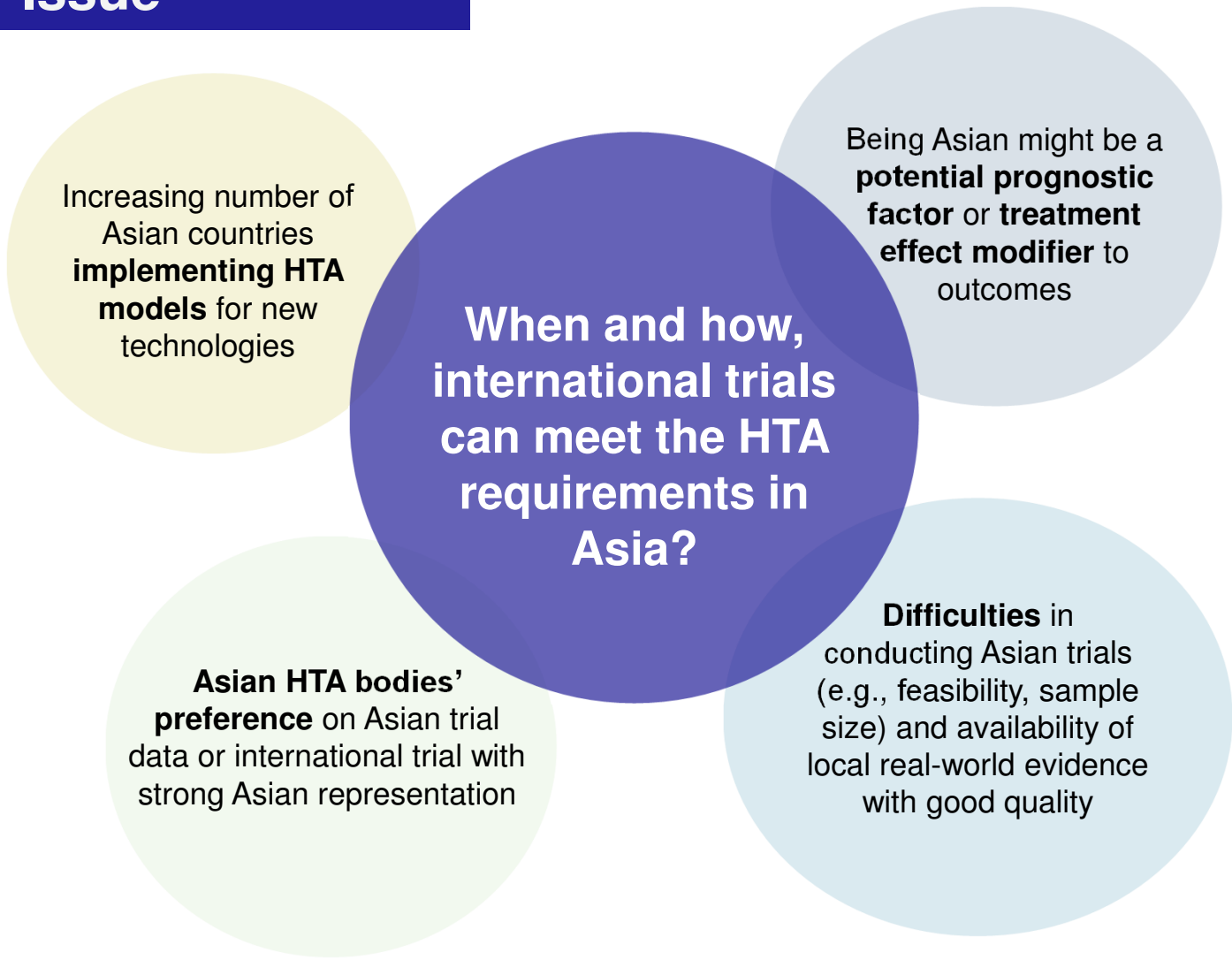
Are International Trials Good Enough to Support the Reimbursement of a New Technology in Asia? When and How?

Issue panel discussion

Virtual ISPOR Asia Pacific Summit 2022

Tuesday, 20 September 2022

Issue


Increasing number of Asian countries **implementing HTA models** for new technologies
Being Asian might be a **potential prognostic factor** or **treatment effect modifier** to outcomes
When and how, international trials can meet the HTA requirements in Asia?
Asian HTA bodies' preference on Asian trial data or international trial with strong Asian representation
Difficulties in conducting Asian trials (e.g., feasibility, sample size) and availability of local real-world evidence with good quality

Poll question 1

Which of the following may not support the use of international trials in reimbursement submissions to Asian HTA bodies?

a) The treatment effect may vary between Asian vs. non-Asian participants

b) The treatment safety (adverse events, dose reductions, treatment discontinuation) may vary between Asian vs. non-Asian participants

c) The clinical practice (e.g., monitoring, co-medications, subsequent treatments) may differ between Asian vs. non-Asian sites and may impact the treatment efficacy and/or safety

d) The use of international trials can support HTA submissions in Asia without concerns

Poll question 2

Which of the following would make an international trial as being "good enough" evidence in reimbursement submissions to Asian HTAs?

a) When Asian participants constitute the majority in the international trial (e.g., > 50%)

b) KOLs and literature reviews suggest that race (Asian vs. non-Asian) does not have a significant impact in treatment efficacy and safety

c) Subgroup analyses or prognostic factor analyses of the international trial demonstrate no significant difference in treatment efficacy and safety between Asian and non-Asian participants

d) Positive reimbursement decisions from other HTA bodies (e.g., NICE, SMC, PBAC, CADTH, GBA, HAS) based on the evidence from the international trial

Poll question 3

If an international/global trial is not considered "good enough" evidence during a reimbursement submission to an Asian HTA body, which of the following can best help overcome this challenge?

a) Conduct an extension trial in Asian countries

b) Show that there are no significant differences between Asian vs. non-Asian participants, based on subgroup analyses and prognostic factor analyses from the international trial

c) Collect real-world evidence in Asian countries to supplement the international data

d) Search for precedent Asian submissions on the targeted disease area to understand challenges and trends in decision making

Panel discussion

Are International Trials Good Enough to Support the Reimbursement of a New Technology in Asia? When and How?

Moderator

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Cytel

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MINISTRY OF HEALTH
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Are International Trials Good Enough to Support the Reimbursement of a New Technology in Asia? When and How?

Dr Louise Goh

20 September 2022

ACE
agency for
care effectiveness

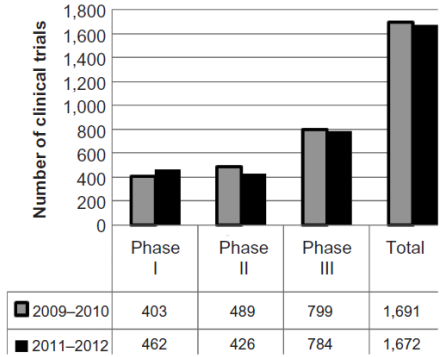
Disclaimer

The opinions expressed herein are for the purpose of this discussion with the position given as to why **Asian trials or international trials with considerable number of Asian patients are preferred**.

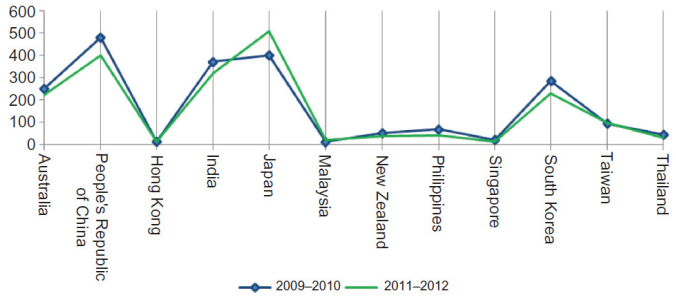
This does not represent ACE's view in any way.

Importance of conducting Asian trials or trials with higher representation of Asians

Number of clinical trials in Asia Pacific relatively stable over time



Number of initiated sites in Asia Pacific mostly declining



- Well implemented clinical trials provide the highest level of evidence on drug efficacy and safety.
- However, only about 17% of trials are performed in Asia.
- The lack of data has been identified as the most important issue in South East Asia and has implications e.g. national rotavirus immunisation.
- More recent data (WHO database study) showed that clinical trials in Asia e.g. in Japan is on the rise, highlighting increasing preference for such data in certain countries.

Published studies highlighted need for better Asian representation in oncology clinical trials

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REVIEW

Evolution of the clinical trial landscape in Asia Pacific

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Introduction: Asia Pacific has and continues to be one of the fastest-growing pharmaceutical markets in the world. This growth has a carry-over effect of driving pharmaceutical research and development investment in the region. Coupled with this, there have been multiple initiatives conducted by governments and other research focused organizations and societies in the region to help support this growth in research. In this report, we discuss the latest developments

Systematic Review

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Race and ethnicity representation in clinical trials: findings from a literature review of Phase I oncology trials

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Aim: To provide an assessment of published literature on the demographic representation in Phase I trials of biopharmaceutical oncology agents. **Materials & methods:** We conducted a rapid evidence assessment to identify demographic representation reported in Phase I clinical trials for biopharmaceutical oncology agents published in 2019. **Results:** Globally, the population was predominantly White/Caucasian (62.2%). In the USA, the distribution was heavily skewed toward White/Caucasian (84.2%), with minimal representation of Blacks/African–Americans (7.3%), Asians (3.4%), Hispanics/Latinos (2.8%) or other race/ethnicity groups. **Conclusion:** Our data highlight that Phase I oncology trials do not reflect the population at large, which may perpetuate health disparities. Further research is needed to understand and address barriers to participation, particularly among under-represented groups

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Asian representation in clinical trials of new drugs for the treatment of cancer.

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Abstract Disclosures

Abstract

6564

Background: In the US, statistics for Asians are often aggregated with ot racial groups. This poses challenges in estimating the cancer burden an defining cancer clinical trial enrollment targets in this demographic subg 'Asian' refers to persons with origins in the Far East, Southeast Asia, or t Indian sub-continent. Asians comprise 6% of the US population and the Asian subgroups in the US are of Chinese (22%), Filipino (19%), Asian Ind (19%), Vietnamese (10%), Korean (9%), and Japanese (7%) descent. The representation of Asian patients in global clinical trials may not be reflec the Asian subgroups in the US. FDA conducted an analysis to describe pa categorized as 'Asian' in clinical trials supporting the approval of new dr **Methods:** We reviewed the marketing applications of 33 new molecular approved for the treatment of solid tumor malignancies between 2011- identify trials that provided the primary evidence of safety and efficacy. A total of 29,941 patients were enrolled; 17 % were Asian. Most Asian pa were enrolled in Korea (20%), Taiwan (20%), mainland China (20%), Japar and US (5%). Few patients were enrolled in India (3%); the Philippines (1 Vietnam (0). In the US, Asian patients comprised 3% of the total numbe patients enrolled. **Conclusions:** Asian patients represented a heterogene mix. A large proportion was enrolled in Taiwan (20%) and Korea (20%), w the largest proportion of US Asians have origins in mainland China (22% Philippines (19%), India (19%), and Vietnam (10%). Nevertheless, althoug Asians share a common ancestry, it is not clear whether data from globa clinical trials are generalizable to Asian patients in the US. Therefore, str to improve the enrollment of US Asian patients in clinical trials are need Among patients enrolled in the US, 3% were Asians, a proportion that is below US Asian population estimates (6%). While most site-specific cancer incidence and death rates are lower in US Asians compared to Whites, the rates of some cancers (e. g., stomach and liver) are higher in this group. Therefore, studies are

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Original Research

Representation of sex, race, and ethnicity in pivotal clinical trials for dermatological drugs

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ABSTRACT

Background: It is of paramount importance that clinical trials are designed with adequate health equity considerations to prevent disproportionate analyses of specific demographics.
Objective: In this study, we investigated the representation of sex, race, and ethnicity in pivotal clinical trials for drugs with dermatological disease indications approved by the U.S. Food and Drug Administration between 1995 and 2019.
Methods: Thirty-six novel drugs with indications to treat dermatological diseases, approved by the U.S. Food and Drug Administration between January 1995 and December 2019 were abstracted from Drugs@FDA. The drug approval label, statistical review, official record, and trial publication were reviewed for data on disease indication, approval year, pathway, number of participants, participant demographics (sex, race, and ethnicity), location, and sponsor type.
Results: The overall female representation was 45.6% (n = 17,492 of 38,320). Adequate female representation was noted for five of six disease indications. Caucasians were predominantly overrepresented (80.4%; n = 28,065 of 34,890); Blacks (9.8%; n = 3242 of 33,240) and Asians (5.5%; n = 1535 of 27,696) were consistently underrepresented. Across sponsor types, there was a significant difference in the distribution of women ($\chi^2 = 6.332$; $p = .042$), as well as Caucasians ($\chi^2 = 12.813$; $p = .002$), Blacks ($\chi^2 = 13.002$; $p = .002$), and Hispanics/Latinos ($\chi^2 = 7.747$; $p = .021$).
Conclusion: Persistence of disparities disproportionately affect the quality of data behind therapies for certain demographics; as such, enrollment practices must continue to address the issue of underrepresentation. Efforts to facilitate demographic equity among clinical trial participants must be supported to ensure that safety and efficacy conclusions are drawn from representative population samples.

Adequate representation of Asian patients in trials ensures transferability

- Insufficient representation may **affect the applicability of results** to Asian population:
  - Significant and inherent variations exist between Caucasians and Asians in terms of disease epidemiology, diagnostic cutoffs and treatment responses; **"Asian phenotype"**
  - For example, esophageal adenocarcinomas (EACs) is the dominant histological type in Western countries vs. esophageal squamous cell carcinomas (ESCCs) in Asia, implications with disease severity as well as treatment benefits

- Local trials need to be replicated or international trials with Asian representation conducted in order to **elucidate differences in drug metabolism and toxicity, and ensure the drug is no worse off** in our population:
  - For regulatory purpose: to assess efficacy and safety of the drug e.g. Japan, Taiwan, South Korea require these data to be submitted for regulatory approval
  - For reimbursement purpose: to inform clinical and cost effectiveness analysis

Can the *same effectiveness be achieved* if the intervention was administered in the local population vs. in the study setting?

Case study #1: Nivolumab in gastric, gastroesophageal junction or oesophageal cancer

- Similar trial populations but without oesophageal adenocarcinoma population in Asian ATTRACTION-4 trial

Study	CheckMate 649	ATTRACTION-4
Intervention	**Nivolumab + chemotherapy**	**Nivolumab + chemotherapy**
Comparator	Chemotherapy (CAPOX or FOLFOX)	Placebo + chemotherapy (CAPOX or SOX)
Design	Randomised (1:1), open-label, phase III trial	Randomised (1:1), double-blind, placebo-controlled, phase III trial
Country	Global trial, 24% of patients were from Asia (China, Hong Kong, Japan, Singapore, South Korea, Taiwan).	Asian trial (Japan, South Korea, Taiwan)
Inclusion / exclusion criteria	The trial included patients: • ≥18 years old with previously untreated, unresectable, advanced or metastatic gastric, GEJ or oesophageal adenocarcinoma (regardless of PD-L1 expression) • With ECOG performance status 0 or 1 Patients with previous adjuvant or neoadjuvant chemotherapy, radiotherapy, or chemoradiotherapy (administered at least 6 months before randomisation) were eligible. The trial excluded patients with known HER2 positive status.	The trial included patients: • ≥20 years old with previously untreated, unresectable advanced or recurrent gastric or GEJ adenocarcinoma (regardless of PD-L1 expression) • With ECOG performance status 0 or 1 Patients who had completed neoadjuvant or adjuvant chemotherapy at least 6 months before recurrence were eligible. The trial excluded patients with HER2 positive or indeterminate gastric cancer.
N	1,581	724

#1: Improvements in PFS but not OS and longer median OS reported in Asian than global trial

- Compared to chemo, nivo + chemo significantly improved OS and reported longer median PFS in *CheckMate 649 trial* while nivo + chemo significantly improved PFS but not OS (though still longer) in *Attraction-4 trial.*
- Longer median OS observed in the Asian trial, likely due to **differences in the proportion of patients receiving subsequent anticancer therapies** (66% vs. 39%).

Study	CheckMate 649	ATTRACTION-4
Results based on the most recent data cut-off (Intervention vs. Comparator)		
Median OS (95% CI), months	All randomised patients **13.8** (12.4 to 14.5) vs **11.6** (10.9 to 12.5) • **OS difference: 2.2** • **HR 0.79** (95% CI 0.71 to 0.88)	All randomised patients **17.45** (15.67 to 20.83) vs **17.15** (15.18 to 19.65) • **OS difference: 0.30** • **HR 0.90** (0.75 to 1.08), p=0.26
Median PFS (95% CI), months	All randomised patients **7.7** (7.1 to 8.6) vs **6.9** (6.7 to 7.2) • **PFS difference: 0.8** • **HR 0.79** (95% CI 0.70 to 0.89)	All randomised patients **10.94** (8.44 to 14.03) vs **8.41** (7.03 to 9.69) • **PFS difference: 2.53** • **HR 0.70** (95% CI 0.57 to 0.86), p=0.0005
Adverse events	Nivolumab + chemotherapy was associated with a higher incidence of TRAEs of any grade (95% vs 89%) and grade ≥3 TRAEs (60% vs 44%) compared with chemotherapy alone. The most frequent grade ≥3 TRAEs were neutropenia (15% vs 12%), neutrophil count decreased (11% vs 9%), and anaemia (6% vs 3%).	Nivolumab + chemotherapy was associated with a higher incidence of grade ≥3 TRAEs compared with placebo + chemotherapy (58% vs 49%). The most frequent grade ≥3 TRAEs were neutrophil count decreased (20% vs 16%), platelet count decreased (9.5% vs 9.2%), and decreased appetite (8% vs 6%).

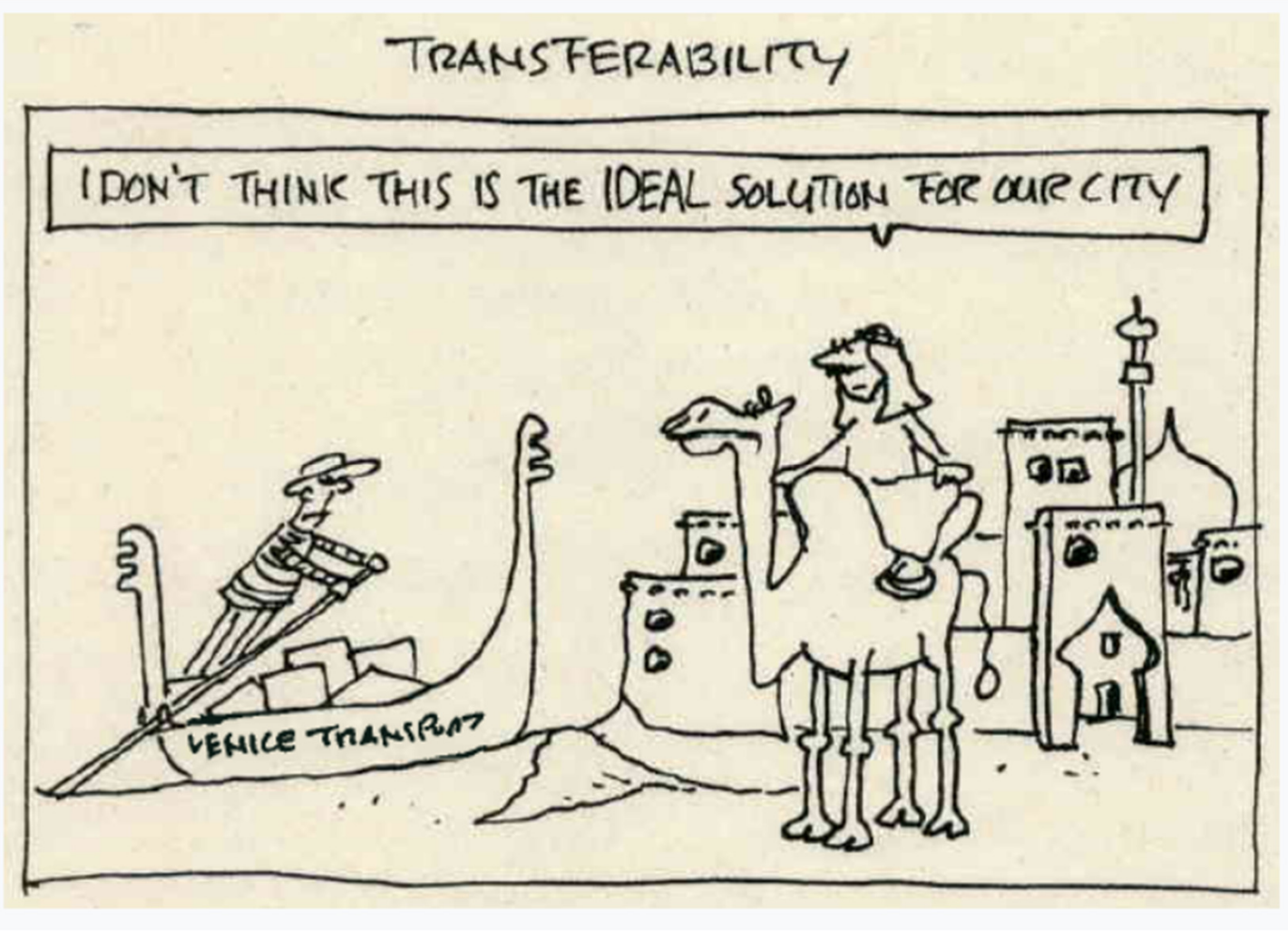
Case study #2: Regorafenib and lonsurf in metastatic colorectal cancer

Study	CORRECT	CONCUR	RECOURSE	TERRA
Intervention[a]	**Regorafenib**	**Regorafenib**	**Lonsurf**	**Lonsurf**
Comparator	Placebo	Placebo	Placebo	Placebo
Design	**Phase 3** RCT, double-blind			
Prior therapies	Almost all patients received ≥2 therapies: 1 (3%), 2 (23%), 3 (26%), ≥4 (48%) All patients had received a biologic drug (targeting VEGF or/and EGFR)	Majority of patients received ≥2 therapies: 0 (2%), 1-2 (35%), 3 (24%), ≥4 (39%) 60% had received a biologic drug (targeting VEGF or/and EGFR)	All patients received ≥2 therapies: 2 (18%), 3 (21%), ≥4 (61%) All patients had received a biologic drug (targeting VEGF or/and EGFR)	All patients received ≥2 therapies: 2 (21%), 3 (27%), ≥4 (52%) 47% had received a biologic drug (targeting VEGF or/and EGFR)
Country	Global	Asian countries (China, Hong Kong, Korea, Taiwan, Vietnam)	US, Europe, Australia, Japan	Asian countries (China, Korea, Thailand)
ECOG score[b]	0 or 1			
N	760	204	800	406

#2: Inconsistent OS results between global and Asian trials, with unclear reasons for differences

- Compared to placebo, **regorafenib** significantly improved median OS with more gains in months observed in the Asian CONCUR trial.
- Although **lonsurf** also significantly improved median OS compared to placebo, the gain in OS was lower in the Asian TERRA trial.

Study	CORRECT	CONCUR	RECOURSE	TERRA
Intervention[a]	**Regorafenib**	**Regorafenib**	**Lonsurf**	**Lonsurf**
Comparator	Placebo	Placebo	Placebo	Placebo
Results (Intervention vs. Comparator)				
Median OS (95% CI), months	6.4 (IQR 3.6 - 11.8) vs 5.0 (2.8 - 10.4) OS gain: **1.4** HR 0.77 (0.64 - 0.94), p=0.0052	8.8 (7.3 - 9.8) vs 6.3 (4.8 - 7.6) OS gain: **2.5** HR 0.55 (0.40 - 0.77), p=0.00016	7.1 (6.5 - 7.8) vs 5.3 (4.6 - 6.0) OS gain: **1.8** HR 0.68 (0.58 - 0.81), p<0.001	7.8 (7.1 - 8.8) vs 7.1 (5.9 - 8.2) OS gain: **0.7** HR 0.79 (0.62 - 0.99), p=0.035
Median PFS (95% CI), months	1.9 (IQR 1.6 - 3.9) vs 1.7 (1.4 - 1.9) HR 0.49 (0.42 - 0.58), p<0.0001	3.2 (2.0 - 3.7) vs 1.7 (1.6 - 1.8) HR 0.31 (0.22 - 0.44), p<0.0001	2.0 (1.9 - 2.1) vs 1.7 (1.7 - 1.8) HR 0.48 (0.41 - 0.57), p<0.001	2.0 (1.9 - 2.8) vs 1.8 (1.7 - 1.8) HR 0.43 (0.34 - 0.54), p<0.001
Adverse events	TRAEs: 93% vs 61% Grade 3 TRAEs: 51% vs 12%	TRAEs: 97% vs 46% Grade ≥3 TRAEs: 54% vs 15%	AEs: 98% vs 93% Grade ≥3 AEs: 69% vs 52%	TRAEs: 90% vs 52% Grade ≥3 TRAEs: 46% vs 10%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Adequate representation of Asian patients in trials improve the certainty in decision making and facilitate uptake

- Good quality trial data demonstrating effectiveness in a population similar to local context will:
  - Facilitate uptake
  - Affect prices at which Asian countries are willing to procure at, considering factors such as clinical need, safety, value for money, estimated annual drug cost as well
  - Allow better comparison with local outcomes research conducted to evaluate the impact of reimbursement decisions on patient outcomes to facilitate changes in listing or subsequent price negotiations

- It also informs the population(s) most likely to benefit from the treatment.

- The trial results can be used to engage clinicians where shifts in prescribing practice are needed as well.

- This ensures fairness as people from diverse ethnic backgrounds can participate in trials and has the potential to reduce health disparities.

Potential barriers to conducting Asian trials (1)

Potential barriers/ misconceptions	Remarks/ clarification of misperception
More time and cost to generate and assess evidence with additional trial sites in Asia	• Faster patient accrual with larger patient pools e.g. liver or gastroesophageal cancer cases in Korea and China • Lower costs reported in Asia (30-40% lower) for procedures, diagnostic tests and visits
Language barriers where English language may not be the native language	Moderate to high English proficiency in Asian countries such as Singapore, Philippines, Malaysia, China, South Korea, India based on the 2021 EF Education First English Proficiency Index
Differences in standard of care	Standard of care in Asia does not differ much from those of Western countries such as breast cancer, lung cancer and diabetes

Potential barriers to conducting Asian trials (2)

Potential barriers/ misconceptions	Remarks/ clarification of misperception
Long regulatory approval timelines	• Competitive approval timelines with Western countries, ~30 working days in Singapore for clinical trial authorisation (https://www.hsa.gov.sg/) though likely to differ across Asian countries • Innovation Office to facilitate the process
Lower quality of clinical data and access to clinical experts	• Clinical trial data in Asia routinely accepted as part of US FDA and EMA regulatory submissions • Key opinion leaders from Asia are often members of international expert groups
Lack of research infrastructure and poor intellectual property (IP) rights protection	• High-quality infrastructure with advanced clinical trial centres coupled with technologically advanced and digitally connected in Asian countries • Strong IP rights protection e.g. Singapore among top 10 (out of 128 countries)

Current issues with RWE/RWD

- Although there is increasing interest in the use of “real-world” outcomes to base reimbursement decisions, there are issues to be worked through:

  - **Variation** and **lack of transparency** in how real-world evidence (RWE) is used to inform decision making

  - Concerns with **quality, completeness and comparability of outcomes** collected in real-world vs. from randomised controlled trials (RCTs)

  - **Lack of infrastructure and funding** (with consideration for “value of information”) to collect real-world data (RWD) in lower income countries

  - In Singapore, as evaluations are shifted upstream instead of several years after market entry where reimbursement decisions are made, real-world data **may not be available** yet or **are limited**

Role of RWE/RWD

- RWE from regional registries can supplement trial data by/for:
  - Providing more certainty about the safety and effectiveness of the proposed medicine in the local setting and/or in an Asian population (which may be underrepresented in clinical trials)
  - Serving as input parameters in economic modelling including for costing of treatments
  - Determining treatment mix in budget impact assessment

Summary

- To ensure transferability, certainty in decision making and to facilitate uptake, there needs to be better representation of Asian patients in trials (where ethnic sensitivity is likely to be present) and should be best practice in situations where:

  - There is high incidence of the disease in Asian patients e.g. esophageal and gastric cancer

  - There is evidence of biological differences and differing drug response between Western and Asian populations

  - Treatment management differ vastly in Western and Asian populations

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Are International Trials Good Enough to Support the Reimbursement of a New Technology in Asia? When and How?

Virtual ISPOR Asia Pacific 2022, September 20-21
Issue Panel
September 20, 11:45 – 12:45 Korean Standard Time (KST)

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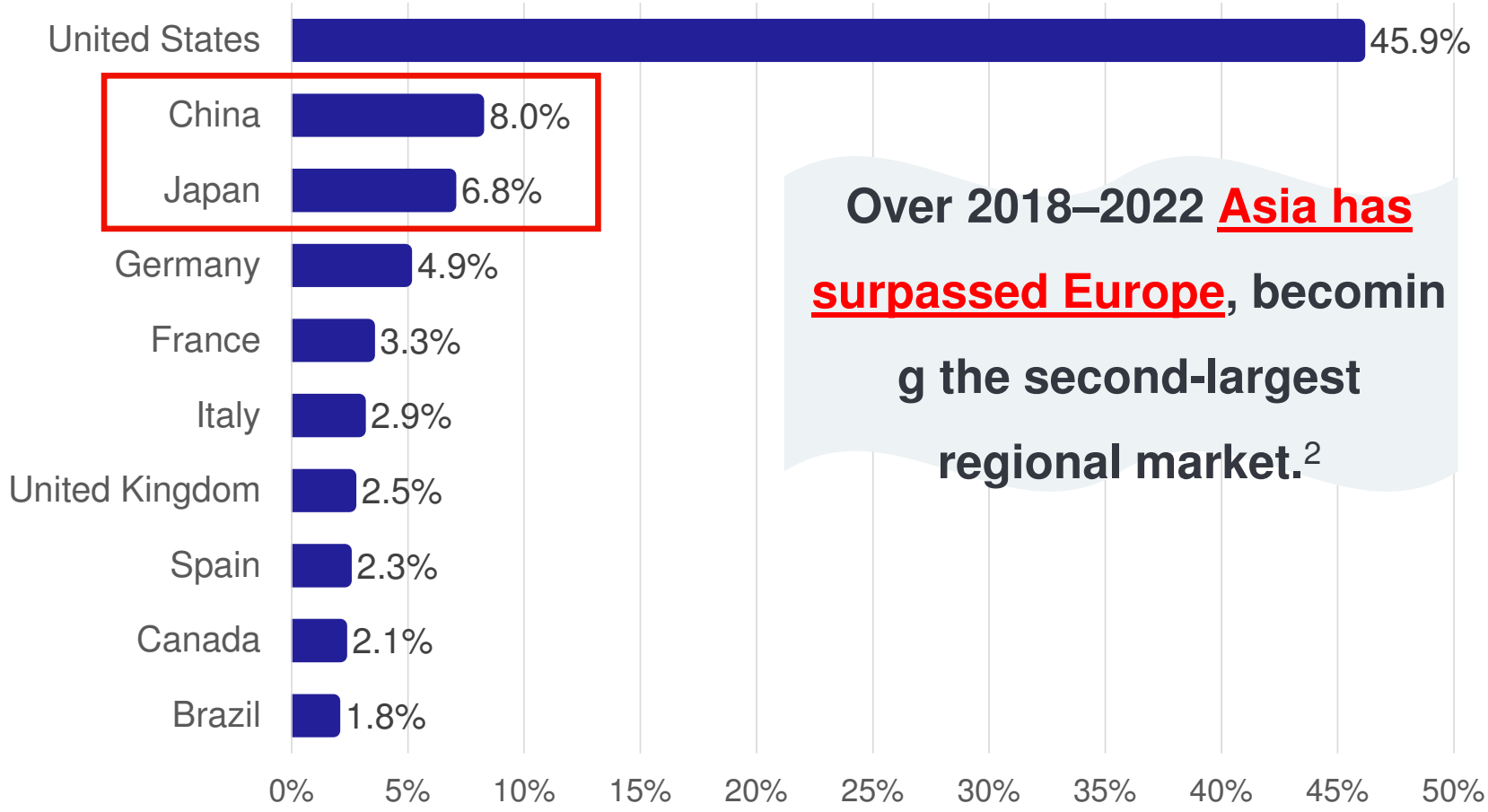
Disclosures

- Employee of Takeda Pharmaceuticals America, Inc
- Views and opinions are my own

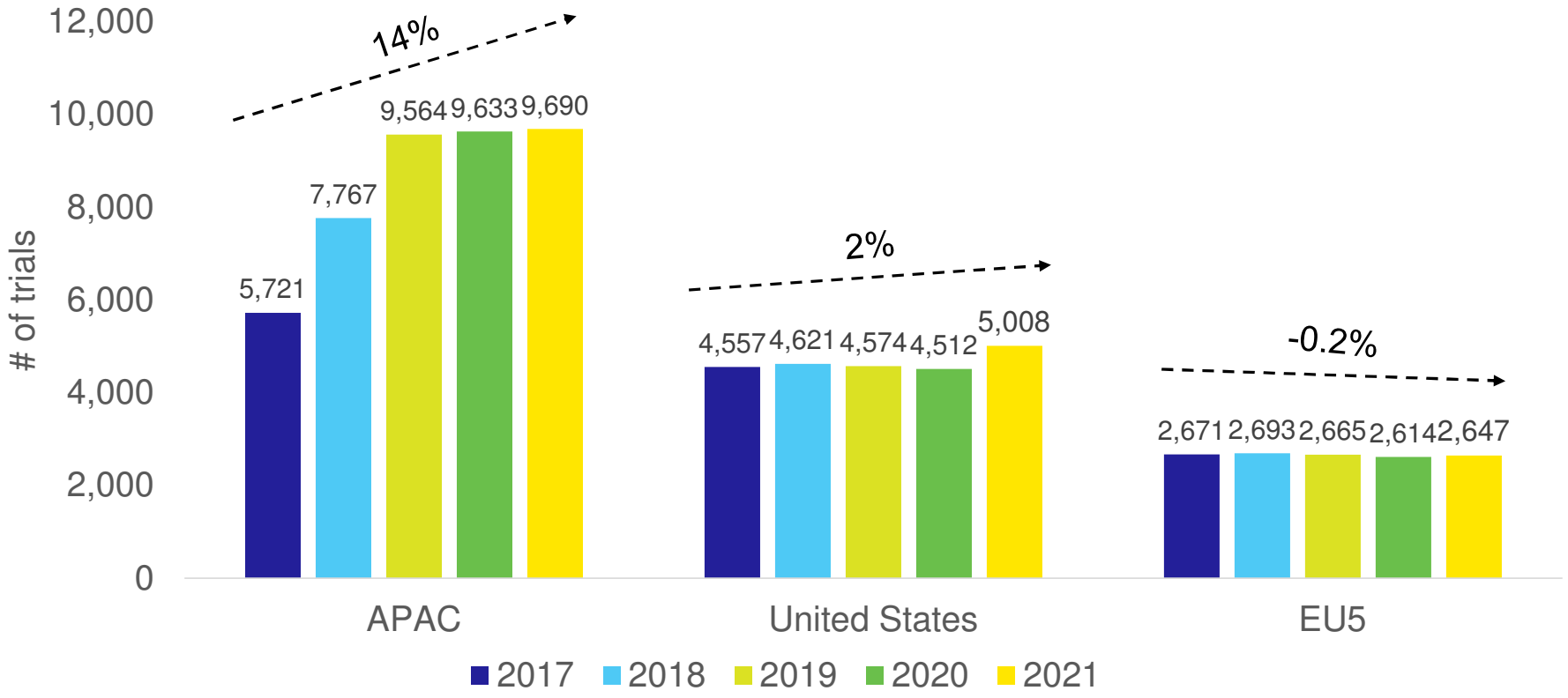
Market share of top 10 national pharmaceutical markets worldwide in 2020[1]



Over 2018–2022 Asia has surpassed Europe, becoming the second-largest regional market.[2]

Sources:
1. QVIA MIDAS, MAT December 2020. https://www.statista.com/statistics/245473/market-share-of-the-leading-10-global-pharmaceutical-markets/
2. Mihajlo J. et al. *Journal of Medical Economics* 2021; 24:sup1, 42-50

From 2017 to 2021 Asia Pacific accounted for over 50% of clinical trial activity across APAC, US, and EU5[1]



Sources:
1. GlobalData Healthcare Consulting. April 19, 2022. https://novotech-cro.com/sites/default/files/2022-05/Evolution%20of%20Clinical%20Trials%20in%20the%20APAC%20Region%20Compared%20to%20the%20US%20and%20the%20EU.pdf

Global trials with considerable number of Asian patients is already a reality [at least in oncology]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Brigatinib versus Crizotinib in *ALK*-Positive Non–Small-Cell Lung Cancer

Asian 39%[1]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer

Asian 46%[2]

JAMA Oncology | Original Investigation

Treatment Outcomes and Safety of Mobocertinib in Platinum-Pretreated Patients With *EGFR* Exon 20 Insertion-Positive Metastatic Non-Small Cell Lung Cancer
A Phase 1/2 Open-label Nonrandomized Clinical Trial

Asian 60%[3]

Amivantamab in EGFR Exon 20 Insertion–Mutated Non–Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study

Asian 49%[4]

Sources:
1. Camidge D.R. *N Engl J Med* 2018; 379:2027-2039
2. Peters S. *N Engl J Med* 2017; 377:829-838
3. Zhou C. *JAMA Oncol* 2021; 7(12):e214761
4. Park K. *Journal of Clinical Oncology* 2021;39(30):3391-3402.

Key challenges from the industry perspective in terms of ensuring Asian representation

Representation of different patient populations and practices across multiple markets

Quality data and robust processes

Enough sample size and follow-up

Possible need for bridging/extension local trials and supplemental RWE (for intervention and comparators)

Multiple market requirements

HTA is still evolving in various Asian markets

Administrative, financial and drugs supply challenges

Patient recruitment and retention, and timelines

Recommendations

For industry

Early identification of prognostic factors and effect modifiers

Integrate Asia into the global development strategy

Identify early and plan for pragmatic or extension local trials and collection of RWD

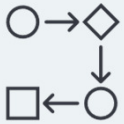
Apply sound statistical methods

For Asian HTA agencies

Consider establishing early scientific advice processes

Expectations for special scenarios (e.g., rare diseases, no SoC)

Clear thresholds for Asian representation in clinical trials, and for locality and quality of RWD



Develop (or implement existing) frameworks for the use of RWD and RWE to support reimbursement in Asia

Are Global Trials Good Enough to Support the Reimbursement of a New Technology in Asia?

When and How
A Methodological Perspective

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Head of RWAA External Research Partnerships/
Senior Research Principal
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20 September 2022
Virtual ISPOR Asia Pacific 2022, September 20-21
Issue Panel
September 20, 11:45 – 12:45 Korean Standard Time

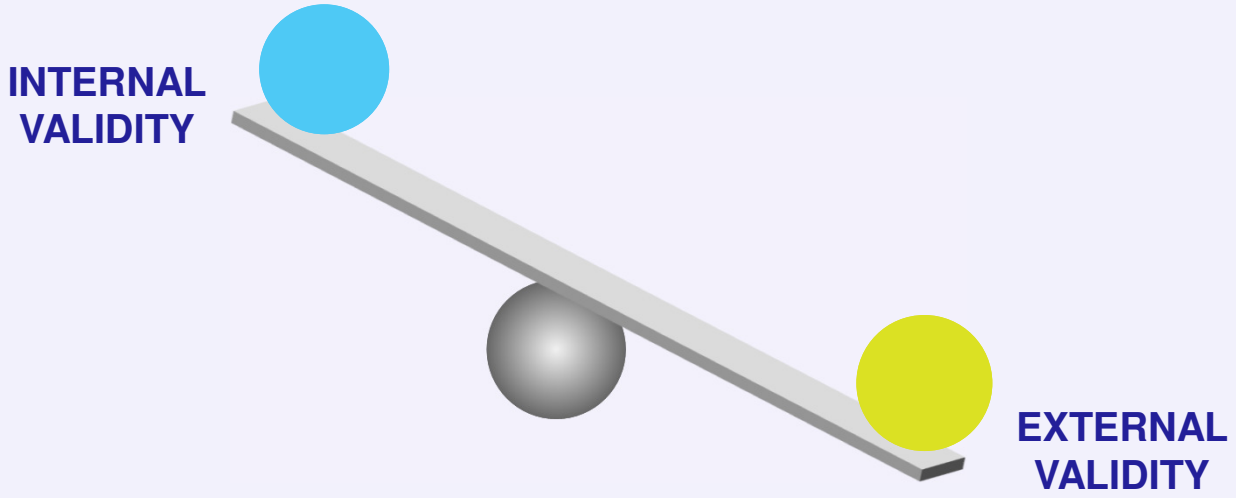
Disclaimer

GS employed by Cytel, Inc.

No other conflicts of interest.

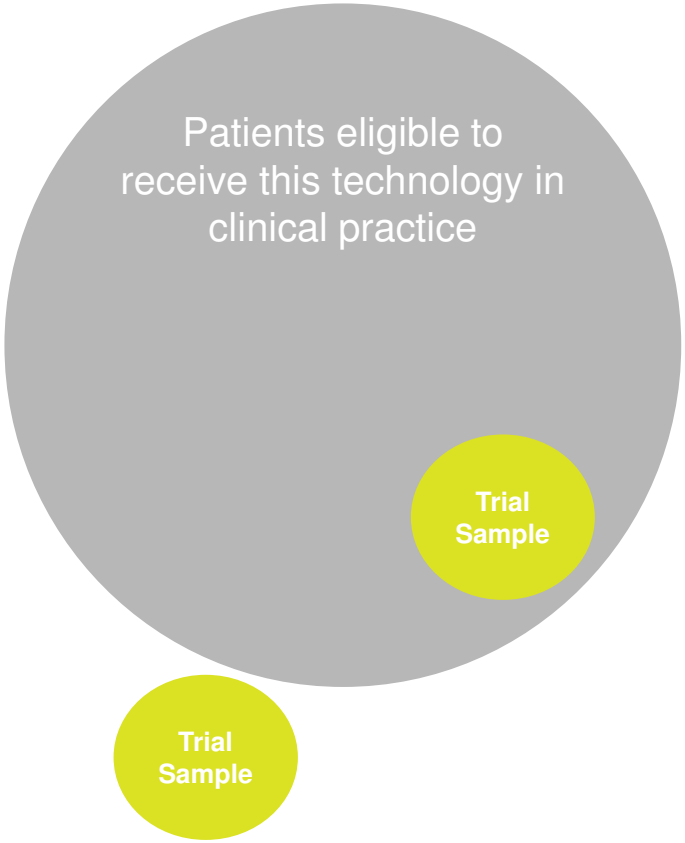
Background

Health technology assessments (HTA) assess the clinical and cost benefits of a health technology focusing on aspects of internal and external validity of supporting evidence.



Differences in Concepts and Measurements

	Internal Validity	External Validity
Question to answer	Is the trial measuring what it is supposed to measure (e.g., study design, patient selection criteria, outcomes)?	Do the results of the trial(s) hold true in a specific clinical practice/country?
Measures	The unbiased causal effect of a health technology	The causal effect of a health technology is transferrable to the population of interest.
HTA decision-making	To estimate the technology's clinical effectiveness vs. standard of care options	To estimate technology will be beneficial for the population in the real world
Supporting evidence	Trial-based evidence with randomised controlled trials (RCT) as the gold standard	Real-world evidence (RWE) from population-based studies



How to Identify if Asian Background is an Effect Modifier or Prognostic Factor? Guidance out there…

Organisation	Title of Guidance Document	Year of Publication	Specific Recommendations
 NICE	NICE health technology evaluations: the manual	2022	Potential effect modifiers should be identified before data analysis through a review of the subject area or discussion with experts in the clinical discipline.
 NICE DSU	TSD 18: Methods for population-adjusted indirect comparisons in submissions to NICE	2016	Thorough review of the subject area or discussion with clinical experts is needed.
 NICE DSU	TSD 7: Evidence synthesis of treatment efficacy in decision making: a reviewer's checklist	2012	Checklist for evidence synthesis of treatment efficacy (question on whether effect modifiers were identified through a literature review, and whether differences in patient populations were accounted for).
 HAS	Indirect comparisons methods and validity	2009	Interaction covariables should be identified through subgroup analyses conducted in the relevant clinical trials and interaction tests.

Abbreviations: DSU = Decision Support Unit; HAS = Haute Autorité de santé; NICE = National Institute for Health and Care Excellence; TSD = technical support document

Challenges

- There is **<u>limited HTA guidance</u>**
- Effect modifiers or prognostic factors may be true for one trial or disease but not for the technology's trial setting.
- Is there a biologic link rationale for why Asian background would constitute an effect modifier?

Evidence Sources to Identify if Asian Background is an Effect Modifier or Prognostic Factor

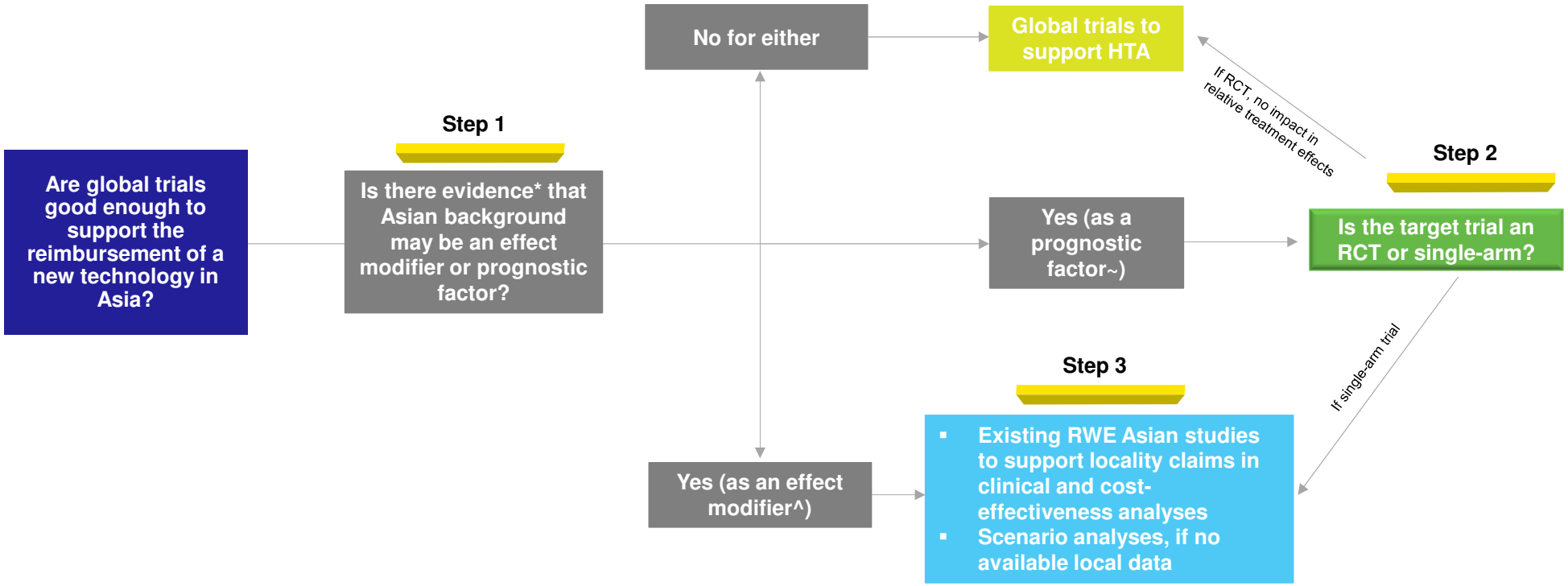
Literature Reviews and Meta-Analyses

- Rarely being conducted on looking at effect modifiers but reviews and meta-analyses of clinical trials can provide subgroup data on factors that can be considered effect modifiers
- Difficulty to manage workload/search process
- Previous cherry-picking approach by researchers
- Need for quality assurance of evidence, ethnicity usually is self reported
- When considering subgroup analyses of trials in the evidence network, one does need to consider that trials are not powered to identify effect modifiers.

Clinical Expert Opinions

- If not conducted in a structured way, clearly depending on clinician's experience on the disease area
- Common confusion about effect modifiers and prognostic factors terminology and risk of classification of a prognostic factors as an effect modifier; usually clinicians focus on patient risk prediction, therefore able to identify prognostic factors
- Validity of clinical experts statements linked to their professional profile
- Difficulty to recruit enough clinicians to increase trust in their statements

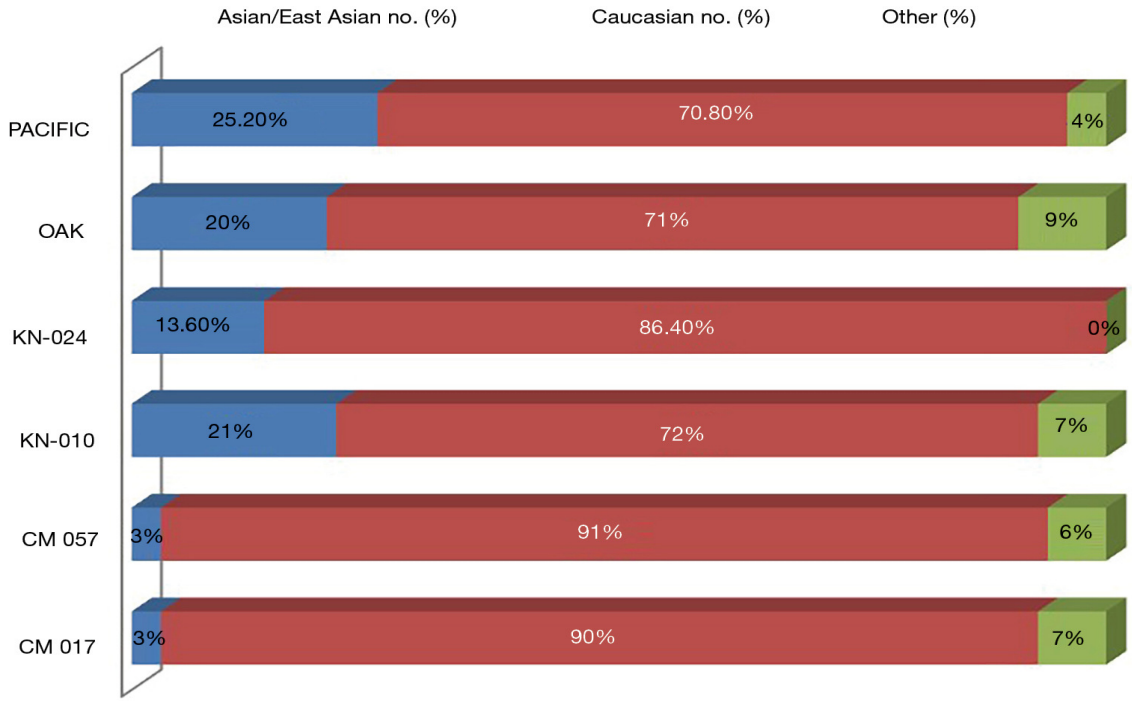
Evaluating the Strength of Global Trials



*Supporting evidence from systematic literature reviews, subgroup trial analyses of other trials in the same indications and clinical expert opinions
^Factor that alters the effect of treatment on a clinical outcome (impacts relative treatment effects)
~Factor that impacts a clinical outcome irrespective of treatment (impacts absolute effects)

Identifying the Role of Asian Background Based on Subgroup Analyses

The proportion of Asian population in previous PD-1/PD-L1 clinical trials



Ref: Immunotherapy in the Asiatic population: any differences from Caucasian population? (2018) Lunxi Peng and, Yi-Long Wu

Caveats

- Studies may not be powered to detect differences between groups (confidence intervals may overlap).
- Evidence of effect modification for one outcome (e.g., progression-free survival) may not stand for other outcomes (e.g., overall survival)
- No standardized quantitative thresholds
- Associations found in an individual patient data (IPD) trial may be true for a particular trial but may not be transferable to other populations at the same line of treatment.
- Clinical judgement is required to inform whether effect modification is present.

Methodological Approaches

When Global trials **Include** Some Asian Patients

Considering limitations around subgroup analyses
(pre-specified/post-hoc design, sample size)
Consistency in findings trends with previous trials and related subgroup analyses

1) Subgroup trial analyses
2) Combining RWE local data with trial analyses

Resolving uncertainty through scenario (sensitivity) and bias adjustment analyses

Main Consideration: **Generalisability**

When Global trials Do **Not** Include Asian Patients

Identifying RWE local data
Challenges associated with local data availability, model parameters and quality

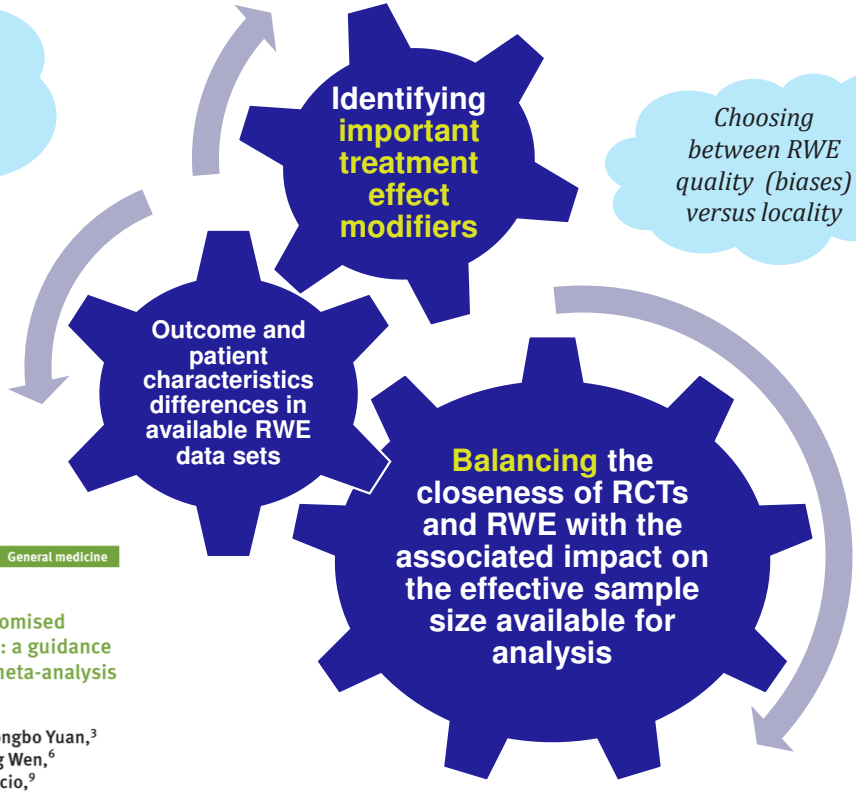
Trial reweighting as the most reliable modelling exercise
Interaction terms between treatment and covariates

Resolving uncertainty through scenario (sensitivity) and bias adjustment analyses

Main Consideration: **Transportability**

RWE Considerations

Can RCT weighting with RWE allow us to estimate the expected treatment benefit had the clinical trial been run in a broader real-world target population?



Choosing between RWE quality (biases) versus locality

Resolving Uncertainty

Reweighting Randomized Controlled Trial Evidence to Better Reflect Real Life – A Case Study of the Innovative Medicines Initiative

Michael Happich[1,*], Alan Brnabic[2], Douglas Faries[3], Keith Abrams[4], Katherine B. Winfree[3], Allicia Girvan[3], Pall Jonsson[3], Joseph Johnston[3], Mark Belger[1] and IMI GetReal Work Package 1

General medicine

Evidence synthesis

Framework for the synthesis of non-randomised studies and randomised controlled trials: a guidance on conducting a systematic review and meta-analysis for healthcare decision making

Grammati Sarri ,[1] Elisabetta Patorno ,[2] Hongbo Yuan,[3] Jianfei (Jeff) Guo,[4] Dimitri Bennett ,[5] Xuerong Wen,[6] Andrew R Zullo ,[7] Joan Largent,[8] Mary Panaccio,[9] Mugdha Gokhale,[10] Daniela Claudia Moga,[11] M Sanni Ali,[12,13,14] Thomas P A Debray [15,16]

Conclusions

Understanding of the role of race in estimates of treatment effects

- Background reviews
- Transferability of findings of effect modification across patient groups and trial settings
- Understanding the role of other factors that may impact the role of race as an effect modifier

Data analysis design

- Availability of RWE data sources to allow trial reweighting
- Model specification and data quality assessments
- Interpretation of Asian transportable effect estimates and exploration of uncertainty sources

Opportunities for better study designs

- Exploration of pragmatic trials and inclusion of local data in the trial development programme
- Validation of results from simulation exercises through planning for local RWE studies

Thank You

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Q & A Session

Thank You
For Your Attention

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