ICH E17科学监管研讨会

ICH E17 Scientific and Regulatory Workshop

PUCRI
Peking University Clinical Research Institute

MRCT
The MRCT Center of Harvard and Brigham and Women's Hospital

MRCT Multi-Regional Clinical Trials

The MRCT Center of Harvard and Brigham and Women's Hospital

Multi-Regional Clinical Trials Center – China Initiative

Building A Learning Community Among Key Stakeholders

Collaborating to Improve Multi-Regional Clinical Trials

To improve the integrity, safety, and rigor of global clinical trials

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

The MRCT Center Administration

BRIGHAM AND WOMEN'S HOSPITAL

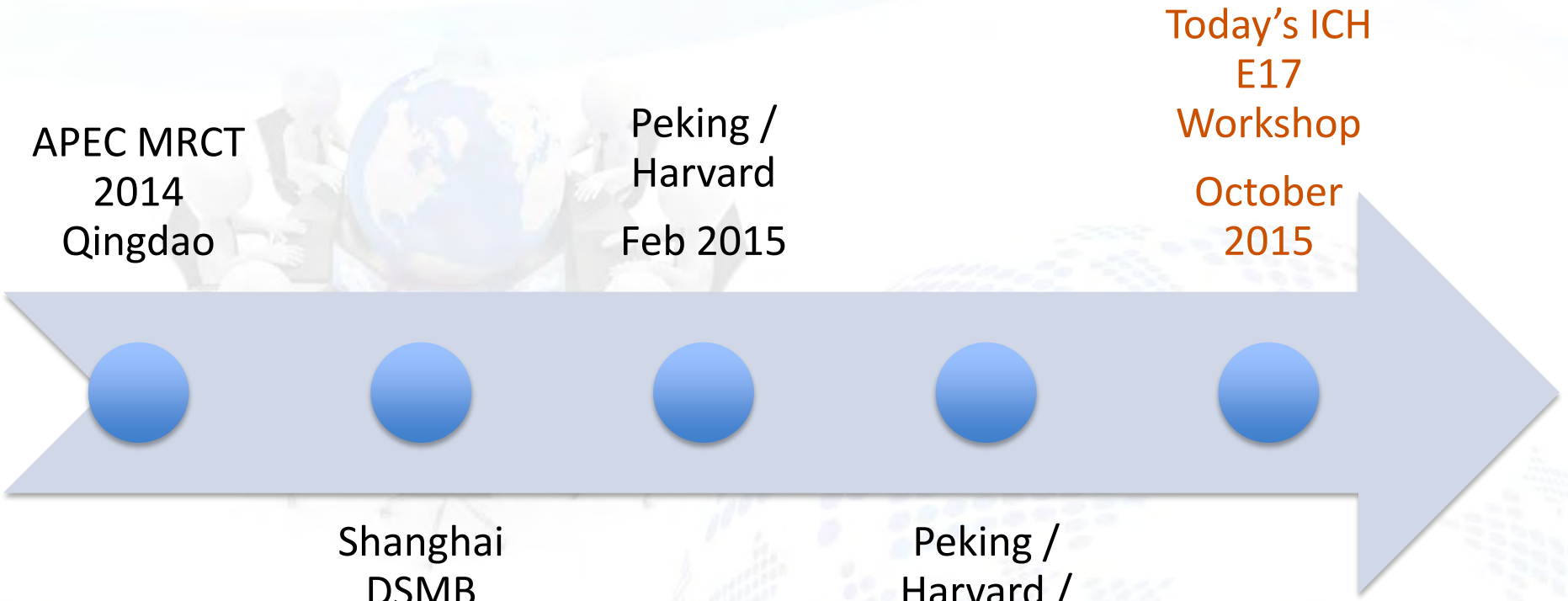
HARVARD UNIVERSITY

- A collaboration with Harvard University, the administrative home of the MRCT Center is the Division of Global Health Equity (DGHE) at the Brigham and Women's Hospital

- The DGHE was established in 2001 under the leadership of Paul Farmer

- DGHE faculty have strong ties to the Ministries of Health in the countries where we work, offering an opportunity for MRCT to build relationships and to influence national policy regarding clinical trials in those nations.

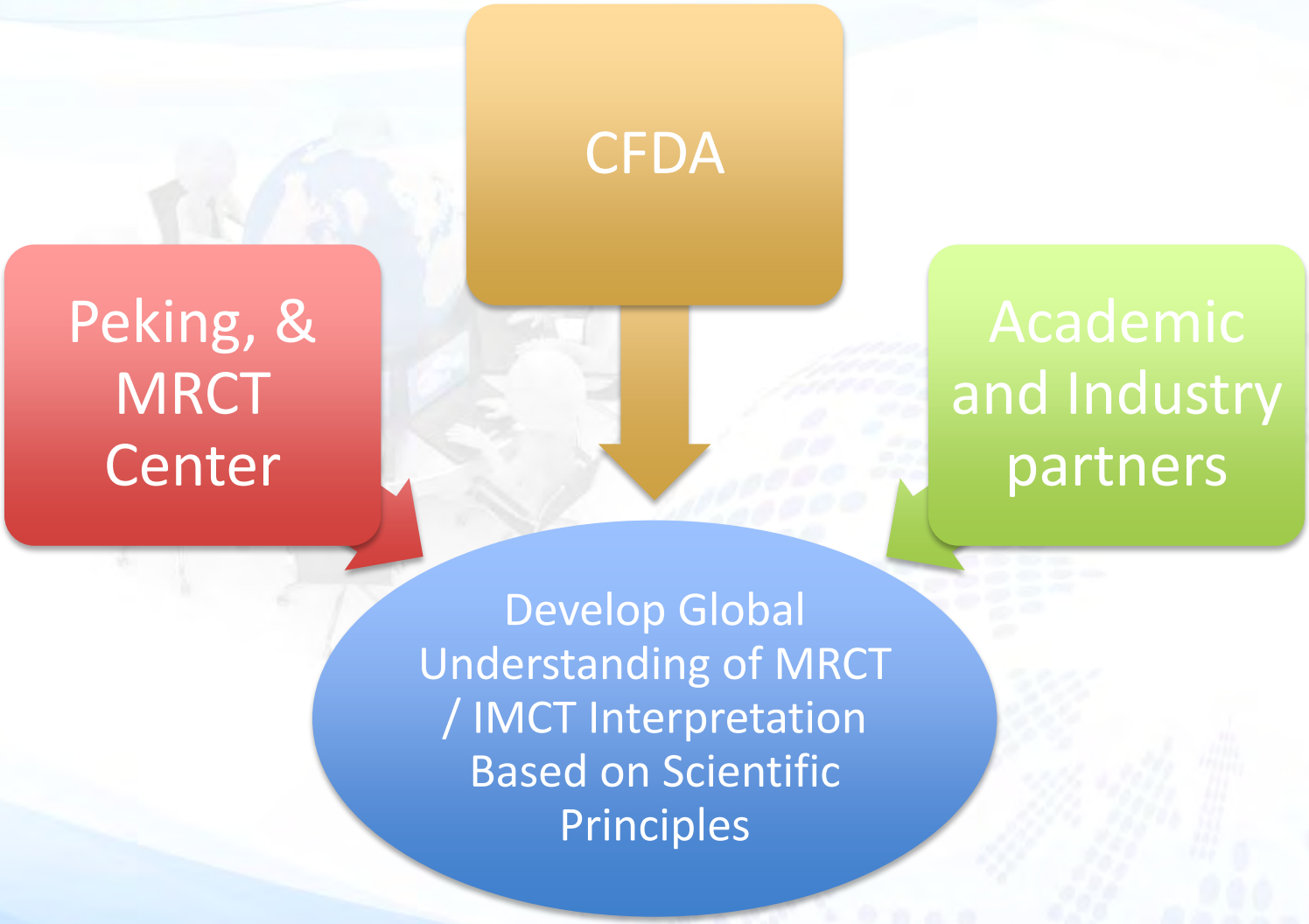
MRCT Center CHINA Engagement



ICH E17 and China's IMCT Guidance

- International guidance offered by ICH E5, E9 and E17
- China's new guidance shows leadership in the area of global clinical trials and the scientific issues that must be considered when considering whether IMCT data can be accepted for registration
- China's new guidance can be interpreted to be consistent with the mission of ICH E17
- Some issues require further clarification – Peking and MRCT Center have partnered to lead the effort on this project with a multi-stakeholder group
- Offers China the opportunity for new thinking and leadership in the area of regulatory science and IMCTs

Project Aims



Ensure China remains at the forefront of scientific thinking in regulatory science and clinical trials

Project Aims

- Understand how to interpret China's IMCT Guidance in light of the international ICH guidelines for MRCTs
- As of March 1, 2015 CFDA issued a final "Guidance for International Multicenter Clinical Trials (IMCT) "Trial Implementation"
  - Offer clarity on how one might consider interpreting
    - » Intrinsic and extrinsic factors (Section IV, p. 3)
    - » Sample size (Section 7, p. 5)
    - » Trend consistency (Section 8, p.6)

We offer a scientific perspective of these guidelines

Scientific Approaches

How to review MRCT / IMCT data considering key factors:

- Defining region
- Consistency vs. Random Variability
- Significance of subgroup variability
- Approaches to determination of trend consistency

Workgroup 1 - Project Objectives Overall:

Workgroup 1

1. Review prior work already done to define region and agree upon a working definition for China

1. Develop methods for analyzing the consistency of regional sub-groups and the overall study data (trend analysis) for key safety and efficacy outcomes

Workgroup 2

1. Develop guidelines on how external and internal factors in different regions may impact drug efficacy and/or safety *(Section V 1-5)*.

Positioning Our Project Work

Objectives for Today's Workshop

1. Discuss how countries may consider the role and importance of ethnic factors in the design and conduct of multi-regional clinical trials
2. Understand the background and rationale of ICH E5, ICH E17
3. Discuss the IMCT guidance - consistency and region and the scientific interpretation of these issues
4. Understand CFDA's future policy trends in multi-regional clinical trials and implications for implementation
5. Discuss a collaborative path forward as a multi-stakeholder group, ensuring China prominence in this work

A Perspective on the ICH E5 Guidance and the (Q&A) Question and Answer Addendum

Robert T O'Neill PhD
Senior Statistical Advisor ,OTS
CDER, FDA

Some history of the E5 Guidance

- Topic proposed to the ICH Steering Committee in 1992 by Japan
- Guidance signed off in February, 1998 after many years of effort regarding what should be its purpose, focus, content, and guidance
- Published June 10, 1998 in U.S. Federal Register
- http://www.fda.gov/cder/guidance/Guidance on Ethnic Factors in the Acceptance of Foreign Clinical Data

Some Issues Considered in developing E5

- What should the guidance be about: ethnicity, foreign data , acceptance of clinical trial data, regulatory standards, etc
- What amount of detail and flexibility in advice to sponsors (decision trees, early emphasis was on Phase 1)
- Operational definition of ethnicity (term region used in general sense)
- Later in the discussions emphasis was placed on 'evidence' needed in each region to conclude efficacy and safety
- Two situations : Retrospective approach - what other data is needed, given a good license application; Prospective approach - multi-regional drug development strategies

Some issues considered (cont.)

- What does it mean for acceptance of data - Generalizability /extrapolation of phase 3 efficacy/safety results
- Algorithms to clearly show paths for sponsors and regulators to follow for acceptance of foreign data
- Triage the amount of information needed according to:
  - profile of the drug, the intended population, clinical experiences with drug (why E5 is not too prescriptive)
- When is additional information needed: Bridging data

Key Features of E5

- Operational definition of ethnic factors
- Clinical Data Package Fulfilling Regulatory Requirements in New Region
- Extrapolation of Foreign Clinical Data to New Region (role of ethnic factors)
- Bridging Studies
- Global Development Strategies

Why the need for a E5 Question & Answer Document ?

- General agreement that misperceptions and misunderstandings exist and other issues are unclear subsequent to E5 publication, causing confusion
- Best way to fix the situation was to identify key questions and topics for which consensus answers can be provided to all regions
- The Q & A document is intended to provide answers to questions that have arisen since the implementation of the E5 guidance in June 1998.
- Q & A's implemented in November, 2003

The Q & A addendum was very helpful and stimulated new thinking, especially Q11

Guidance for Industry

E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data

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Questions and Answers

Key Features of the Q & A's

- Clarified some points of ambiguity in the initial guidance - indicated more experience needed and we would learn more
- Introduced the multi-regional trial concept for bridging - actually that design is very prevalent today - but also potentially problematic to interpret if not planned or conducted well

The Multi-Regional Trial for Bridging

Q11: There seems to be an impression that the E5 bridging study would always be conducted after data in the original region is complete. Is this correct?

It may be desirable in certain situations to achieve the goal of bridging by conducting a multi-regional trial under a common protocol that includes sufficient numbers of patients from each of multiple regions to reach a conclusion about the effect of the drug in all regions. Please provide points to consider in designing, analyzing and evaluating such a multi-regional trial.

A11: Bridging data should allow for extrapolation of data from one region to another. Although E5 speaks generally to extrapolation of data to a new region, E5 was not intended to suggest that the bridging study should necessarily follow development in another region. In the answer to Q1, it is made clear that it is also possible to include earlier studies conducted in several regions in a global drug development program so that bridging data might become available sooner. This can expedite completion of a global clinical development program and facilitate registration in all regions. A bridging study therefore can be done at the beginning, during or at the end of a global development program. For a multi-regional trial to serve as a bridging study for a particular region, it would need to have persuasive results in that region, because it is these regional results that can convince the regulators in that region that the drug is effective, and can "bridge" the results of trials in other regions in the registration application.

The Multi-Regional Trial for Bridging

A multi-regional trial for the purpose of bridging could be conducted in the context of a global development program designed for near simultaneous world-wide registration. The objectives of such a study would be: (1) to show that the drug is effective in the region and (2) to compare the results of the study between the regions with the intent of establishing that the drug is not sensitive to ethnic factors. The primary endpoint(s) of the study should be defined and acceptable to the individual regions and data on all primary endpoints should be collected in all regions under a common protocol. In instances where the primary endpoints to be used by the regions are different, data for comparison purposes on all primary endpoints should be collected in all regions.

Relevance to E17 and using the MRCT without bridging

- Almost 13 years of experience post Q & A
- E5 expressed the opinion that with increased experience with studies, including MRCT's, the need for bridging studies would lessen (see Q & A 10)
- After years of experience with MRCT's, some lessons learned can be incorporated into E17 to further advance the use of MRCT's without separate bridging studies

MRCT and Bridging Data Evaluation in China

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- Sample size allocation: perspectives from medical needs
- Issues in ethnicity evaluation: perspectives from PK/PD
- MRCT and bridging data evaluation: Where are we standing now?

- Sample size allocation: perspectives from medical needs
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Medical needs and Measures

- Medical needs differ across countries/geographical regions over the time due to the various factors like clinical practices, health care system, food, habit and etc.

- Quantitative measures can be helpful to describe the medical needs, e.g.,

  - mortality,
  - years lived with disease(YLDs),
  - disability adjusted life years (DALYs),

  and etc.

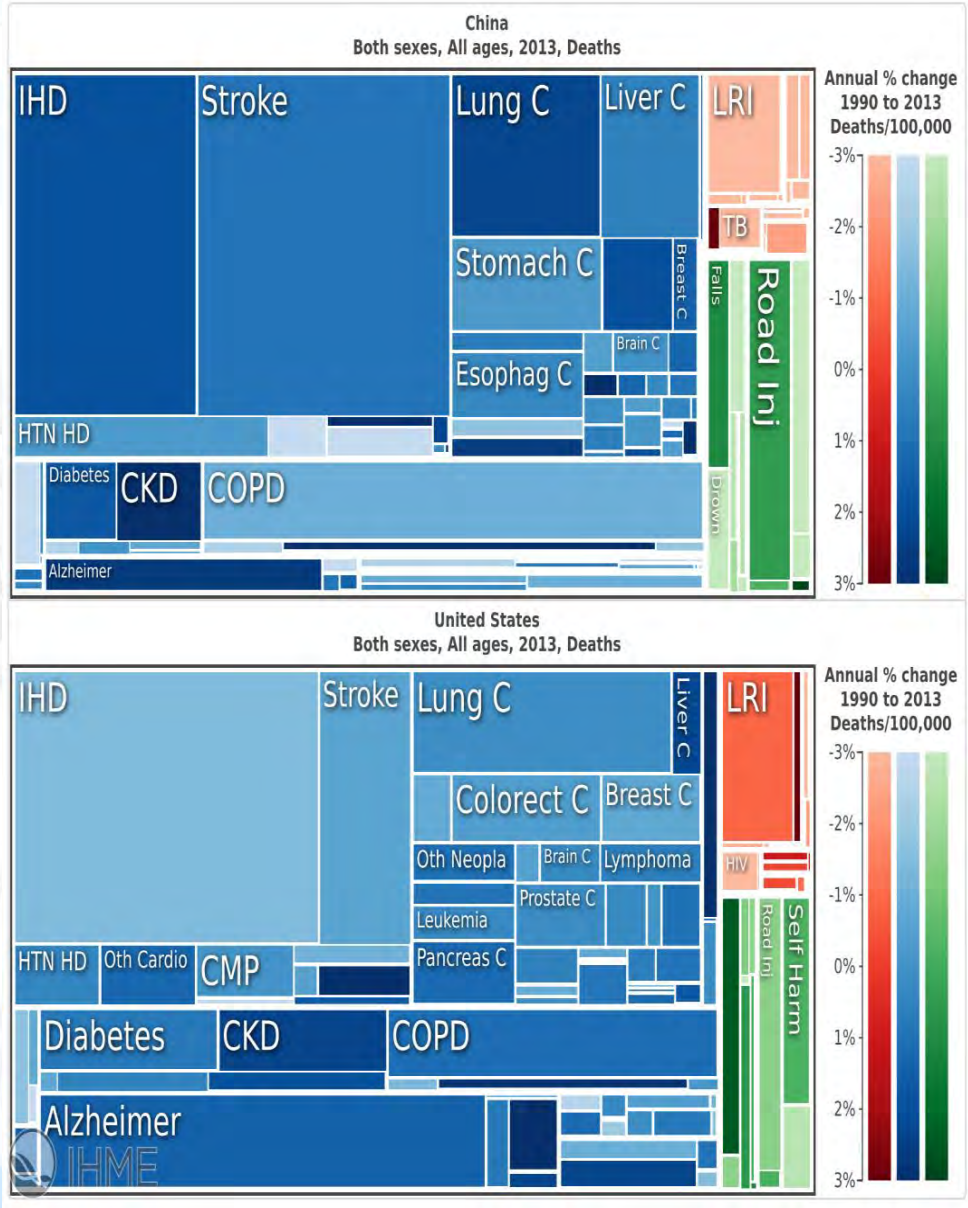
Mortality

- ✓ Mortality can inform medical needs for diseases with high fatality

- ✓ For example, big differences between China and US in causes of death profiles inform the different needs in cardiovascular disease, cancer and Alzheimer:

  - Stomach C. and Esophagi C. are more common in China, but Colorect C., Prostate C. and Lymphoma are more common in the US

  - Lung C. and Liver C. are both common in China and the US but former is increasing and later decreasing in China. The opposite trend is observed in US

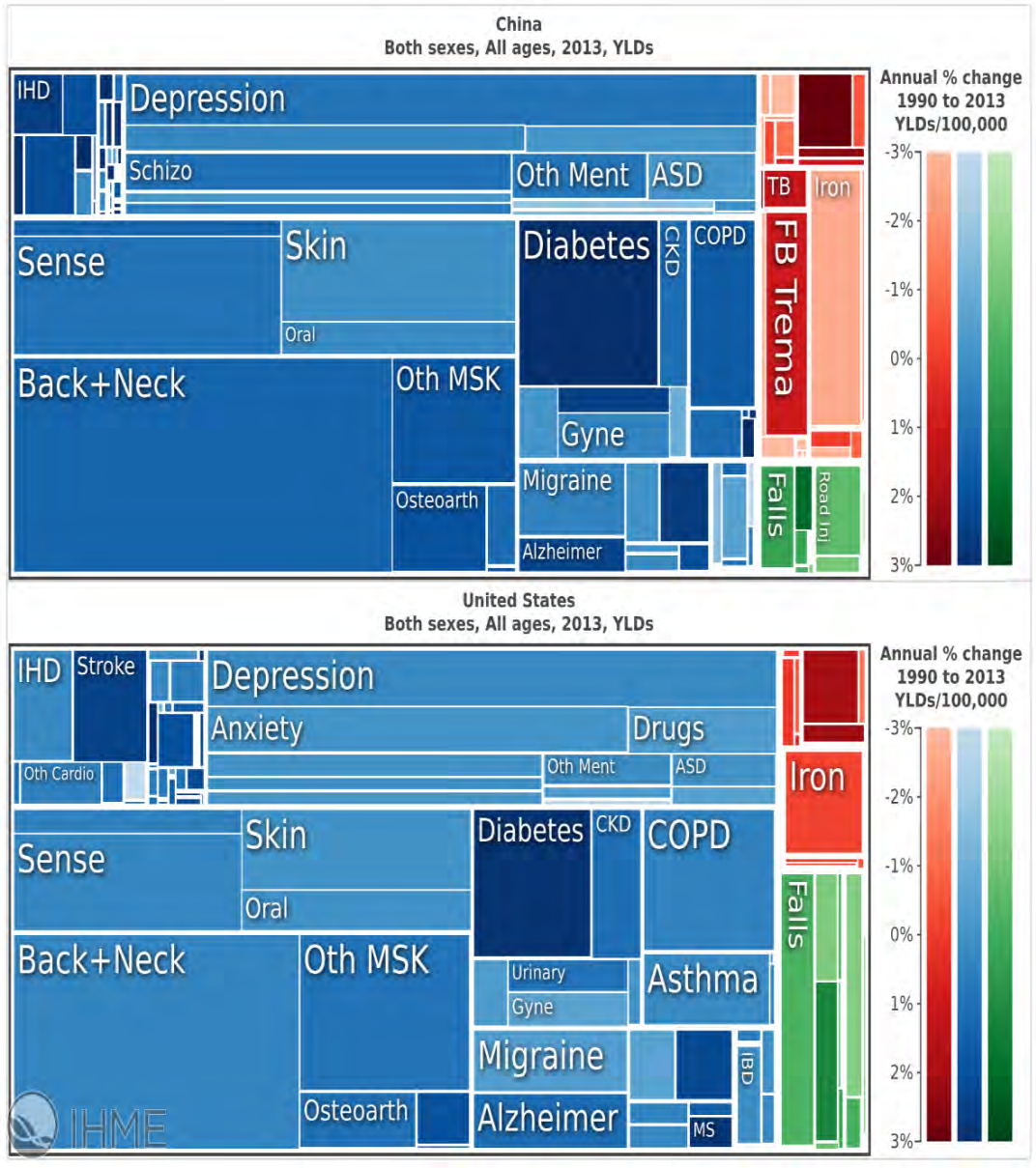


Years lived with disease(YLDs)

- ✓ YLD could inform the medical needs for diseases with low fatality
- ✓ For example, China and US similarly share many of such diseases:

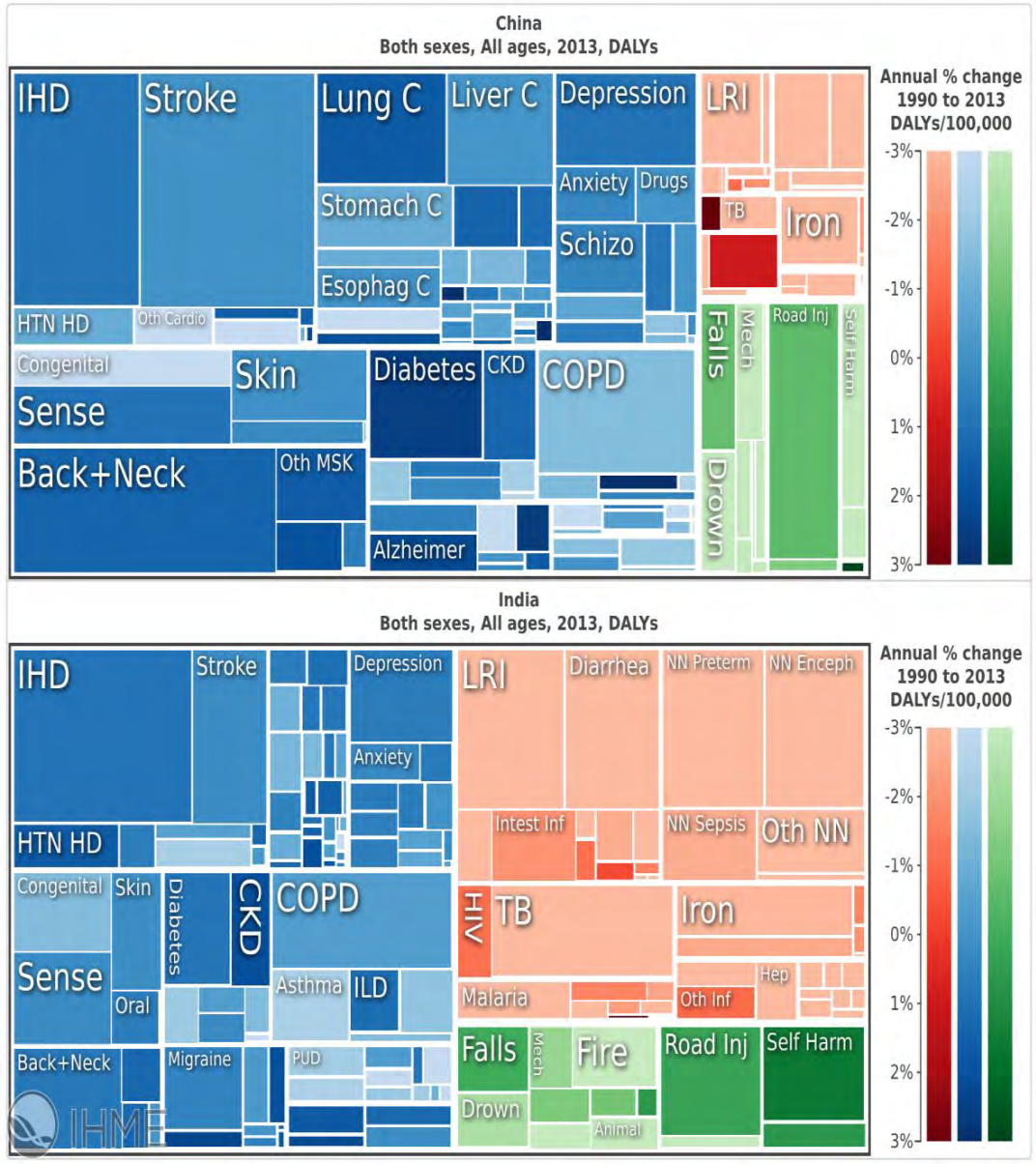
  - Back and neck
  - Sense
  - Diabetes
  - Skin
  - Depression
  - Alzheimer

  and etc.

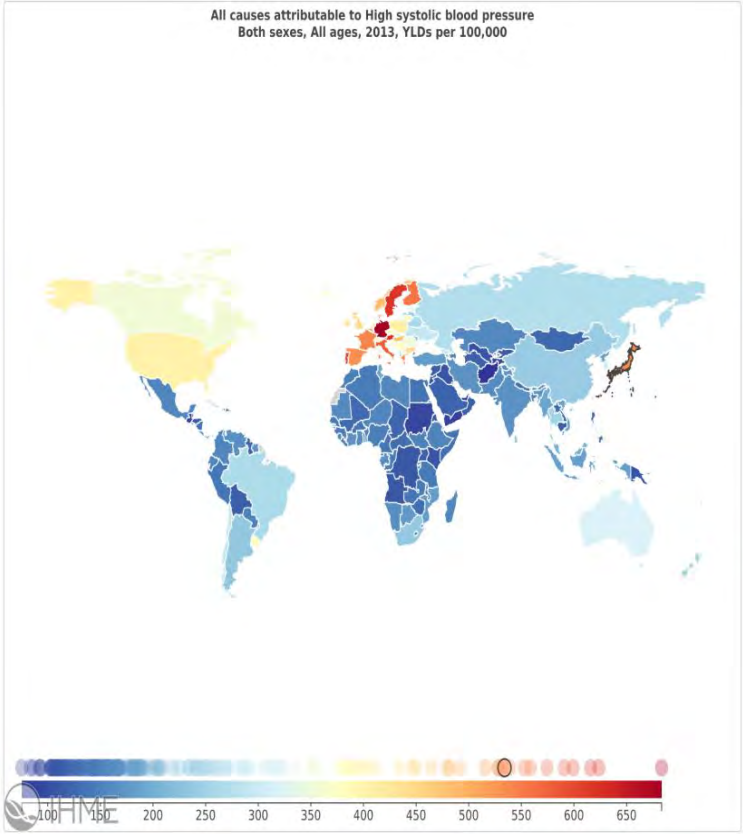


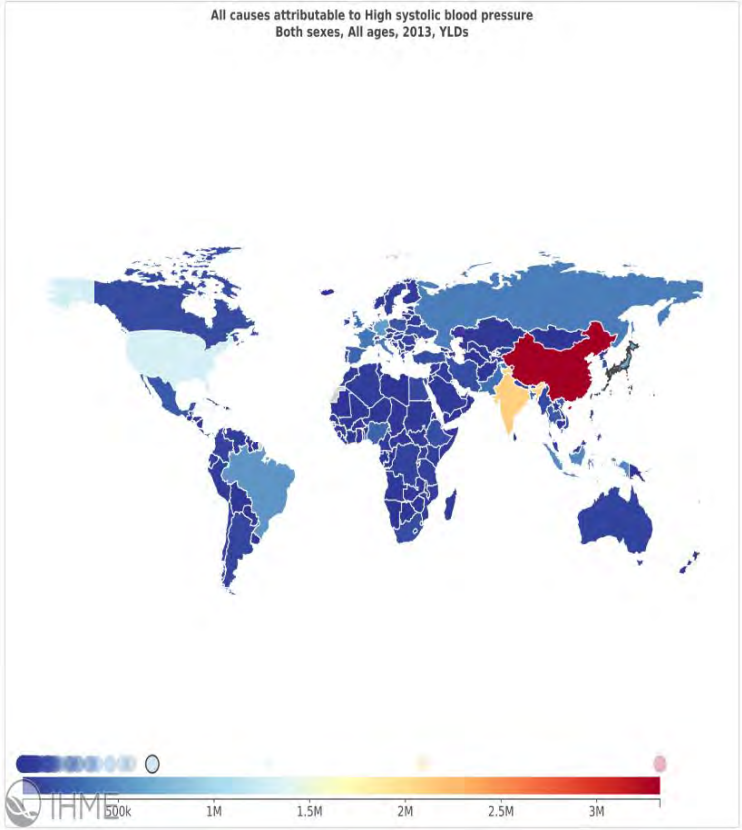
Disability adjusted life years (DALYs)

- ✓ DALYs is a 'composite' outcome that informs burden of disease contributed jointly from death and low QoL.
- ✓ DALYs reflect medical needs and health care burden for both life threatening and not life threatening diseases
- ✓ Different trend in changes over the year has been observed among countries



Representativeness for each country in sampling of MRCT





The total number of patients should be considered rather than the rates (incidence/prevalence/mortality) of the disease.

Sample size allocation in a MRCT - Perspectives from sampling

- Scientifically, a MRCT should be done **at least** in a **representative** (unbiased), **minimum sample** of all patients of the world. The population in a MRCT ideally should be reflective to the disease distribution in the countries/regions

- With the practical challenges of implementing perfect sampling schemes at every country from operational perspectives, there is a non-avoidable needs of allowing for regulators to assess relevance of trial data for their jurisdiction while facilitating relevant/ scientific consideration of trial results

- The sample size drawn appropriately from the country should allow for the health authority to have a good base for the safety/benefit evaluation for the local population when a MRCT is considered for the drug/device registration,

- Sample size allocation: perspectives from medical needs
- **Issues in ethnicity evaluation: perspectives from PK/PD**
- MRCT and bridging data evaluation: Where are we standing now?

Sensitivity to Ethnic Factors

More Likely

- clearance by an enzyme showing genetic polymorphism
- steep dose-response curve

Less Likely

- lack of metabolism or active excretion
- wide therapeutic dose range
- flat dose response curve
- much clinical experience with other members of the drug class in the new region

Critical characteristics for ethnic evaluation considered by CFDA

Drug dispositions

- Initiative absorption, first pass effect, food effect
- Metabolized by CYP2C9, 2C19, 2D6, 1A2, 2A6,N-acetyltransferase (NATs) or UGTs (which showed polymorphisms)
- Elimination through renal tubular secretion
- Elimination through bile associated by transporter which showing genetic polymorphism

PD profiles

- Steep dose-response curve
- Narrow therapeutic windows
- Acceptability of biomarker is to be discussed
- Less clinical experience with other members of the drug class in the new region

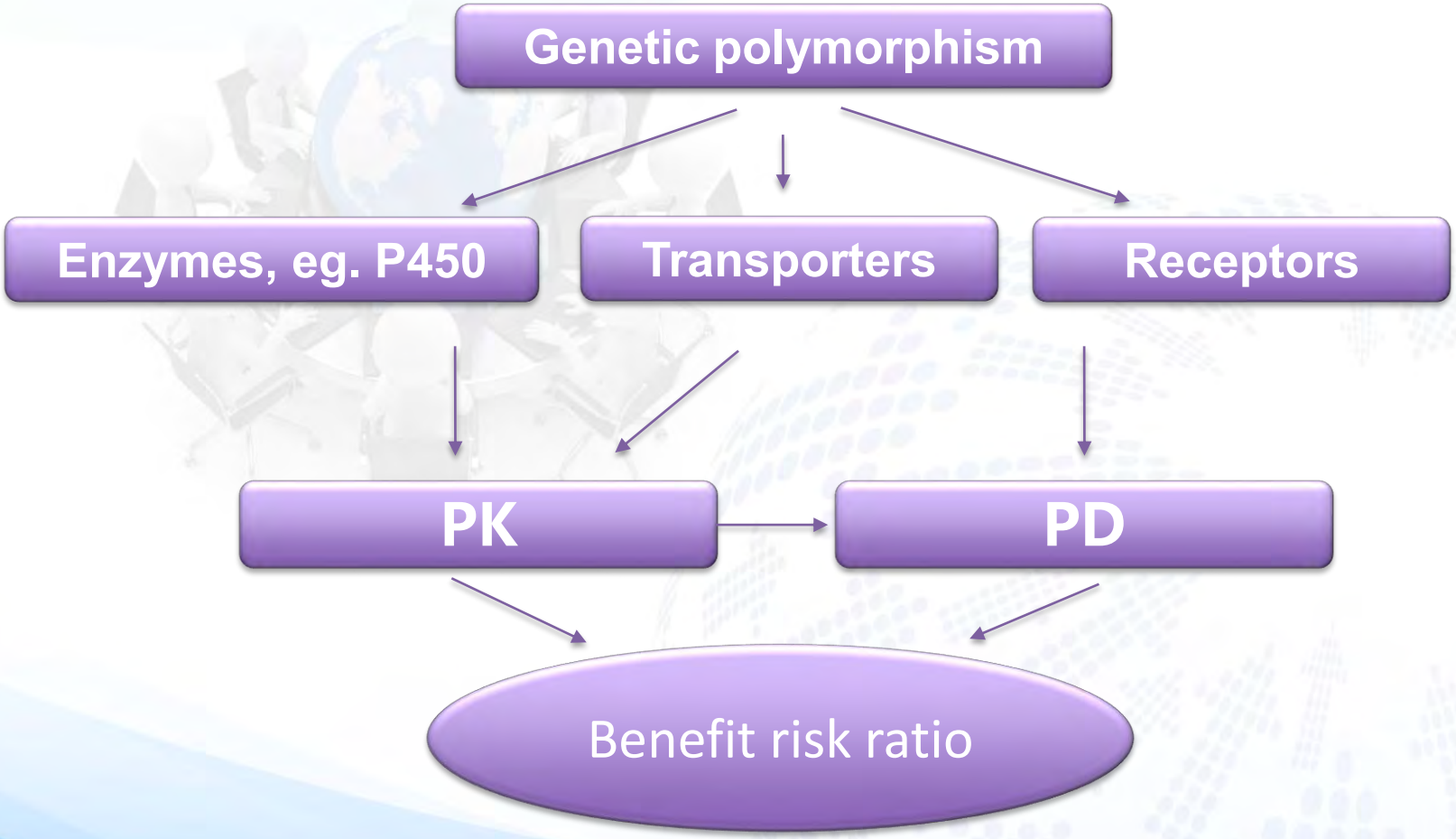
Issues in ethnic evaluation

- What percentage of drugs exhibit significant PK or PD differences? (what is significant/)
- What magnitude of difference exists?
- Are there patient characteristics that increase this risk? (e.g., age, disease, nutrition)
- Do PK/PD differences have clinical consequences (e.g., adverse events)
- Why the perspectives are different between the authorities represented drug-import countries or drug-export countries? (ethnic difference vs individual difference)

Issues in ethnic evaluation

- What percentage of drugs exhibit significant PK or PD differences? (what is significant/)
  - Intrinsic factors
    - Genetic polymorphism of the drug metabolism & transportation links with race
    - Disease model (or progress) is different of races
  - Extrinsic factors
    - Medical practice
    - Disease definition/Diagnostic
    - Therapeutic approach
    - Drug compliance

Effect of genetic polymorphism on PK/PD/Safety



Example 1

15 %

CYP2D6

Codein

CYP3A4

O-demethylation

Glucuronidation

N-demethylation

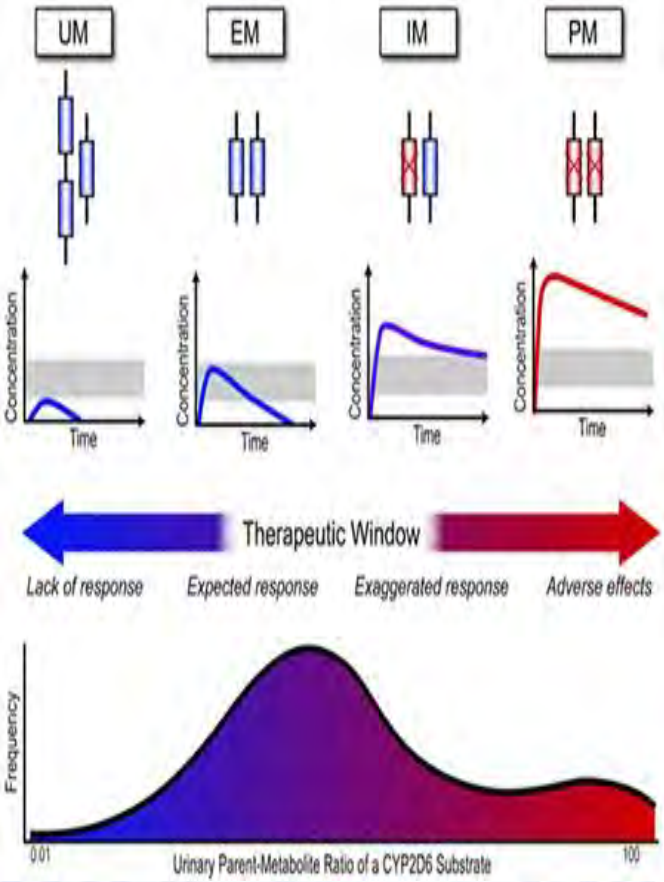
morphine

norcodeine

M3G

codei-6-G

norcodeine-6-G



FDA Drug Safety Communication: Codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death

Example 2

- Sertraline vs. Pimozidete (For Tourette's syndrome, 13 death
  - Sertraline: CYP2D6, Pimozidete: CYP3A4
  - Therapeutic window: narrow
  - AUC 37%
- PK, n=32 (HV)
- CYP2D6
- EM/IM/PM

N=15

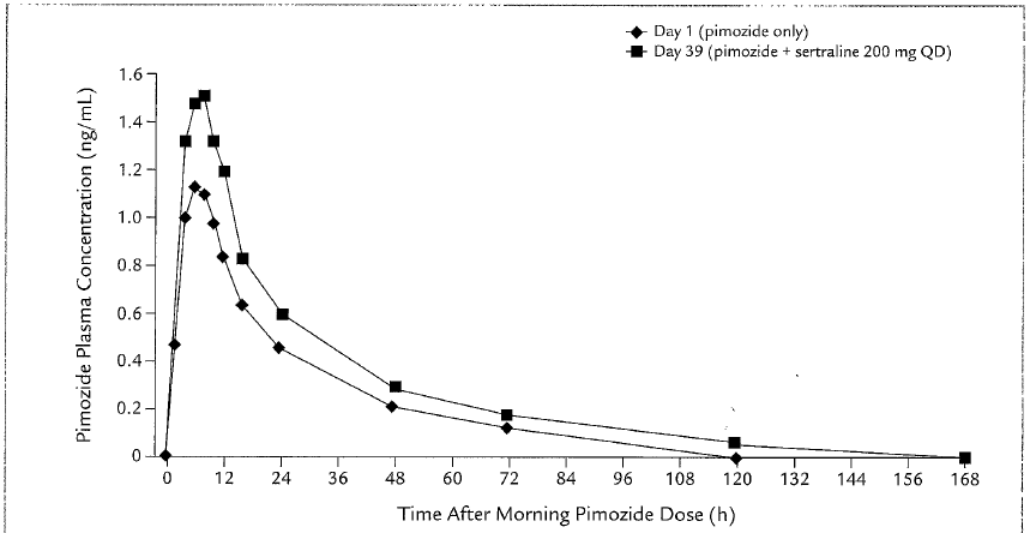
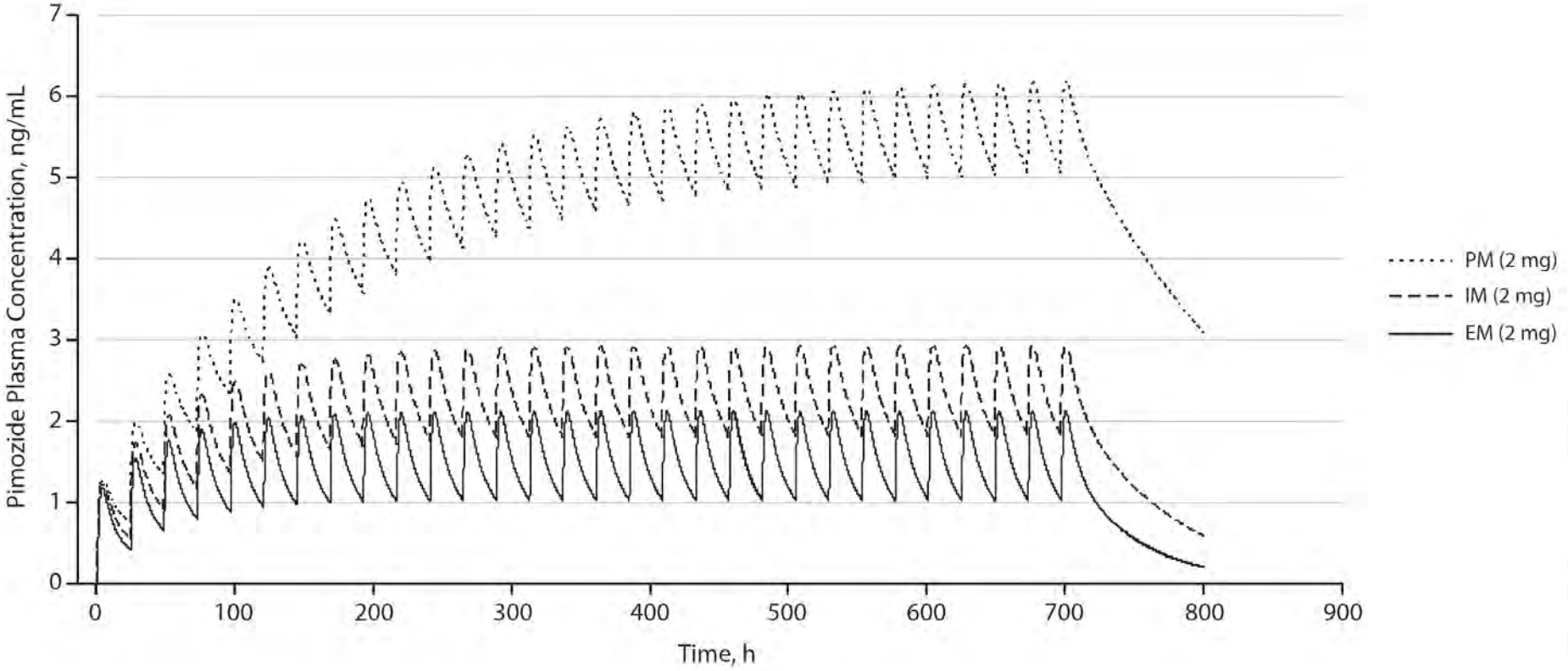


Figure 2. Mean pimozide plasma concentrations from 0 to 168 hours postdose on days 1 and 39.

Example 2

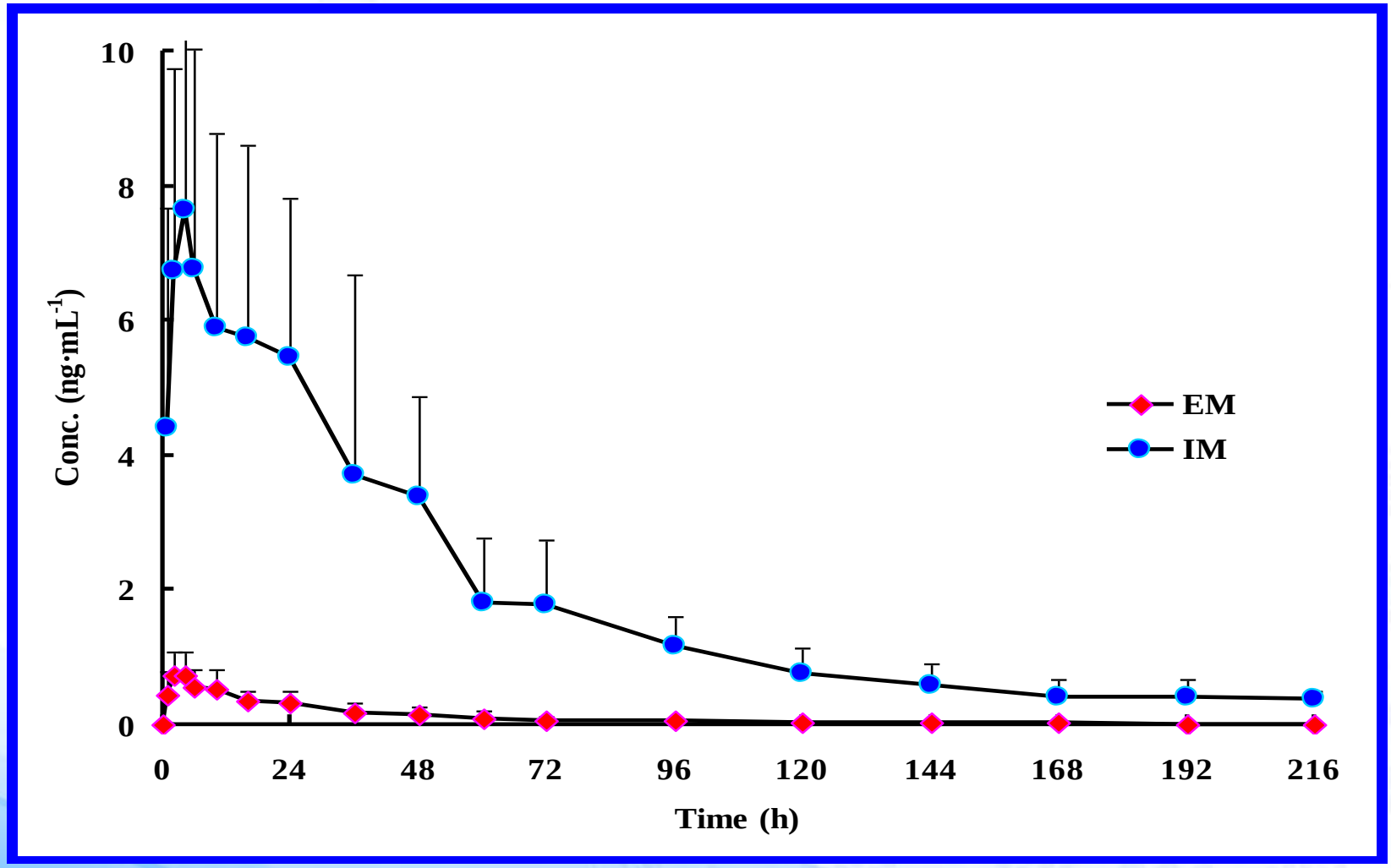
- Pimozidete 2mg：EM/IM/PM



J Clin Psychiatry. 2012 Sep;73(9):1187-90.

Example 3

- Drug X Substrate of CYP2D6



Example 4
Single-dose study

NA causes flush and GI tract AE

	PK parameter	Chinese	Non-Chinese
NA	AUC0-t (μg·hr/mL)	25.1	7.14
	Cmax (μg/mL)	9.86	2.483
	Tmax (hr)	4	4
Urine (μmol)	NA	1650	480
	NUA	1860	1566
	MNA	3120	2170
	2PY	5630	7524
	Total	=12260	=12288(LSGM)

Example 4
Multiple-Dose study

	PK parameter	Chinese	Non-Chinese
NA	AUC0-t (μg·hr/mL)	44.4	6.99
	Cmax (μg/mL)	17.5	3.24
	Tmax (hr)	4	4
Urine (μmol)	NA	2210	497
	NUA	1950	1490
	MNA	9030	3360
	2PY	6390	4200
	Total	=19580	= 9309 (LS mean)

Least-Squares Geometric Mean for AUC0-24hr and Cmax , Median for Tmax.

Worldwide distribution of poor metabolizers (PMs) of CYP2D6 and CYP_{mp}

Population	Debrisoquine Hydroxylase (CYP2D6)	Mephenytoin Hydroxylase (CYP_{mp})
Caucasians	3-9.2%	2.5-6.7%
Arabians/Egyptians	1-1.4%	?
Asian Indians	?	20.8%
East Asians	0-2.4%	17.4-22%
Amerindians	0-5.2%	0%
Hispanics	4.5%	4.8%
Subsaharan Africans	0-8.1%	?
Sans Bushman	19%	?
African-Americans	1.9%	18.5%

From: Keh-Ming Lin and Russell E. Poland, Ethnicity, Culture, and Psychopharmacology

Distribution of the percentage of poor metabolizers (PMs) of CYP2C19

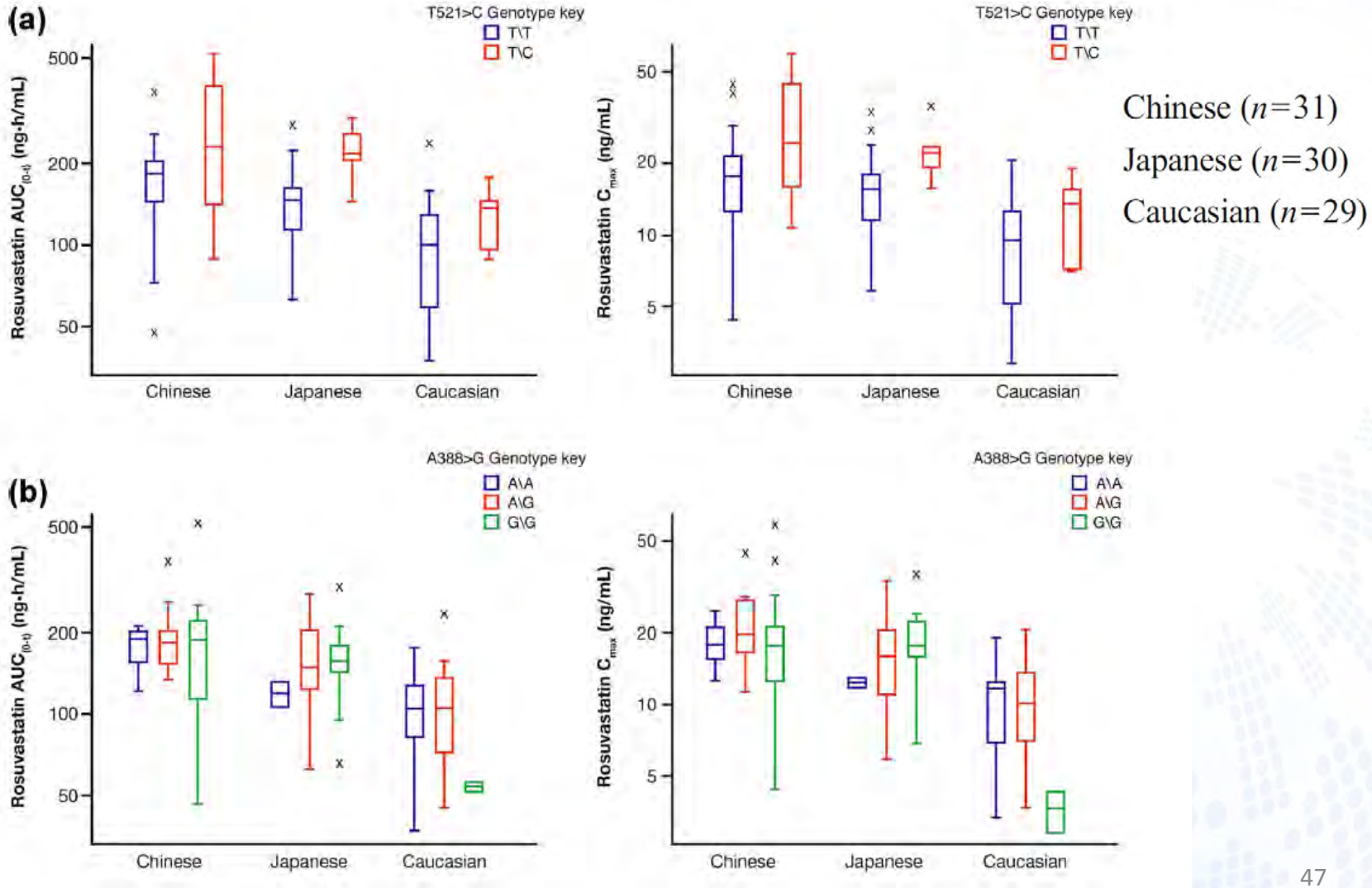
表2 不同种族间人群中 *CYP2C19* 代谢型分布比较 [n(%)]

RACE	NUMBER	*CYP2C19* 代谢型				
		UM	EM	IM	PM	UNKOWN
Indian	183	38 (20.8)	114 (62.3)	16 (8.7)	7 (3.8)	8 (4.4)
Caucasian	615	150 (24.4)	289 (47.0)	110 (17.9)	32 (5.2)	34 (5.5)
African	99	32 (32.3)	33 (33.3)	19 (19.2)	6 (6.1)	9 (9.1)
mulatto	315	94 (29.8)	128 (40.6)	63 (20.0)	11 (3.5)	19 (6.0)
Mongoloi	140	NA	62 (44.3)	65 (46.4)	13 (9.3)	NA

注：印第安人、高加索人、非洲人，黑白混血人的资料来自参考文献 [4]；NA，未检测。

重庆地区汉族人群CYP2C19基因多态性分布与不同种族间比较.《临床检验杂志》,2013年08期.

Example 5: Rosuvastatin (OATP1B1)



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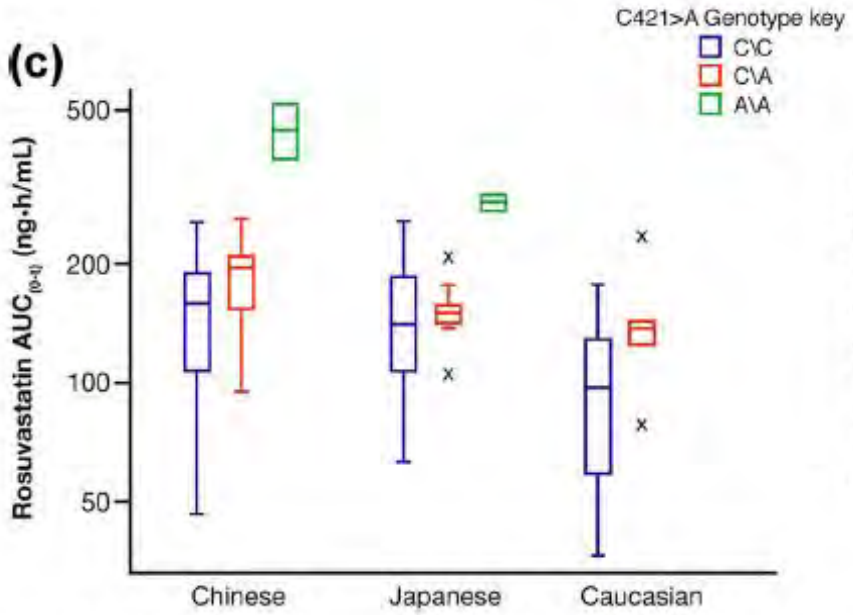
Example 5: Rosuvastatin (BCRP)

Chinese (n=31)
Japanese (n=30)
Caucasian (n=29)



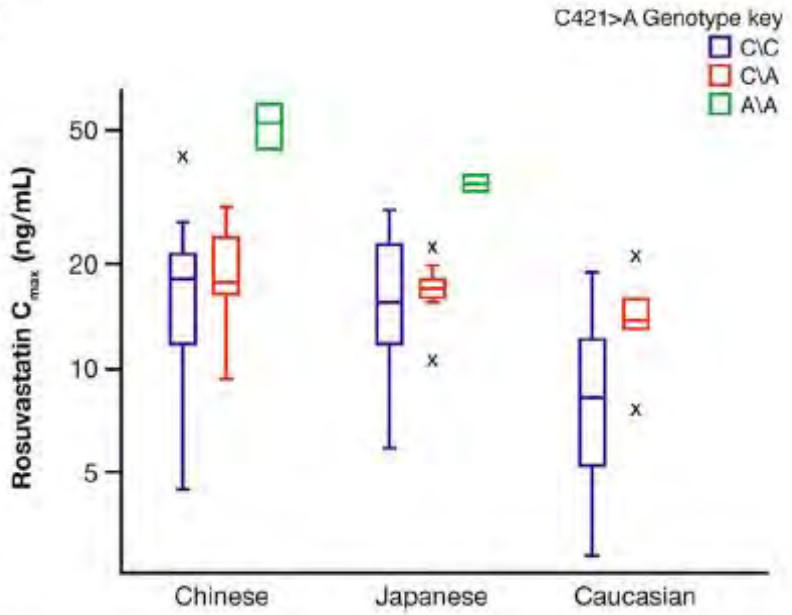


Fig. 1 Box-and-whisker plots of rosuvastatin $AUC_{(0\text{-}t)}$ (*left panels*) and C_{max} (*right panels*) by **a** *SLCO1B1* T521>C and **b** *SLCO1B1* A388>G and **c** *ABCG2* C421>A genotype. The upper and lower edges of the *box* represent the 75th and 25th percentiles, respectively. The *horizontal line* through the *box* represents the median. The *upper and lower whiskers* represent the highest and lowest datum within 1.5×interquartile range, whilst the *crosses* represent the extreme values

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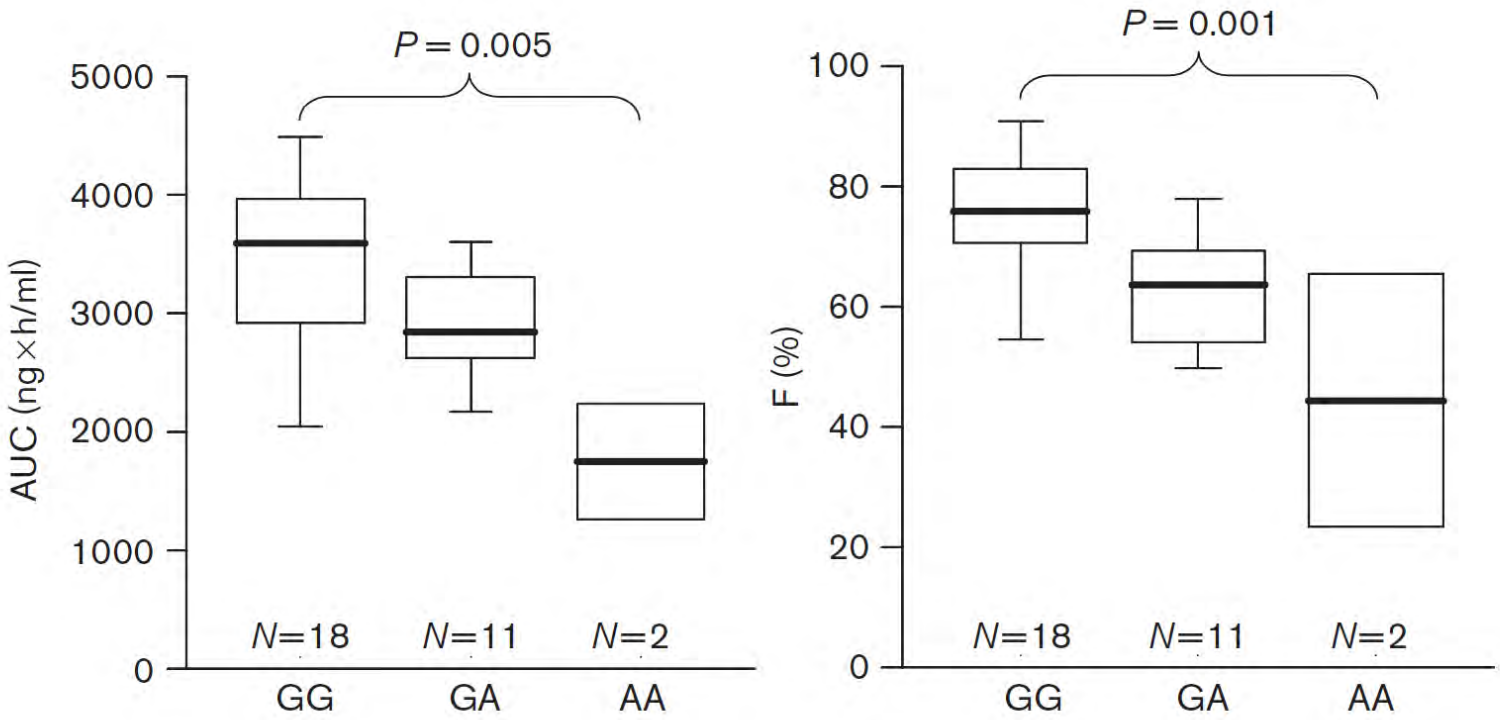
Example 6: Talinolol (MRP2)

Talinolol: BCS3，high solubility and low permeability

Inverse concentration gradient secretion, 1:4200

31例，MRP2：1249G >A in exon 10.



Pharmacogenetics and Genomics 2008, 18:357–365

Ethnic Differences on PD

- Propranolol is more effective in reducing blood pressure and heart rate in Chinese than in Caucasians.
- Patients in China are prescribed much lower doses of propranolol than patients in the US and Europe.
- Paradoxically, Chinese patients metabolize propranolol more rapidly than Caucasian patients.
  - Total blood clearance for Chinese patients is 76% greater.

- HBV-specific T-cell repertoires are divergent in the two ethnic groups, with T-cell epitopes frequently found in Caucasian patients seldom detected in Chinese patients.
- The discordance between HBV-specific CD8 T-cell repertoires present in Caucasian and Chinese has implications for the rational development of therapeutic and prophylactic vaccines for worldwide use.

http://cobb.nmanet.org/images/uploads/Racial_and_Ethnic_Differences_in_Response_to_Medicine.pdf

The Effects of TCMs on DMPK

The traditional Chinese medicines (TCM) are essential components of alternative medicines in China. Many TCMs are known to alter the expression of hepatic drug-metabolizing enzymes and transports.

Methodologies for analyzing bridging studies data

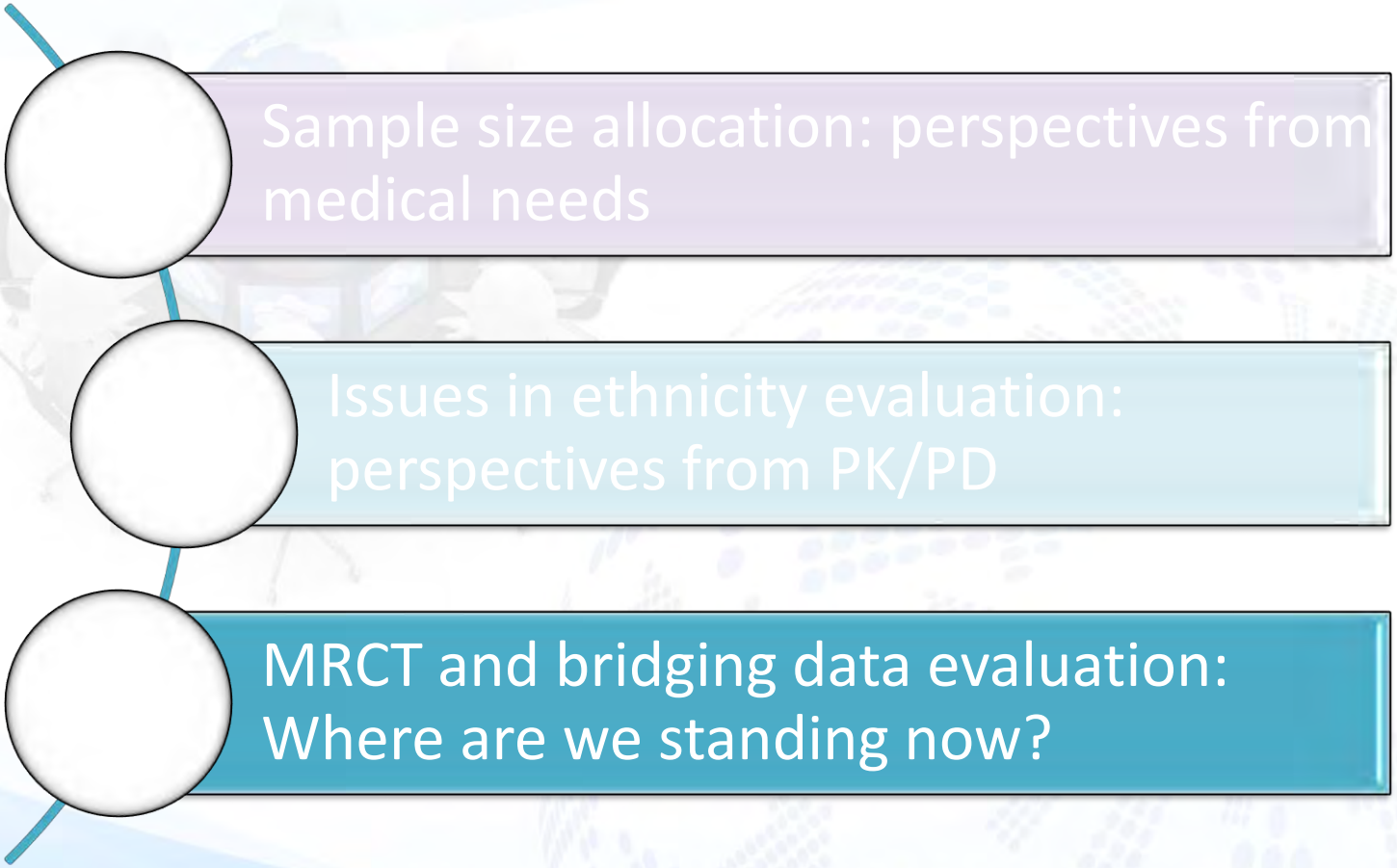
- Application of population approach
- Pharmacometrics approach

- Phase I studies should reach international standards further.
- the PK/PD link study should be emphasized by sponsors and investigators.
- based on the PK and PK/PD from phase 1 studies, modeling/simulation and the population approach will be applied more in phase 2 and phase 3 trials in the future.
- model based clinical study design will be developed in China.

Summary

- In order to extrapolate clinical data cross populations, it is important to study inter-ethnic differences in drug response and toxicity, ethnic diversity in pharmacokinetics and clinical outcomes.

- The perspectives may be different between the authorities represented drug-import countries or drug-export countries.


Sample size allocation: perspectives from medical needs
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MRCT and bridging data evaluation: Where are we standing now?

Operational challenges of China joining MRCT

- Level of experience of investigators/sites and clinical practice can vary markedly

- Still a developing country requiring more clinical operation support from sponsor compared to more mature countries for the quality

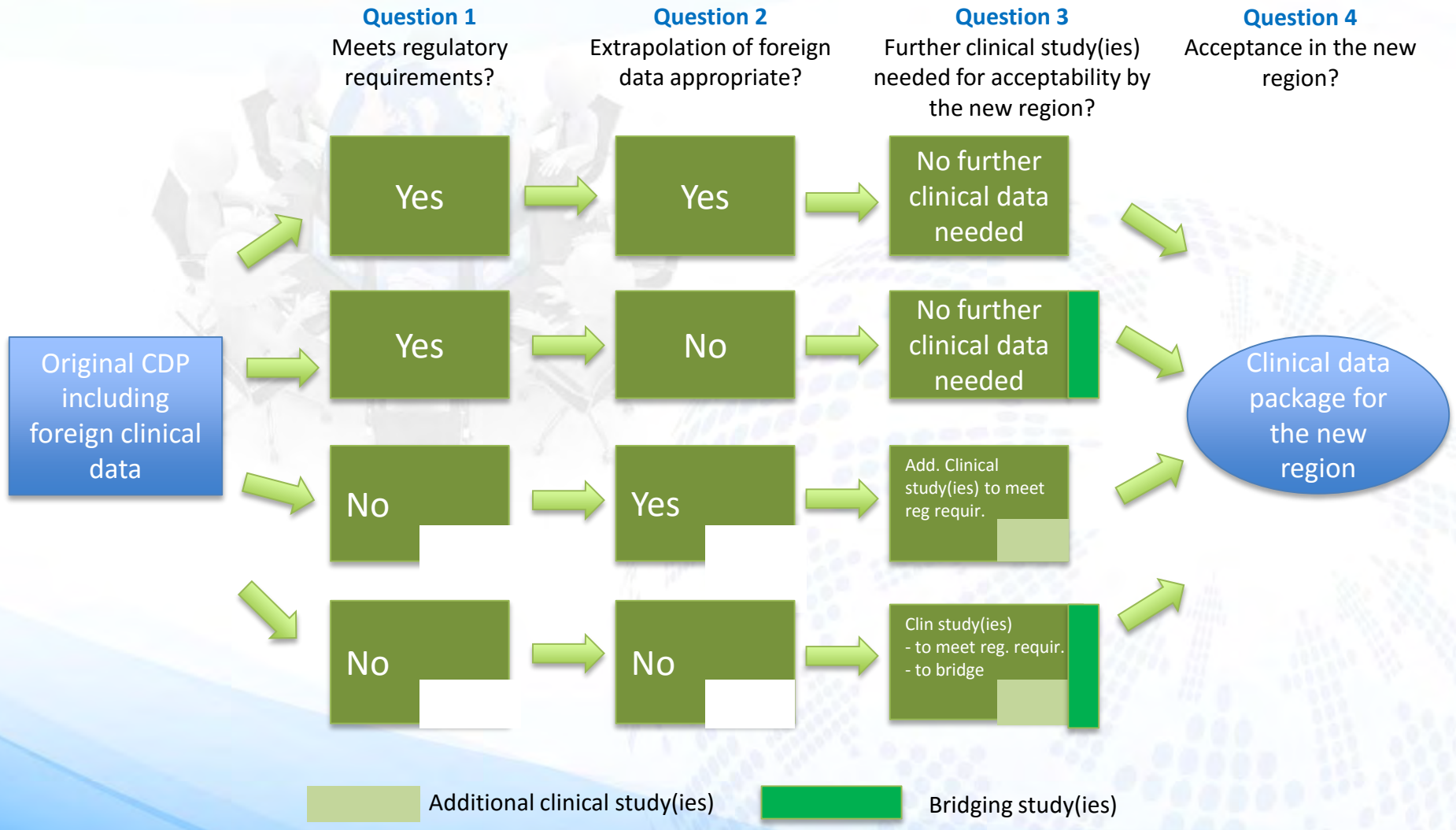
- Still limited GCP certified sites limiting the pool of investigator sites
- Medical records not shared between hospitals

- Relatively lacking behind in readiness for new technologies, e.g. ePRO

- Very competitive resources and capacities of the researchers

- Further development of collaborative platform for research and operation

ICH E5 - Assessment of the clinical data package (CDP) for acceptability



Questions remains for an evaluation algorithm

Meet regulatory requirement?

- Phase I PK study?
- Minimal sample size (e.g., 100 pair) for rare diseases?
- Consistent treatment effect in Chinese subpopulation vs. non-Chinese, Asian vs. Non-Asian from MRCT (per IMCT)?

Extrapolation appropriate?

- Intrinsic/extrinsic factors relevant to diseases (e.g., rare diseases vs. common)?
- Relevant patient demographics in the country?
- Acceptable differences allowing for extrapolation?
- a similar concentration (dosage) – response between Chinese and foreign countries?
- PK or PD data that can be used to determine dosage or predict safety and efficacy in Chinese?

Further clinical data/studies needed?

- The time lag result from CPP dependence?
- Designation criteria for Bridging study waver?
- Allow for bridging study for safety only?
- Designing guidance for designing a RCT?

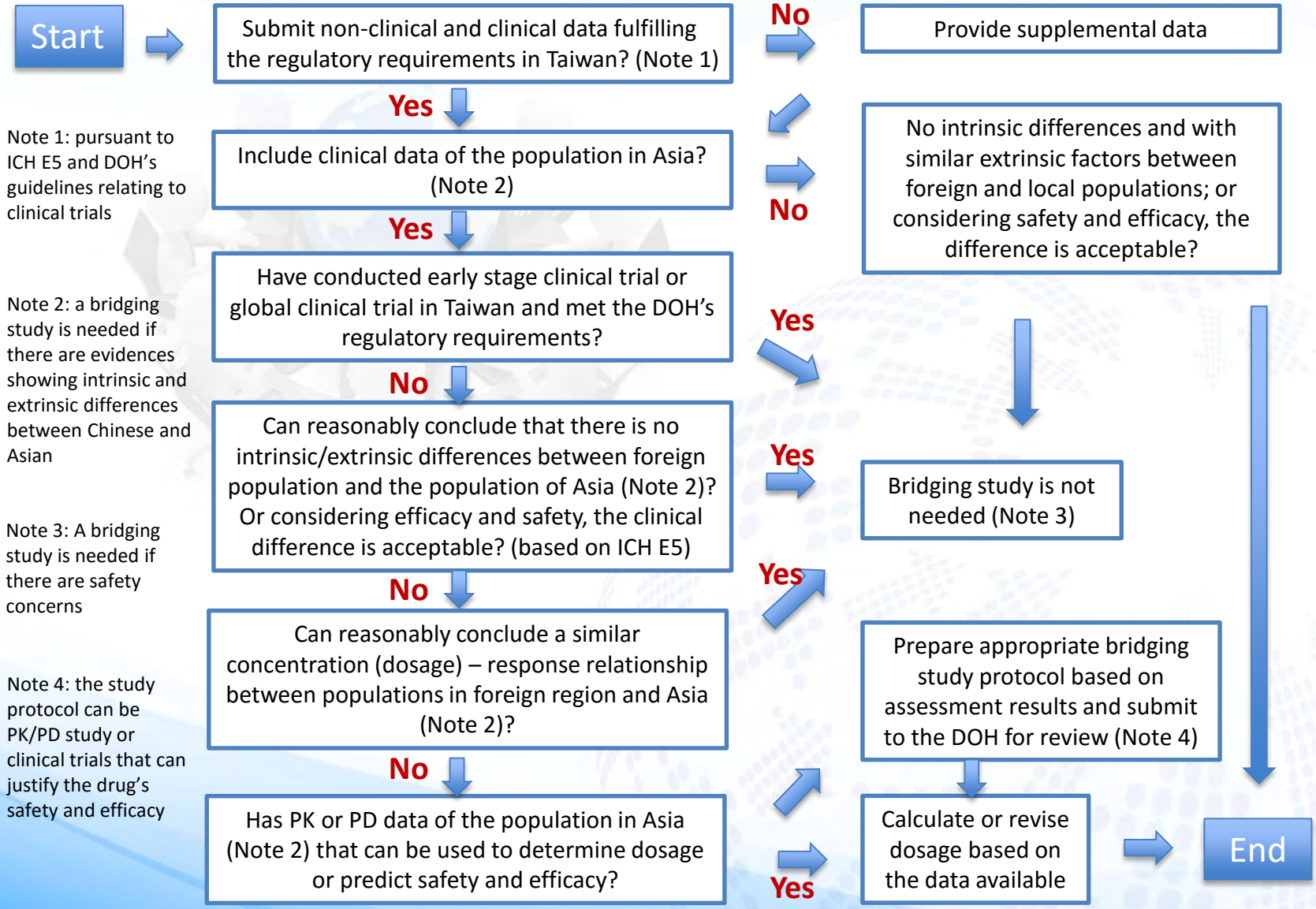
- Suggestions and proposal to be discussed and aligned

Reference

Thank you

ICH E17科学监管研讨会
ICH E17 Scientific and Regulatory Workshop

Taiwan – Flowchart of assessing the necessity of a Bridging Study



Note 1: pursuant to ICH E5 and DOH's guidelines relating to clinical trials

Note 2: a bridging study is needed if there are evidences showing intrinsic and extrinsic differences between Chinese and Asian

Note 3: A bridging study is needed if there are safety concerns

Note 4: the study protocol can be PK/PD study or clinical trials that can justify the drug's safety and efficacy

MRCT - Consistency and Sample Size

China MRCT Consistency Workgroup

October 2015, Beijing

Positioning Our Project Work

Our project work is globally impactful:

- Defines consistency for MRCTs
- Foundational for the E17 workgroup

Outline

- MRCT introduction: why; challenges, regulatory guidance
- Disease categories and level of consistency
- Statistical methods, sample sizes and examples
- Summary

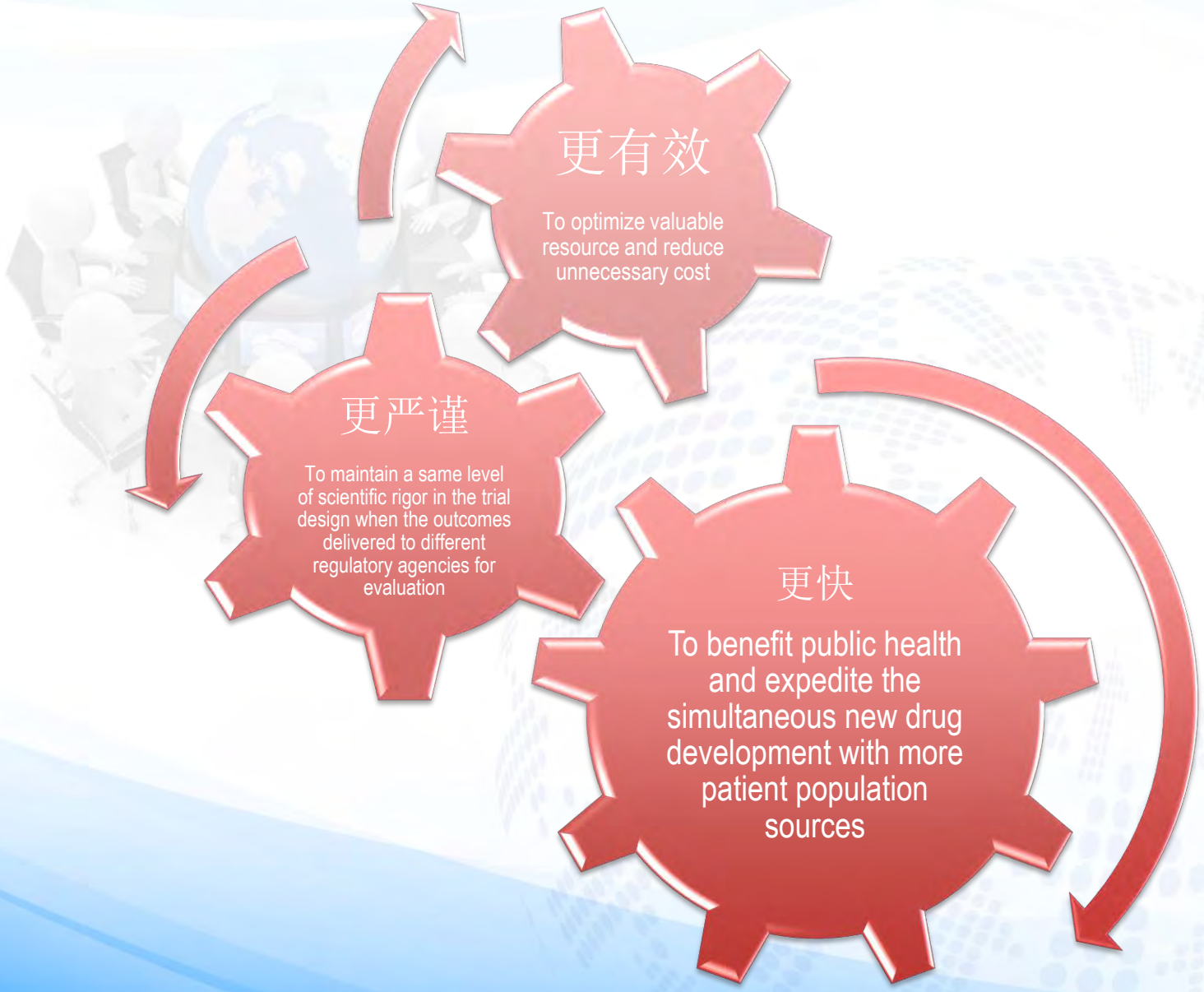
国际多中心临床试验（MRCT）定义
（CFDA国际多中心药物临床试验指南（试行））

- 国际多中心药物临床试验（MRCT）
  - 在多个区域的多个中心按照同一临床试验方案、同时开展临床试验（多区域临床试验）
  - 不同国家的多个中心按照同一临床试验方案、同时开展的临床试验（区域性临床试验）
  - （国际多中心药物临床试验数据用于在我国申报药品注册的）至少需涉及包括我国在内的两个国家

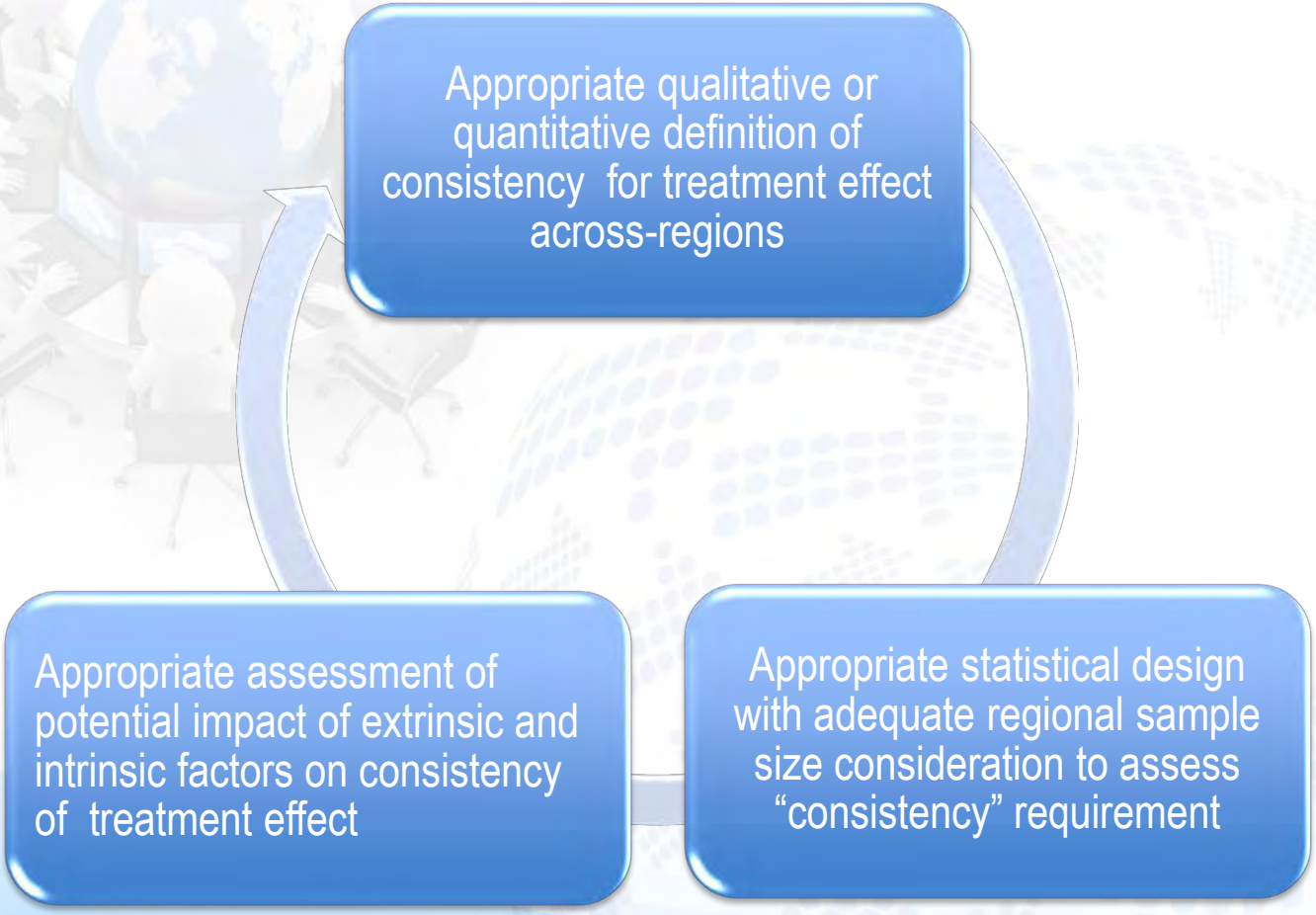
MRCT for a New Drug Approval Globally Needs to Be:

- Flawlessly conducted
- Internally consistent
- Statistically persuasive
- Favorable benefit risk ratio

Why MRCT?


更有效
To optimize valuable resource and reduce unnecessary cost
更严谨
To maintain a same level of scientific rigor in the trial design when the outcomes delivered to different regulatory agencies for evaluation
更快
To benefit public health and expedite the simultaneous new drug development with more patient population sources

Challenges in Assessing Internal Consistency of MRCT Results



Regulatory Guidelines

- 1998 ICH-E5 bridging
  Ethnic Factors in the Acceptability of Foreign Clinical Data
- 2006 ICH-E5 Q&A No.11
- 2007 日本药物监管部门(MHLW): method 1 , method 2
  Basic Principles on Global Clinical Trial
- 2012日本药物监管部门 (MHLW)
  Basic Principles on Global Clinical Trials (Reference cases)
- 2015 CFDA IMCT guidance
  国际多中心药物临床实验指南 （试行） **Guidance for International Multicenter Clinical Trials (IMCT)**
- Coming ICH E17

Disease Categories and Consistency

Considering medical needs and potential impact of ethnic factors in clinical practice, three different disease categories can 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

Disease Categories and Consistency

According to different disease categories, we can consider 3 levels of "consistency" between region and the overall：

Level 1: Treatment effects share the same trend → disease category1

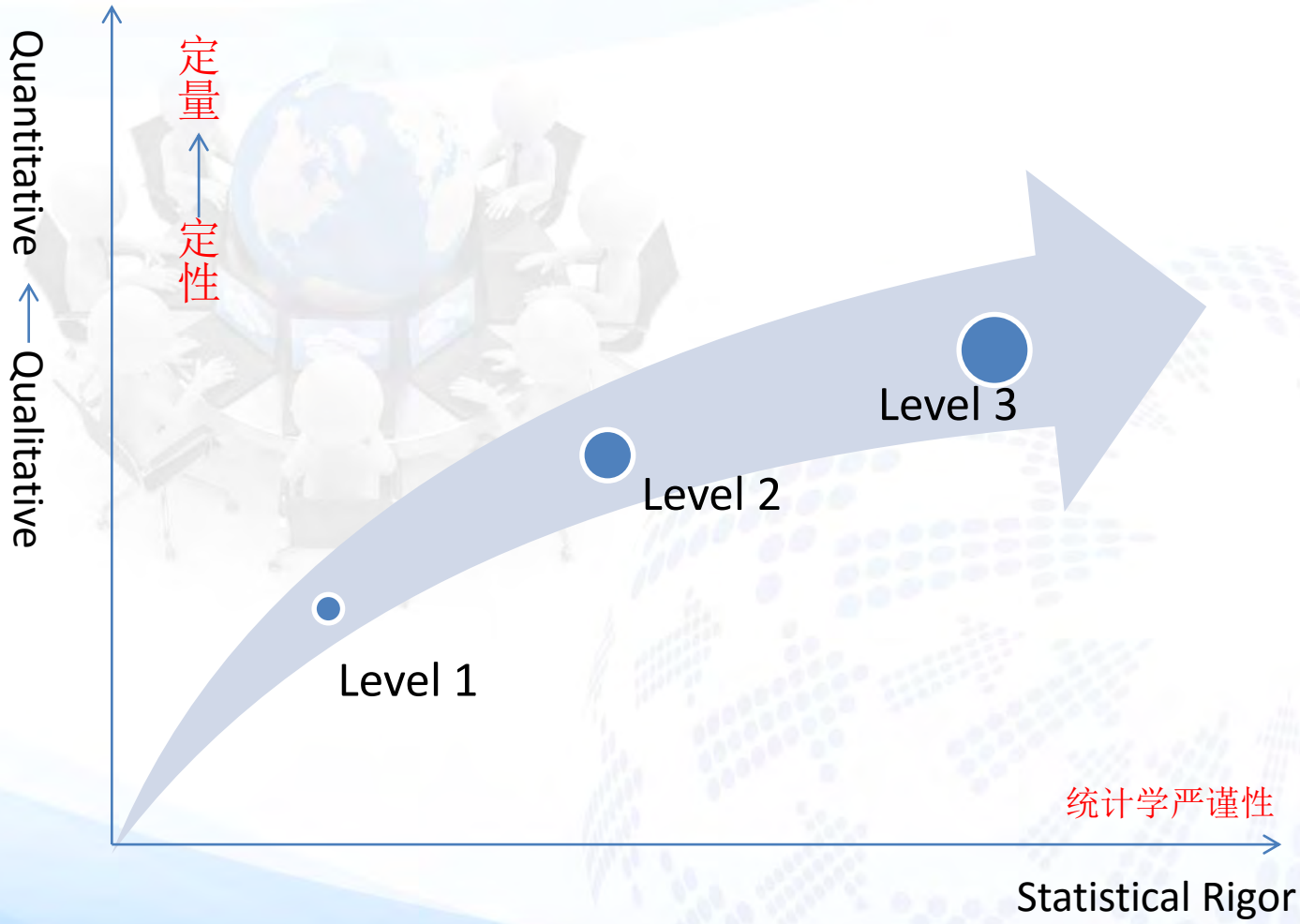
Level 2: Treatment effects are proportional → disease category2

Level 3: The treatment effect in the region also demonstrates clinical significance with statistical rigor → disease category3

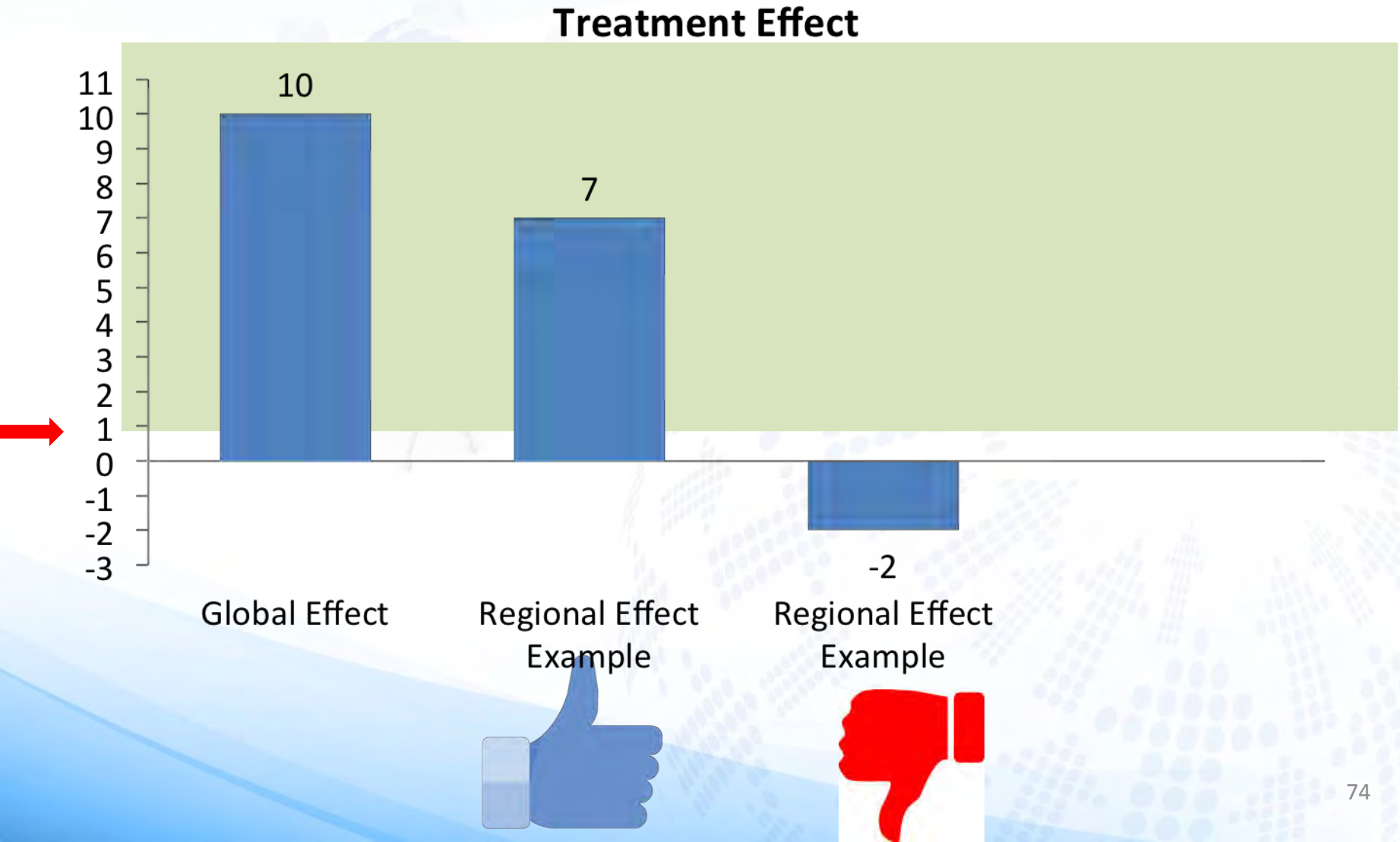
Level of Consistency Required for Different Disease Categories

Disease Category 1	Disease Category 2	Disease Category 3
• 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.	• 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	• 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.

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



Level 1 Consistency; Observational trend; Illustration: All treatment effects > 0

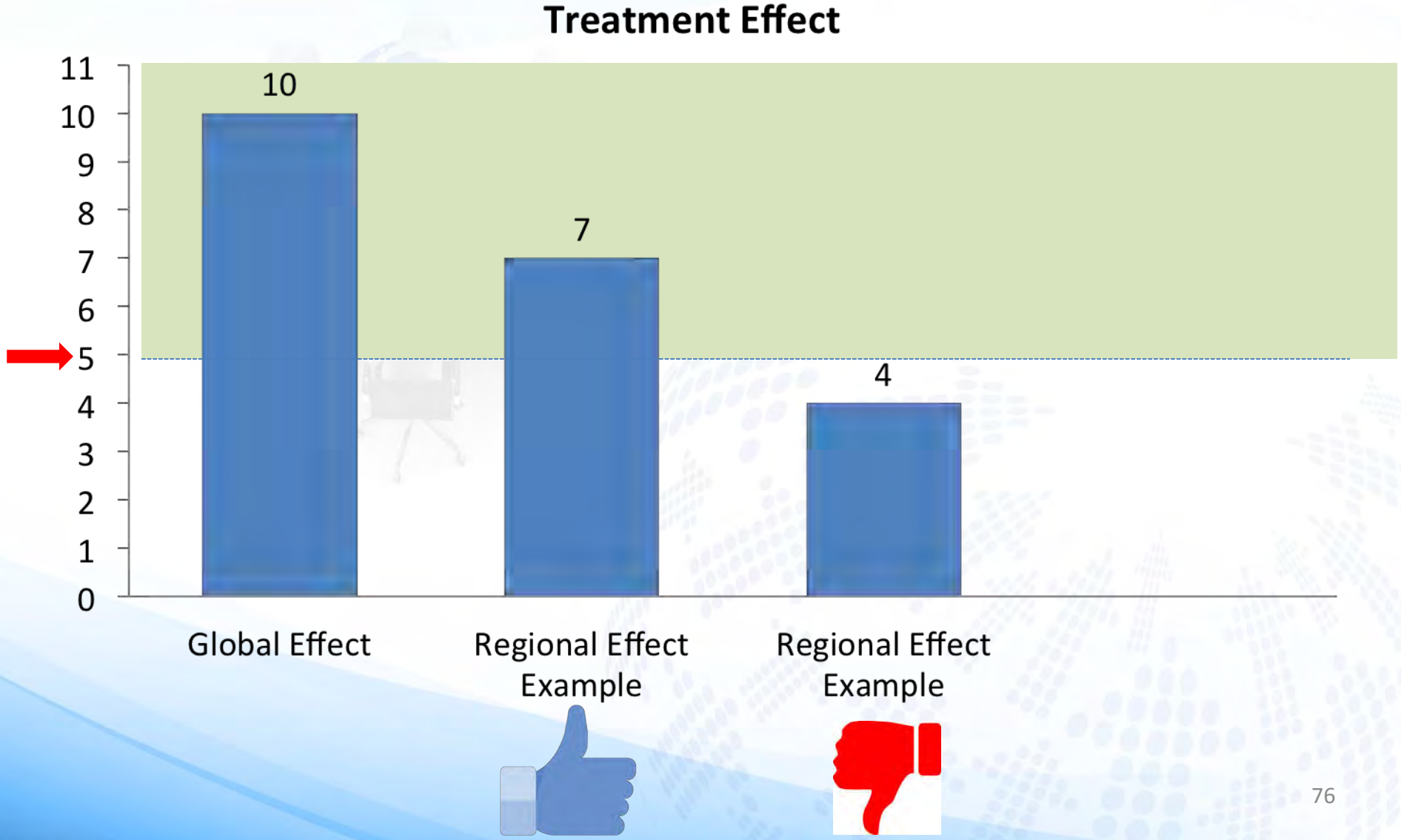


Level 1 Consistency: Sample size consideration, example

- Adequate same size to achieve required precision of CI or other quantitative assessment methods
- Example: MRCT size=500, MRCT effect size = 0.25 = regional effect size , Power =80%.

Method	Regional sample size(%)
Both treatment effects positive	46 (9%)

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



Level 2 Consistency: Sample size consideration example, calculation based on PMDA Guidance Method 1

Treatment effects are proportional between the region and overall:

- proportion >=30%(region/overall):

Study power	proportion of regional patients For 80% probability of consistency
80%,	17%
90%	13%

- proportion >=50%(region/overall)

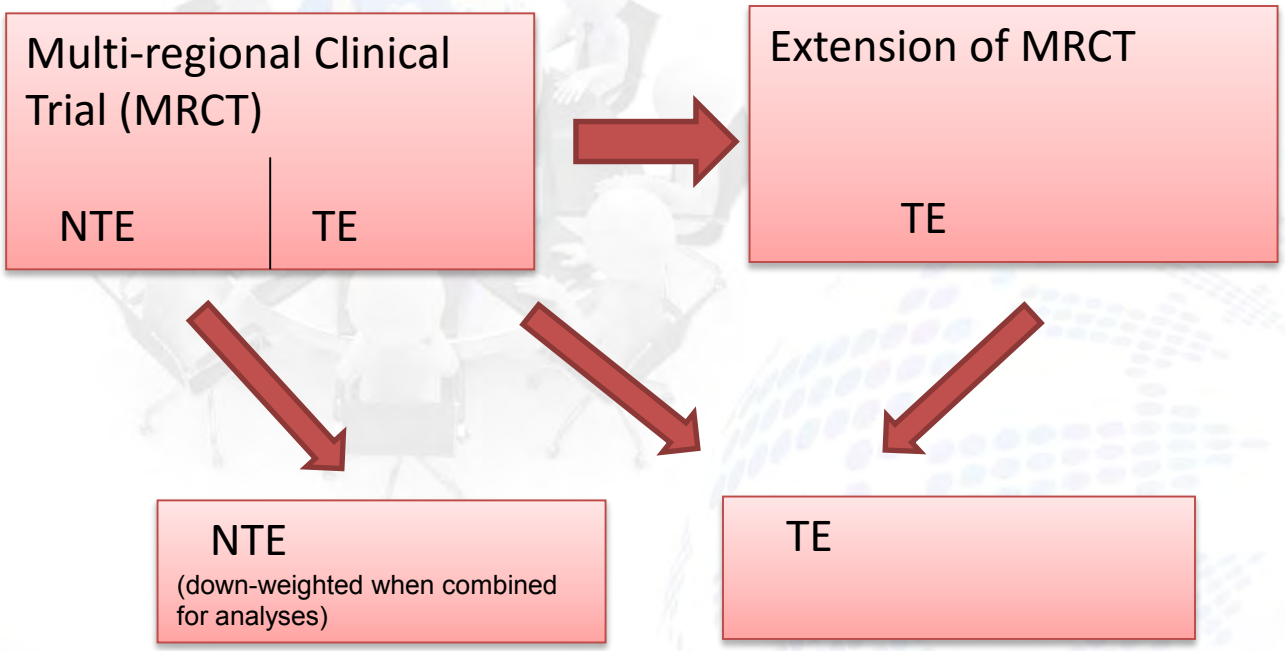
Study power	proportion of regional patients For 80% probability of consistency
80%,	28%
90%	22%

Quan H, Zhao P-L, Zhang J, RoessnerM, Aizawa K.Sample size considerations for Japanese patients in a multi-regional trial based on MHLW Guidance.Pharmaceutical Statistics 2010; 9(2):100–112.

Level 3 Consistency: The treatment effects for both region and the overall achieve the required clinical significance with statistical rigor

- To achieve statistical rigor for both overall and a region subgroup either using data within MRCT OR the data from MRCT plus extension if the sample size planed in MRCT may not be adequate to assess clinically meaningful treatment effect with statistical rigor.
- 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

Level 3 Consistency: Considering MRCT with extension



TE: targeted ethnic group
NTE: non-targeted ethnic group

Level 3 Consistency: Sample size consideration, Example

- MRCT size=500 with 10% TE pts, MRCT effect size = 0.25, table shows the sample Size for the MRCT extension.

Weight (wt)	TE (region) group effect size		
	0.15	0.20	0.25
0%	1346	735	453
10%	683	371	225
20%	493	266	159
30%	**370**	**198**	**117**
40%	277	148	85
50%	203	107	60
60%	142	74	40
70%	90	45	23

*Q. Huang, G. Chen, Z. Yuan, G. Lan (2012). Design and Sample Size Consideration for Simultaneous Global Drug Development Program, *Journal of Biopharmaceutical Statistics*.

Summary

- 3 levels of consistency have been considered to assess whether the treatment effects between the region and overall are consistent for the different disease categories.
  - Level 1 consistency focus on unmet medical needs or rare disease:
  - Level 2 consistency focus on common disease with no evidence for ethnic difference
  - Level 3 consistency focus on common disease with evidence for ethnic difference:
- Safety profile of a new treatment should be an important factor in the consideration of consistency level requirement.
- Conducting a MRCT is complex and challenging. More factors need to be considered, including how to design, monitor and analyze such study.
- We here only considered the consistency for treatment effect. Next we need also consider how to “quantify” safety and clinically meaningful benefit/risk of a new therapy.
- In addition to the sample size estimate for each region, we need also to consider different desirable country-specific risk-benefit profiles.

Thanks!

M&CT Q&A

Conducting a MRCT is complex and challenging. More factors need to be considered, including how to design, monitor and analyze such study.

- For Ethnic difference, can we use published data of the same class drug for reference?
- Can we simultaneously do PK/PD study to get early evidence on existence of ethnic difference?
- For rare disease, is it necessary to have adequate regional data to test level 1 consistency?
- We here only considered the consistency for treatment effect. For safety, can we also quantify the “consistency”?
- Can we define different desirable, clinically meaningful country-specific risk-benefit profiles and how can we assess quantitatively risk/benefit ratio?

A New Vision for “Region”

Why have we focused on Regions in MRCTs?

- **MRCT's are conducted in order to efficiently allow regulatory agencies around the world to make approval decisions for their populations.**
  - Requires analysis of sub-population data which either comes from the relevant population and/or from others similar enough to allow for conclusions to be drawn about benefit-risk
- **Typically Geographic focus (regions or countries) used:**
  - Allows for consideration of needs of different regulatory jurisdictions
  - Geography is considered to be a "surrogate" for key features of populations which may impact drug effects .
    - » BUT Important intrinsic and extrinsic factors do not always sort by geographic boundaries
- For discussion:

  Is there a better way to define sub-populations while facilitating relevant/ scientific consideration of results and allowing for regulators to assess relevance of trial data for their jurisdiction?

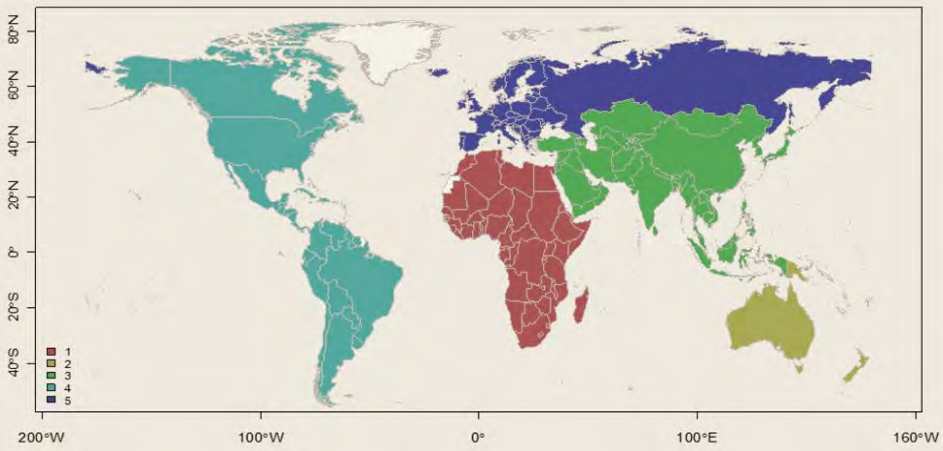
What is Region?

Defining Region by Geography

Traditionally, region has been defined geographically.

Typically a region = a continent

For example, the U.N. has identified 5 regions (below), with 23 subregions.1



1. Yoko Tanaka et al., "Points to Consider in Defining Region for a Multiregional Clinical Trial: Defining Region Work Stream in PhRMA MRCT Key Issue Team." Drug Information Journal, Vol. 45, pg 575-85 (2011), pg 577.

Problems with Geographically-Defined Region

Relying on geographic region may have drawbacks:

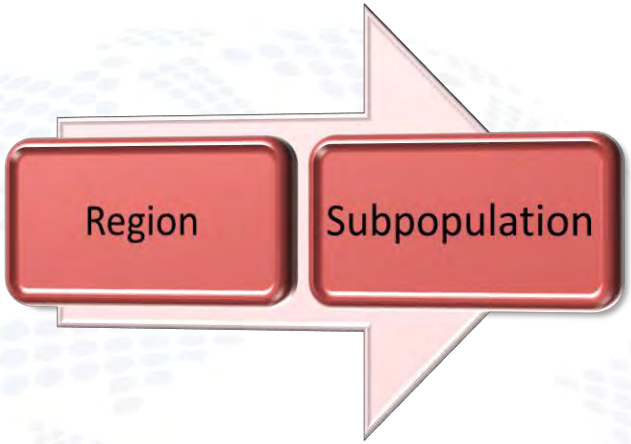
- Geographically-defined regions are often determined arbitrarily, rather than by scientific or statistically rigorous approaches.[1]
- MRCTs require a relatively homogenous population (defined by strict inclusion/exclusion criteria) – however, patients within geographically-defined regions may still be quite different, leading to:
    - Excessive heterogeneity of treatment effect
    - Need to increase sample size requirements
    - Potential to necessitate separate trials.[2]
- Defining region by geography alone **excludes** consideration of important **intrinsic and extrinsic factors** which may potentially impact study outcomes.[3]

1. Yoko Tanaka et al., "Points to Consider in Defining Region for a Multiregional Clinical Trial: Defining Region Work Stream in PhRMA MRCT Key Issue Team," Drug Information Journal, Vol. 45, pg 575-85 (2011), pg. 576.
2. Id. at 580.
3. Id.

A Shift from "Region" to "Subpopulation"

Recognition of these drawbacks has led to a proposal to define "subpopulation" rather than "region":

- "Subpopulation" is more a dynamic term than "region," and should include **other extrinsic and intrinsic factors**:
  - race or ethnicity, disease epidemiology, medical practice, and geographic proximity.[1]
- Different drugs/diseases/studies may justify different definitions of "subpopulations"



•**Subpopulation** should be **predefined** at the time of study design that incorporates the factors described above and plan how these factors will be assessed.[2]

1. Yoko Tanaka et al., "Points to Consider in Defining Region for a Multiregional Clinical Trial: Defining Region Work Stream in PhRMA MRCT Key Issue Team," Drug Information Journal, Vol. 45, pg 575-85 (2011), pg. 575.
2. Id.

A Shift from "Region" to "Subpopulation"

Intrinsic and Extrinsic Factors[1]

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

1. Appendix A, ICH E5 Guideline

"Region" in ICH E5

ICH E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data

- The ICH E5 Glossary includes the following regulatory definitions related to region:
  "ICH Regions" – European Union, Japan, The United States of America.
  "New Region" – The region where product registration is sought.

- These definitions indicate *A* basis for defining region.[1]
- However, the guidance also focuses on ethnic factors that lead to heterogeneity within a region – highlighting a key weakness in geographically-defined regions to be considered in ICH E17.

[1] e.g., ICH E5 1.3

From “Region” to “Subpopulation” in ICH E17

ICH E17 General Principle on Planning/Designing Multi-Regional Clinical Trials

- ICH E17 is still being drafted, to be completed in Winter 2017.
- This draft will have significant impact in the planning and design of multi-regional trials.
- The guidance may incorporate a new focus on the concept of **sub-population** rather than region.
- Will still address the separate needs of regulatory jurisdictions and the need to work with health authorities when planning MRCT’s and defining subpopulations .
- Ability to draw inferences from relevant subpopulations will be critical to acceptance of MRCTs for drug approvals.

"Region" in the IMCT Guidance

Announcement on Promulgating the Guidance for International Multicenter Clinical Trials (IMCT)

- Refers to "different regions of the world" without specifying how region will be defined. [1]
- The phrase "country or region" in reference to requirements indicating a geographic orientation.[2]
- Recognizes the heterogeneity within geographic regions.[3]

1. IMCT Guidance Section II
2. E.g., IMCT Guidance Section V.1, V.6
3. IMCT Guidance Section IV

Why “Sub-population” Matters in China

IMCT guidance relies heavily on a geography; the importance of intrinsic and extrinsic factors is recognized.

Is there an opportunity to consider these factors as sub-populations are defined?

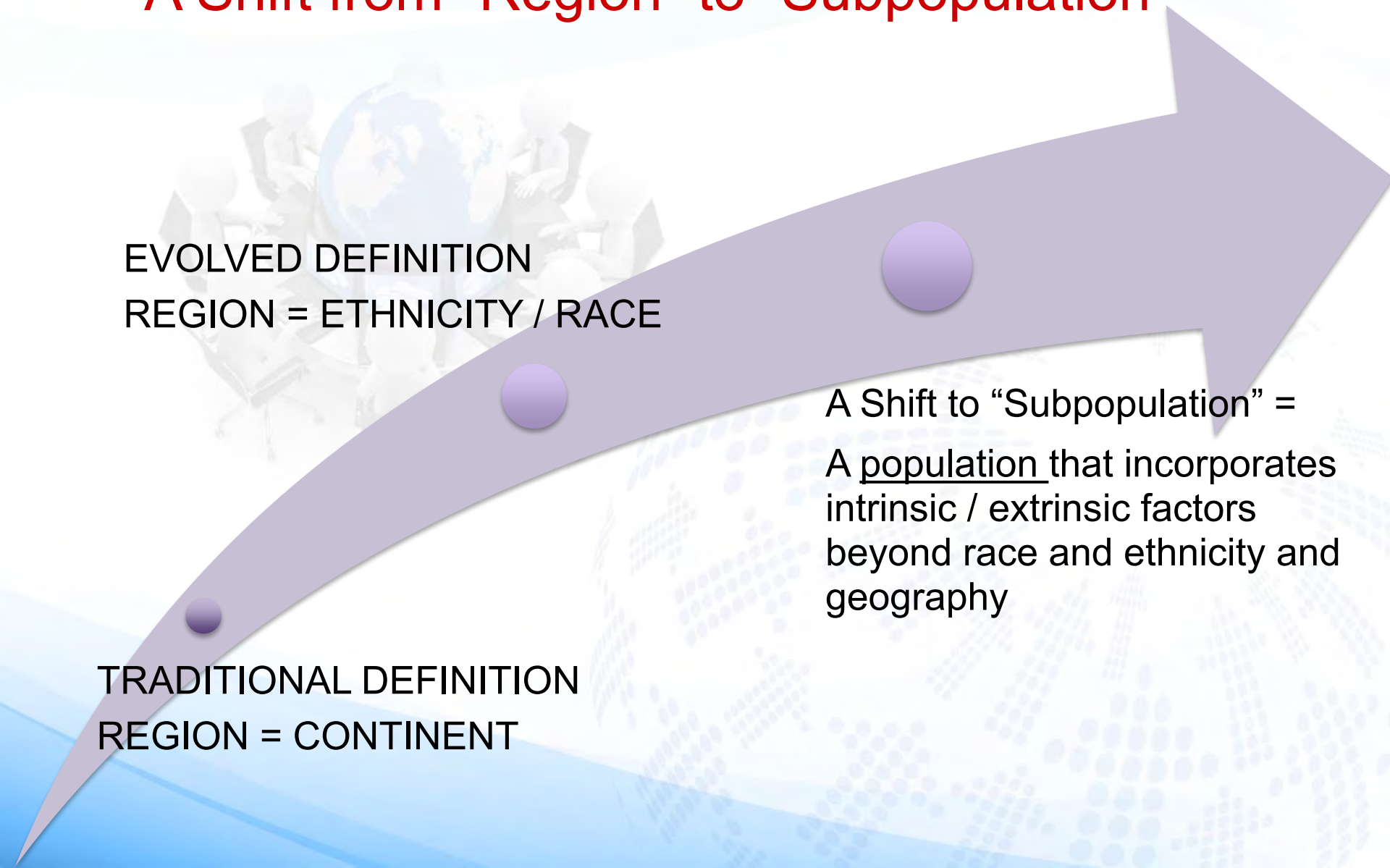
- There are Chinese ethnicity all over the world – even limiting region to Asia may not be the best way to assess these populations.

- Focusing on “subpopulation” will enable researchers to isolate the intrinsic and extrinsic factors that have been identified as essential to the inquiry.

For Example - Simvastatin

- In 2011, the Simvastatin label was *revised* to warn against prescribing 80 mg for patients of Chinese descent also on niacin
- The basis of this warning was new safety information showing higher rates of muscle injury at the 80-mg dose in patients with a genetic variant 521T>C in codon 174 – a critical transporter in the disposition of statins
- Potential implications of redefining “region” include that a safety issue such as this could have been caught earlier if subpopulation had been pre-defined differently and not equivalent to country

A Shift from “Region” to “Subpopulation”



EVOLVED DEFINITION

REGION = ETHNICITY / RACE

A Shift to “Subpopulation” =

A population that incorporates intrinsic / extrinsic factors beyond race and ethnicity and geography

TRADITIONAL DEFINITION

REGION = CONTINENT

MRCT's: Defining Sub-Population

Some thoughts:

- There is little benefit to a strictly geographic definition because any findings in these subgroups will lead to a search for extrinsic and intrinsic factors to explain any differences.

- Consider scientific basis for defining subpopulation– include consideration of extrinsic and intrinsic factors.

- Subpopulation definition should be pre-specified and based on best available information in order to ensure its effectiveness and freedom from bias.
- By defining relevant sub-populations and associated statistical analyses, drug development can more efficiently allow for consideration by health authorities of new therapies for patients around the world.

Summary

- Defining trial subpopulations solely on geography without consideration of intrinsic/extrinsic factors may create unintended heterogeneity, rather than the intended homogeneity. This may impact trial results /interpretation.
- Geographical groupings may not allow for needed flexibility
- With other approaches to subpopulation definition, different factors can be considered depending on therapeutic area /disease state .
- New thoughts concerning regions, reflected in part by the ICH guidances, are beginning to shift the definition of subpopulation.

Region Workgroup

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Reference

Example of Defining Subpopulation

1. Identify intrinsic/extrinsic factors that might lead to differences in treatment effect via checklist.
2. Run *k*-means cluster algorithm with respect to the factors in (1). Examine different *k*s to decide *k*.
3. Define ‘subpopulation’ based on results from (2).
4. Estimate subpopulation sample size as part of the overall sample size estimation.
5. Control ‘subpopulation’ for primary efficacy analysis as well as predefined consistency assessment.

Summary

- Points to consider include metabolism, excretion, and many other factors. The work ahead is to come up with a common approach to “commonality” – covered by the new approach of ICH E17.
- Regulators/sponsors need to work together toward a plan which includes adequate pre-approval data with post-approval plans for collecting/monitoring any relevant information
- Defining subpopulation is sponsors’ responsibility overall, and each country has local requirements , so need to be agreed with regulators.
- Transition from well controlled trials to real world utility .