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
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

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

When and how, international trials can meet the HTA requirements in Asia?
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
Are International Trials Good Enough to Support the Reimbursement of a New Technology in Asia? When and How?

Panel discussion

Moderator
Yannan Hu, PhD
Associate Director & Research Principal

Speaker 1
Louise Goh, PhD
Lead Specialist, Ministry of Health (Singapore)

Speaker 2
Luis Hernandez, PhD MPH MSc
Head, Global Health Economics Takeda Oncology

Speaker 3
Grammati Sarri, PhD
Chair of the Comparative Effectiveness Research Special Interest Group, ISPE & Head of RWAA External Research Partnerships/Senior Research Principal

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

Dr Louise Goh

20 September 2022
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.
Driving Better Decision-Making in Healthcare

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

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

Race and ethnicity representation in clinical trials: findings from a literature review of Phase 1 oncology trials

D Peng Cyparros1, Haisong Wang4, Karen T Steyer1, Ira Jacob2**, Lucien J Lee1, Zdenka Aleskerov3, Justin McGinn2 and Yousef Zakzouk1

1Department of Medical Oncology, University of California Hospital, Aurora, CO 80036, USA
2University of California, San Francisco Comprehensive Cancer Center, 505 Parnassus Ave, San Francisco, CA 94143, USA
3Wayne State University, Detroit, MI 48201, USA
4University of Miami, Baptist Cancer Center, Miami, FL 33133, USA

**Corresponding author. Tel: +1 720 539 8096; fax: +1 720 539 8095

Abstract

To provide an assessment of published literature on the demographic representation in Phase 1 trials of biopharmaceutical oncology agents. Material & Methods: We conducted a rapid evidence assessment to identify demographic representation reported in Phase 1 clinical trials for biopharmaceutical oncology agents published in 2010. Results: Globally, the population was predominantly White Caucasian (62.2%). In the US, the distribution was heavily skewed toward White/Caucasian (64.2%), with minimal representation of Pacific Islanders/Americas (1.3%), Asians (4.4%), Hispanics/Latinos (2.8%) or other races/ethnicity groups. Conclusion: Although demographic representation in Phase 1 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.
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

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

#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%).

<table>
<thead>
<tr>
<th>Study</th>
<th>CheckMate 649</th>
<th>ATTRACTION-4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median OS (95% CI), months</strong></td>
<td>All randomised patients</td>
<td>All randomised patients</td>
</tr>
<tr>
<td></td>
<td>13.8 (12.4 to 14.5) vs 11.6 (10.9 to 12.5)</td>
<td>17.45 (15.67 to 20.83) vs 17.15 (15.18 to 19.65)</td>
</tr>
<tr>
<td></td>
<td>• OS difference: 2.2</td>
<td>• OS difference: 0.30</td>
</tr>
<tr>
<td></td>
<td>• HR 0.79 (95% CI 0.71 to 0.88)</td>
<td>• HR 0.90 (0.75 to 1.08), p=0.26</td>
</tr>
<tr>
<td><strong>Median PFS (95% CI), months</strong></td>
<td>All randomised patients</td>
<td>All randomised patients</td>
</tr>
<tr>
<td></td>
<td>7.7 (7.1 to 8.6) vs 6.9 (6.7 to 7.2)</td>
<td>10.94 (8.44 to 14.03) vs 8.41 (7.03 to 9.69)</td>
</tr>
<tr>
<td></td>
<td>• PFS difference: 0.8</td>
<td>• PFS difference: 2.53</td>
</tr>
<tr>
<td></td>
<td>• HR 0.79 (95% CI 0.70 to 0.89)</td>
<td>• HR 0.70 (95% CI 0.57 to 0.86), p=0.0005</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>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%).</td>
<td>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%).</td>
</tr>
</tbody>
</table>
**Case study #2: Regorafenib and Lonsurf in metastatic colorectal cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>CORRECT</th>
<th>CONCUR</th>
<th>RE COURSE</th>
<th>TERRA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Regorafenib</td>
<td>Regorafenib</td>
<td>Lonsurf</td>
<td>Lonsurf</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Phase 3 RCT, double-blind</td>
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</table>

**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)
- 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)

<table>
<thead>
<tr>
<th>ECOG score</th>
<th>N</th>
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<tbody>
<tr>
<td></td>
<td>760</td>
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</tbody>
</table>
#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.

<table>
<thead>
<tr>
<th>Study</th>
<th>CORRECT</th>
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<tbody>
<tr>
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</tr>
<tr>
<td>Comparator</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

### Results (Intervention vs. Comparator)

<table>
<thead>
<tr>
<th>Median OS (95% CI), months</th>
<th>CORRECT</th>
<th>CONCUR</th>
<th>RE COURSE</th>
<th>TERRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.4 (IQR 3.6 - 11.8) vs 5.0 (2.8 - 10.4)</td>
<td>8.8 (7.3 - 9.8) vs 6.3 (4.8 - 7.6)</td>
<td>7.1 (6.5 - 7.8) vs 5.3 (4.6 - 6.0)</td>
<td>7.8 (7.1 - 8.8) vs 7.1 (5.9 - 8.2)</td>
<td></td>
</tr>
<tr>
<td>OS gain: 1.4</td>
<td>OS gain: 2.5</td>
<td>OS gain: 1.8</td>
<td>OS gain: 0.7</td>
<td></td>
</tr>
<tr>
<td>HR 0.77 (0.64 - 0.94), p=0.0052</td>
<td>HR 0.55 (0.40 - 0.77), p=0.00016</td>
<td>HR 0.68 (0.58 - 0.81), p&lt;0.001</td>
<td>HR 0.79 (0.62 - 0.99), p=0.035</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Median PFS (95% CI), months</th>
<th>CORRECT</th>
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<th>RE COURSE</th>
<th>TERRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.9 (IQR 1.6 - 3.9) vs 1.7 (1.4 - 1.9)</td>
<td>3.2 (2.0 - 3.7) vs 1.7 (1.6 - 1.8)</td>
<td>2.0 (1.9 - 2.1) vs 1.7 (1.7 - 1.8)</td>
<td>2.0 (1.9 - 2.8) vs 1.8 (1.7 - 1.8)</td>
<td></td>
</tr>
<tr>
<td>HR 0.49 (0.42 - 0.58), p&lt;0.0001</td>
<td>HR 0.31 (0.22 - 0.44), p&lt;0.0001</td>
<td>HR 0.48 (0.41 - 0.57), p&lt;0.001</td>
<td>HR 0.43 (0.34 - 0.54), p&lt;0.001</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>CORRECT</th>
<th>CONCUR</th>
<th>RE COURSE</th>
<th>TERRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRAEs: 93% vs 61%</td>
<td>TRAEs: 97% vs 46%</td>
<td>AE: 98% vs 93%</td>
<td>TRAEs: 90% vs 52%</td>
<td></td>
</tr>
<tr>
<td>Grade 3 TRAEs: 51% vs 12%</td>
<td>Grade ≥3 TRAEs: 54% vs 15%</td>
<td>Grade ≥3 AE: 69% vs 52%</td>
<td>Grade ≥3 TRAEs: 46% vs 10%</td>
<td></td>
</tr>
</tbody>
</table>

- 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.

- **Regorafenib** and **lonsurf** are medications that were used in the studies. **OS** stands for Overall Survival, **PFS** for Progression-Free Survival, and **TRAEs** for Treatment-Related Adverse Events. **HR** stands for Hazard Ratio, which is a measure of the risk of an event occurring in one group compared to another.
TRANSFERABILITY

I don't think this is the ideal solution for our city

VENICE TRANSFER?
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)

<table>
<thead>
<tr>
<th>Potential barriers/ misconceptions</th>
<th>Remarks/ clarification of misperception</th>
</tr>
</thead>
</table>
| 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)

<table>
<thead>
<tr>
<th>Potential barriers/ misconceptions</th>
<th>Remarks/ clarification of misperception</th>
</tr>
</thead>
</table>
| Long regulatory approval timelines                         | • Competitive approval timelines with Western countries, ~30 working days in Singapore for clinical trial authorisation ([https://www.hsa.gov.sg/](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
References


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)

Luis G. Hernandez, PhD MPH MSc
Head, Global Health Economics
Global Oncology Patient Value, Policy & Access
Takeda Oncology
Disclosures

- Employee of Takeda Pharmaceuticals America, Inc
- Views and opinions are my own
Market share of top 10 national pharmaceutical markets worldwide in 2020¹

<table>
<thead>
<tr>
<th>Country</th>
<th>Market Share</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>45.9%</td>
</tr>
<tr>
<td>China</td>
<td>8.0%</td>
</tr>
<tr>
<td>Japan</td>
<td>6.8%</td>
</tr>
<tr>
<td>Germany</td>
<td>4.9%</td>
</tr>
<tr>
<td>France</td>
<td>3.3%</td>
</tr>
<tr>
<td>Italy</td>
<td>2.9%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>2.5%</td>
</tr>
<tr>
<td>Spain</td>
<td>2.3%</td>
</tr>
<tr>
<td>Canada</td>
<td>2.1%</td>
</tr>
<tr>
<td>Brazil</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

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

Sources:
From 2017 to 2021 Asia Pacific accounted for over 50% of clinical trial activity across APAC, US, and EU5¹

Sources:
   https://novotech-cro.com/sites/default/files/2022-05/Evolution%20of%20Clinical%20Trials%20in%20the%20Asia%20Pacific%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]

Asian 39%¹

Asian 46%²

Asian 60%³

Asian 49%⁴

Sources:
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

<table>
<thead>
<tr>
<th>For industry</th>
<th>For Asian HTA agencies</th>
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</thead>
<tbody>
<tr>
<td>Early identification of prognostic factors and</td>
<td>Consider establishing early scientific advice processes</td>
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<tr>
<td>effect modifiers</td>
<td></td>
</tr>
<tr>
<td>Integrate Asia into the global development</td>
<td>Expectations for special scenarios (e.g., rare diseases, no SoC)</td>
</tr>
<tr>
<td>strategy</td>
<td></td>
</tr>
<tr>
<td>Identify early and plan for pragmatic or</td>
<td>Clear thresholds for Asian representation in clinical trials, and</td>
</tr>
<tr>
<td>extension local trials and collection of RWD</td>
<td>for locality and quality of RWD</td>
</tr>
<tr>
<td>Apply sound statistical methods</td>
<td>Develop (or implement existing) frameworks for the use of RWD and</td>
</tr>
<tr>
<td></td>
<td>RWE to support reimbursement in Asia</td>
</tr>
</tbody>
</table>
Are Global Trials Good Enough to Support the Reimbursement of a New Technology in Asia?

When and How
A Methodological Perspective

Grammati Sarri, PhD, MSc, DiDS
Chair of Comparative Effectiveness Research ISPE
Special Interest Group &
Head of RWAA External Research Partnerships/
Senior Research Principal
Cytel
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

<table>
<thead>
<tr>
<th></th>
<th>Internal Validity</th>
<th>External Validity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Question to answer</strong></td>
<td>Is the trial measuring what it is supposed to measure (e.g., study design, patient selection criteria, outcomes)?</td>
<td>Do the results of the trial(s) hold true in a specific clinical practice/country?</td>
</tr>
<tr>
<td><strong>Measures</strong></td>
<td>The unbiased causal effect of a health technology</td>
<td>The causal effect of a health technology is transferrable to the population of interest.</td>
</tr>
<tr>
<td><strong>HTA decision-making</strong></td>
<td>To estimate the technology's clinical effectiveness vs. standard of care options</td>
<td>To estimate technology will be beneficial for the population in the real world</td>
</tr>
<tr>
<td><strong>Supporting evidence</strong></td>
<td>Trial-based evidence with randomised controlled trials (RCT) as the gold standard</td>
<td>Real-world evidence (RWE) from population-based studies</td>
</tr>
</tbody>
</table>
How to Identify if Asian Background is an Effect Modifier or Prognostic Factor? Guidance out there…

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Title of Guidance Document</th>
<th>Year of Publication</th>
<th>Specific Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICE</td>
<td>NICE health technology evaluations: the manual</td>
<td>2022</td>
<td>Potential effect modifiers should be identified before data analysis through a review of the subject area or discussion with experts in the clinical discipline.</td>
</tr>
<tr>
<td>NICE DSU</td>
<td>TSD 18: Methods for population-adjusted indirect comparisons in submissions to NICE</td>
<td>2016</td>
<td>Thorough review of the subject area or discussion with clinical experts is needed.</td>
</tr>
<tr>
<td>NICE DSU</td>
<td>TSD 7: Evidence synthesis of treatment efficacy in decision making: a reviewer’s checklist</td>
<td>2012</td>
<td>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).</td>
</tr>
<tr>
<td>HAS</td>
<td>Indirect comparisons methods and validity</td>
<td>2009</td>
<td>Interaction covariables should be identified through subgroup analyses conducted in the relevant clinical trials and interaction tests.</td>
</tr>
</tbody>
</table>

Challenges

- There is limited HTA guidance
- 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?

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

Step 1
Are global trials good enough to support the reimbursement of a new technology in Asia?

Step 2
Is there evidence* that Asian background may be an effect modifier or prognostic factor?

Step 3
Yes (as a effect modifier^)

Global trials to support HTA

Existing RWE Asian studies to support locality claims in clinical and cost-effectiveness analyses
Scenario analyses, if no available local data

Is the target trial an RCT or single-arm?

No for either

If RCT, no impact in relative treatment effects

If single-arm trial

^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)

*Supporting evidence from systematic literature reviews, subgroup trial analyses of other trials in the same indications and clinical expert opinions
Identifying the Role of Asian Background Based on Subgroup Analyses

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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Asian/East Asian no. (%)</th>
<th>Caucasian no. (%)</th>
<th>Other (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACIFIC</td>
<td>25.20%</td>
<td>70.80%</td>
<td>4%</td>
</tr>
<tr>
<td>OAK</td>
<td>20%</td>
<td>71%</td>
<td>9%</td>
</tr>
<tr>
<td>KN-024</td>
<td>13.60%</td>
<td>86.40%</td>
<td>0%</td>
</tr>
<tr>
<td>KN-010</td>
<td>21%</td>
<td>72%</td>
<td>7%</td>
</tr>
<tr>
<td>CM 057</td>
<td>3%</td>
<td>91%</td>
<td>6%</td>
</tr>
<tr>
<td>CM 017</td>
<td>3%</td>
<td>90%</td>
<td>7%</td>
</tr>
</tbody>
</table>


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

<table>
<thead>
<tr>
<th>When Global trials <strong>Include</strong> Some Asian Patients</th>
<th>When Global trials <strong>Do Not</strong> Include Asian Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Considering limitations around subgroup analyses</strong>&lt;br&gt;(pre-specified/post-hoc design, sample size)&lt;br&gt;Consistency in findings trends with previous trials and related subgroup analyses</td>
<td><strong>Identifying RWE local data</strong>&lt;br&gt;Challenges associated with local data availability, model parameters and quality</td>
</tr>
<tr>
<td><strong>1) Subgroup trial analyses</strong>&lt;br&gt;<strong>2) Combining RWE local data with trial analyses</strong></td>
<td><strong>Trial reweighting as the most reliable modelling exercise</strong>&lt;br&gt;Interaction terms between treatment and covariates</td>
</tr>
<tr>
<td><strong>Resolving uncertainty through scenario (sensitivity) and bias adjustment analyses</strong></td>
<td><strong>Resolving uncertainty through scenario (sensitivity) and bias adjustment analyses</strong></td>
</tr>
<tr>
<td><strong>Main Consideration: Generalisability</strong></td>
<td><strong>Main Consideration: Transportability</strong></td>
</tr>
</tbody>
</table>
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?

Outcome and patient characteristics differences in available RWE data sets

Balancing the closeness of RCTs and RWE with the associated impact on the effective sample size available for analysis

Identifying important treatment effect modifiers

Choosing between RWE quality (biases) versus locality

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

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, Elisabetta Patomo, Hongbo Yuan, Jianfei (Jeff) Guan, Dimitri Bennett, Xuerong Wen, Andrew R Zullo, Joan Largent, Mary Panaccio, Mugdha Gokhale, Daniela Claudia Moga, M Sanni Ali, Thomas P A Debray
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

Grammati Sarri
Grammati.sarri@cytel.com
Q & A Session
Thank You
For Your Attention

Yannan Hu, Associate Director
(Shanghai, China)

Yannan.hu@cytel.com
(+86) 181-1626-7182
yannanhu_cheese

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