSCLC patients showed different response rates in different regions and populations**

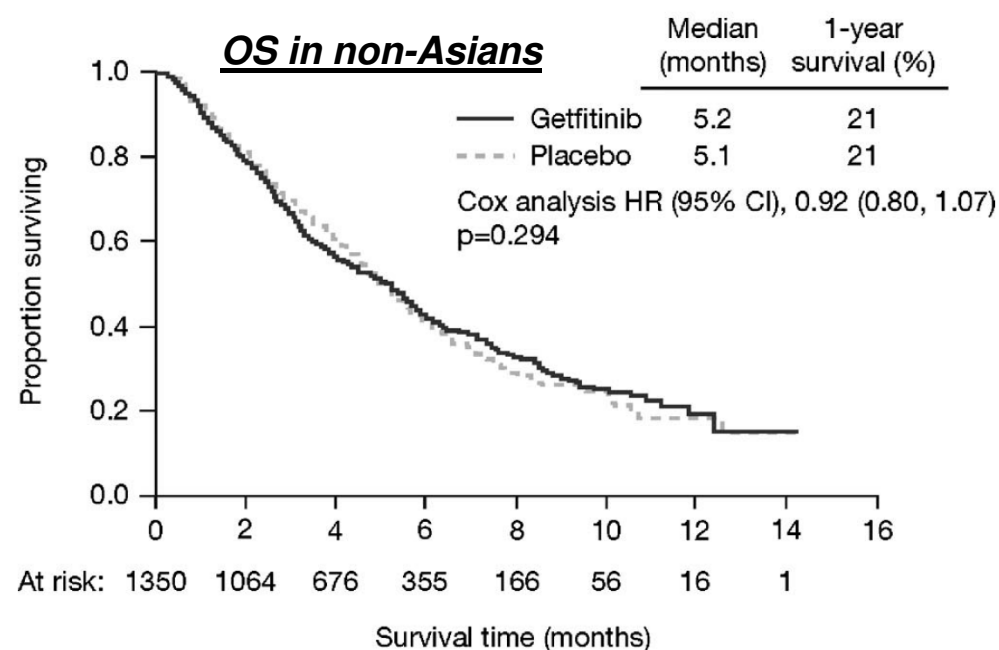
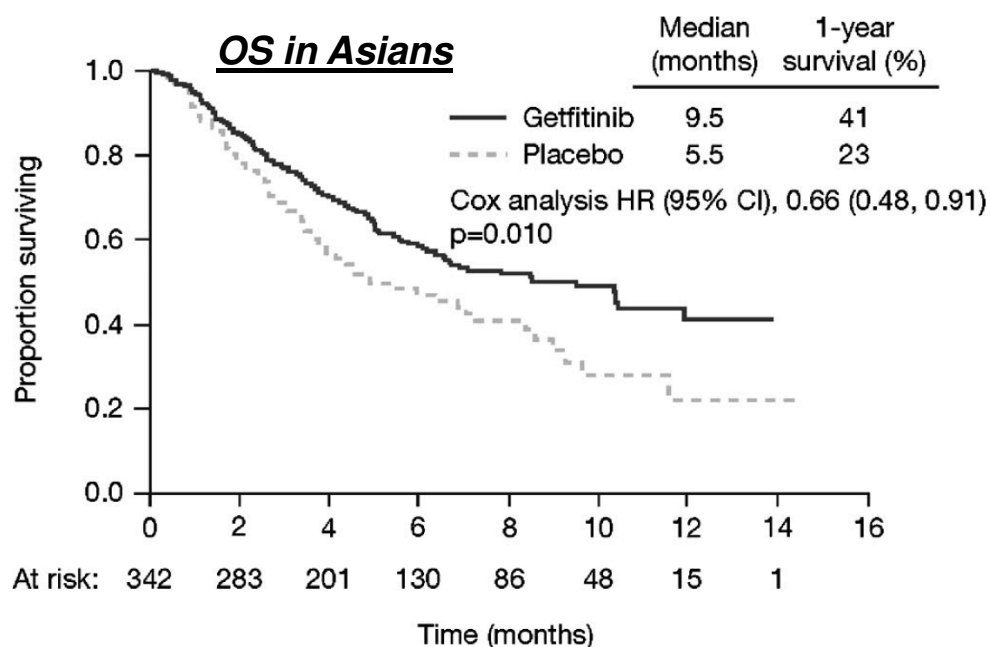
EGFR: epidermal growth factor receptor
TKI: tyrosine kinase inhibitor
NSCLC: non–small cell lung cancer

Phase II studies

	IDEAL I	IDEAL II
Conducted in	Mainly in Europe and Japan	US
Population	Advanced NSCLC patients	
Demography	49% of enrolled subjects were Japanese	93% of enrolled subjects were White and Hispanic
Overall response rate	18.4 % (gefitinib 250mg) 19.0% (gefitinib 500mg) • Response rate was higher for Japanese than non-Japanese (27.5% vs. 10.4%) • Population PK didn't reveal any difference between Japanese and non-Japanese	11.8% (gefitinib 250mg) 8.8% (gefitinib 500mg)

Phase III study (ISEL): survival effect was seen only in Asians

- ISEL was conducted in advanced NSCLC patients
- 75% of enrolled subjects were Caucasians and 20% were Asian



(Both subgroup analyses were pre-planned)

Why did gefitinib work in Asians?

No obvious explanation for the lack of treatment effect on overall survival in Caucasian patients

- **The importance of tumour genetics such as EGFR mutation status was considered**

Further studies were done to investigate the differences in treatment effects by region

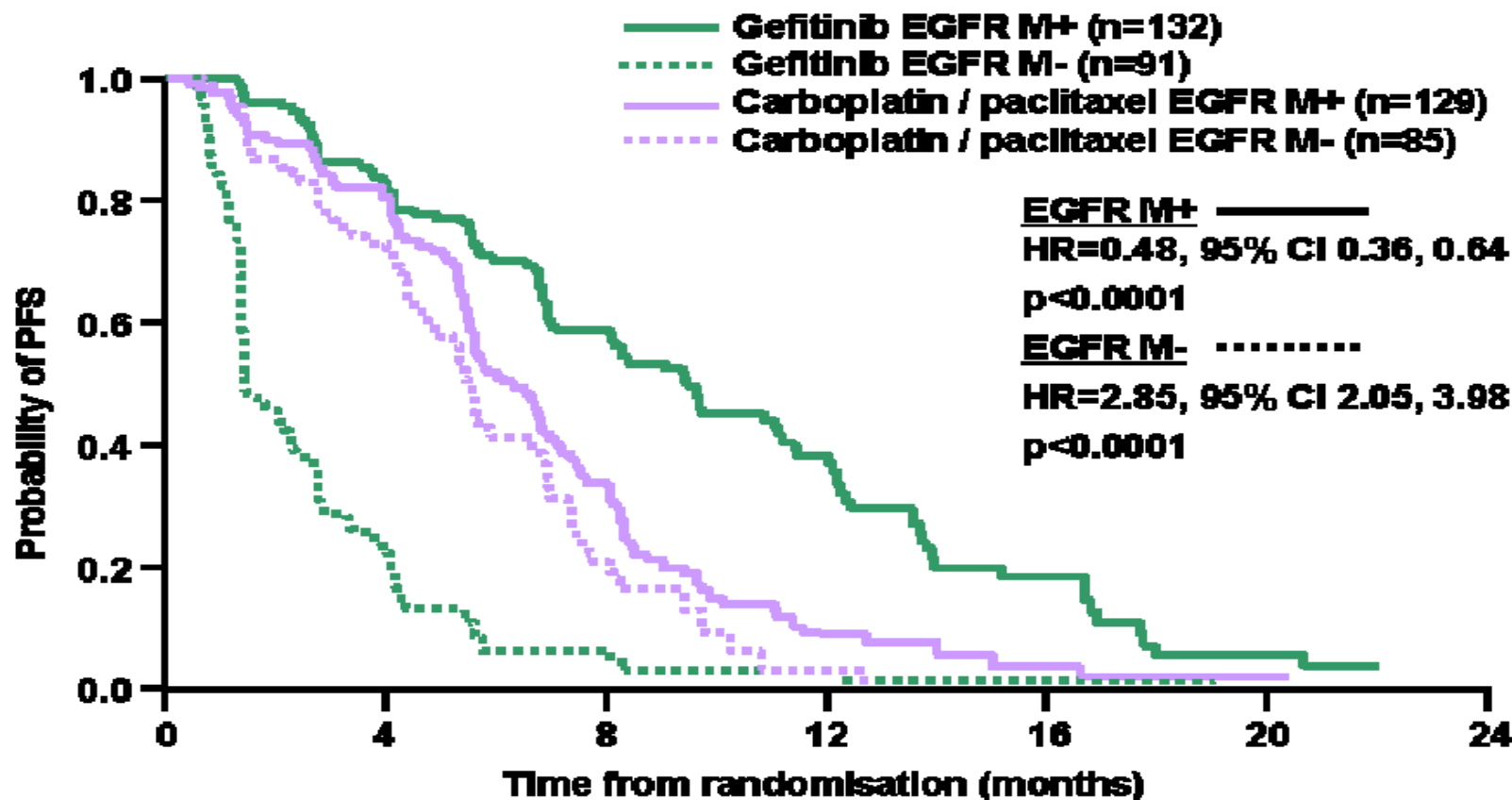
- **INTEREST study**

- Conducted in Europe, Asia and America
- Enrolled patients regardless of EGFR mutation status
- Based on limited tissue samples, higher prevalence of EGFR mutations was observed in Asians compared to Caucasians (36.4% versus 10%)
 - Suggested that gefitinib might work in non-Asians with EGFR mutation

- **IPASS study**

- Conducted in Asia
- Enrolled patients regardless of EGFR mutation status
- Showed gefitinib worked only in EGFR mutation positive patients (see next slide for further details)

IPASS: Gefitinib effective mainly in EGFR mutation-positive NSCLC



Then how about Caucasians?

→ IFUM study was conducted:

- Enrolled only EGFR mutation positive Caucasians
- Showed gefitinib was effective in Caucasians with EGFR mutation

How was the specific effect of gefitinib detected?

- **Inconsistent results in regions and populations were explained by different proportions of patients with EGFR mutations**
- **INTEREST study showed that Asians had higher prevalence of EGFR mutation compared to non-Asians.**
- **IPASS and IFUM assured that gefitinib worked in EGFR mutation-positive patients, regardless of whether they are Asians or non-Asians**

Example 2: Conclusion

- **Consider if the treatment effect is sensitive to an intrinsic factor**
- **When an intrinsic factor is suspected to potentially impact the drug response it is recommended to stratify randomization based on the suspected intrinsic factor**