Recognizing cultural diversity in patient centered outcomes for health care decision making

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Topics for Today’s Discussion

- Cultural Differences and Their Impact
- Patient-Reported Outcomes in Health Technology Assessments in Asia
- Methods and Solutions to Recognize Cultural Differences

Genetic and PK/PD Differences Pertinent to Asian Patients

- ACE inhibitor
  - Higher risk of cough
- Carbamazepine
  - Higher risk of Stevens-Johnson syndrome
- Clopidogrel
  - Decreased response
- Allopurinol
  - Higher risk of cutaneous reactions
- Eltrombopag
  - Lower starting dose due to increased plasma exposure

Case Study

Astellas Announces Positive Topline Results from Two Phase 3 Pivotal Global Trials of Fezolinetant for the Nonhormonal Treatment of Vasomotor Symptoms in Postmenopausal Women

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Feb 19, 2021

TOKYO, February 19, 2021 – Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D., "Astellas") today announced positive topline results from the Phase 3 pivotal SKYLIGHT 1™ and SKYLIGHT 2™ clinical trials for fezolinetant, an investigational oral, nonhormonal compound being studied for the treatment of moderate to severe vasomotor symptoms (VMS) – i.e., hot flashes associated with menopause.

Astellas Announces Topline 12-week Results from Phase 3 Study of Fezolinetant for the Nonhormonal Treatment of Vasomotor Symptoms in Women in Asia

Astellas' MOONLIGHT 1™ clinical trial evaluating investigational fezolinetant 30 mg administered once daily

TOKYO, March 15, 2022 – Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D., "Astellas") today announced topline results from the ongoing Phase 3 MOONLIGHT 1™ clinical trial investigating the efficacy and safety of fezolinetant, an investigational oral, nonhormonal compound being studied for the treatment of moderate to severe vasomotor symptoms associated with menopause (VMS), in women in Asia. VMS, characterized by hot flashes (also called hot flushes) and/or night sweats, are common symptoms of menopause.[1,2]

Based on the 12-week data analysis in 302 participants, fezolinetant 30 mg once daily (QD) in women in China, Korea and Taiwan did not meet the pre-defined endpoints for efficacy. While numerical improvements from baseline were observed in the fezolinetant 30 mg treatment group, the results did not meet statistical significance. The 12-week safety data in

Moderate VMS: Sensation of heat with sweating/dampness, but was able to continue activity. If at night, participant woke up because she was feeling hot and/or was sweating, but no action was necessary other than rearranging the bed sheets.

Severe VMS: Sensation of intense heat with sweating, caused disruption of activity. If at night, participant woke up hot and was sweating and needed to take action (e.g., remove layers of clothes, open the window, or get out of bed).

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Cultural Differences and Their Impact

Ari Gnanasakthy, MBA, MSc
RTI-HS

Background

- Pharmaceutical research mostly carried out in global north
- But – 60% of the global population lives in Asian region[1]
- Approximately two-thirds of Asian nations are classified as low- and middle- income countries

[1] Population by Regions in the World (2022) - Worldometer (worldometers.info)

Impact of Culture in Clinical Trials

- What is culture?
- Cultural norms and taboos
- Physiological differences
- Reporting outcomes
- Concepts and translation
- Literacy

What is Culture?

Culture . . . can be thought of as a set of practices and behaviors defined by customs, habits, language, and geography that groups of individuals share.

[T]he effect of cultural systems of values on health outcomes is huge, within and across cultures, in multicultural settings, and even within the cultures of institutions established to advance health."

Napier et al. Culture and health. The Lancet. 2014; 314: 1607-39

Impact of Culture on Illness

- Care seeking
- Coping
- Support of family & community
- Treatment pathway
- Change in health

> *Cultural meanings of illness have real consequences in terms of whether people are motivated to seek treatment, how they cope with their symptoms, how supportive their families and communities are, where they seek help (mental health specialist, primary care provider, clergy, and/or traditional healer), the pathways they take to get services, and how well they fare in treatment.*

Chapter 2 Culture Counts: The Influence of Culture and Society on Mental Health. Available from: https://www.ncbi.nlm.nih.gov/books/NBK44249/

Cultural Norms Can Vary substantially

> *In many societies—especially those in which malnutrition is ubiquitous—obesity is often mistaken for health, whereas in other cultures (Brazil, for instance) the right to be beautiful (as it is culturally defined) might extend to plastic surgery for poor people*

Napier et al. Culture and health. The Lancet. 2014; 314: 1607-39

Cultural Norms and Taboos May Impact Outcomes

- In westerns countries disease is seen because of natural scientific phenomena that needs treated with medicines that combat microorganisms or use sophisticated technology.
- Some illnesses and treatments may not be accepted as cultural norms
  - In Vietnamese culture, mystical beliefs explain physical and mental illness.
  - Russian patients find it difficult to question a physician and to talk openly about medical concerns
  - The extended family has significant influence in decision making among Asians and Pacific Islanders
  - Diagnosis of severe mental illness may not be accepted in India / Pakistan
  - Cancer is taboo among south Asian women

Editorial, Lancet Oncology (2017)
Hearn M., et.al, The Lancet (2020)

https://www.euromedinfo.eu/how-culture-influences-health-beliefs.html/

There Are Physiological Differences

- Patients from East Asia has hyper-coagulability
  - Risk-benefit ratio during antithrombotic treatment would be relatively different compared with the Western population
- Differences in tumor biology and metabolism of anticancer drugs may lead to differences in hematological toxicities between Asians and non-Asians with breast cancer

Gan Sushrima, Diabetes Care (2020); 43:1948-1957

How Outcomes are Reported May Differ Between Cultures

- Asian patients are more likely to report their somatic symptoms, such as dizziness, while not reporting their emotional symptoms
- Interpretations of the EQ-VAS vary across Asian respondents.
- Greek women with IBS are more seriously affected mentally by their disease than Swedish women
- Pain and bloating related to irritable bowel disease in China may be perceived to be on a continuum whereas in Europe they are related concomitants of gastrointestinal disturbance
- Reporting by women of midlife-symptoms varies between China and Japan

https://www.ncbi.nlm.nih.gov/books/NBK44249/

Simon GE, et. al, New England Journal of Medicine. 1999;341(18):1329-35.

Tan RL-Y, et. al, The Patient - Patient-Centered Outcomes Research. 2021 2021/03/01;14(2):283-93.

Faresjo A, et. al.. Health-related quality of life of irritable bowel syndrome patients in different cultural settings. 2006.

Drossman DA and Weinland SR., Eur J Gastroenterol Hepatol. 2008 Jul;20(7):593-5.

Gawlicki MC. et. al, Health and Quality of Life Outcomes. 2014 Feb;12.

Shea JL. Am J Hum Biol. 2006 Mar-Apr;18(2):219-22

Implication of Heterogeneity in PRO data

- There are many factors that can impact PRO data in multiregional studies
  - Cultural background of patients
  - Attitude and stigma associated with diseases
  - Literacy that may impact health literacy and hence outcomes
- PRO measures are not always culturally neutral
- Inflation of variation in data due to these factors may impact the conclusion from multinational studies
  - Increased possibility of type 2 error
- It is important to consider cultural issues during the planning and analysis stages of clinical trials with PRO data

Regnault A. et. al, Qual Life Res. 2015; 24: 273-7

Patient-Reported Outcomes in Health Technology Assessments in Asia

Jipan Xie, MD PHD
XL Source, Inc.

China

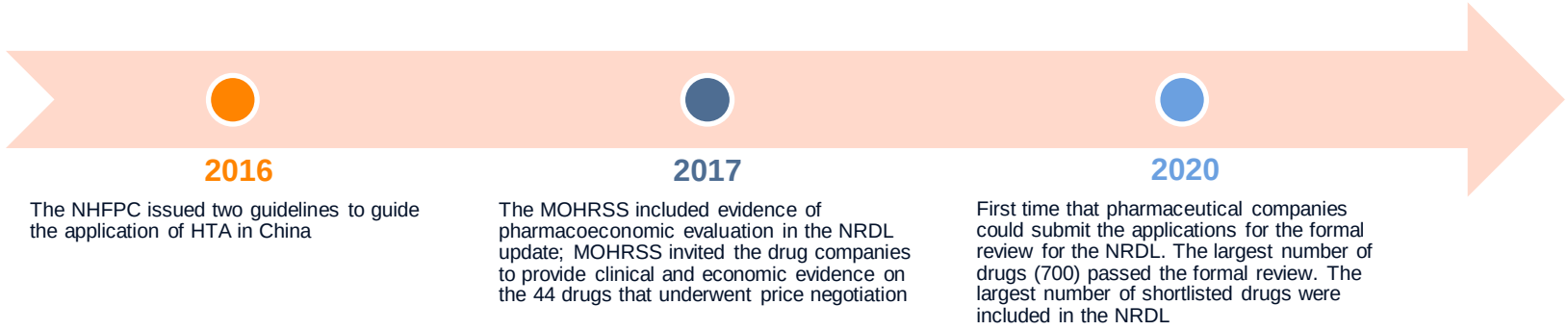
Japan

S. Korea

Taiwan

China

- Brief history of HTA in China



- *The China Guidelines for Pharmacoeconomic Evaluations 2020 Edition* recommends
  - CUA with QALY as the outcome measure
  - Health utility is measured using indirect methods with generic utility instruments, such as EQ-5D and SF-6D
  - The scoring algorithm is based on the preference of the general population in China
  - Direct methods, such as SG, TTO and DCE, can be used if indirect methods are not available or suitable
  - Published utility scores from a systematic literature review can be used if direct methods are not available

https://www.ispor.org/docs/default-source/heor-resources-documents/pe-guidelines/china-guidelines-for-pharmacoeconomic-evaluations-2020.pdf?sfvrsn=446b6f6_3

NHFPC= National Health and Family Planning Commission, MOHRSS= Ministry of Human Resources and Social Security, NRDL= National Reimbursement Drug List
CUA= cost-utility analysis, QALY= quality-adjusted life year, EQ-5D=European quality of life five dimensions, SF-6D=short form six dimensions, SG=standard gamble, TTO=time-trade off, DCE=discrete choice experiment

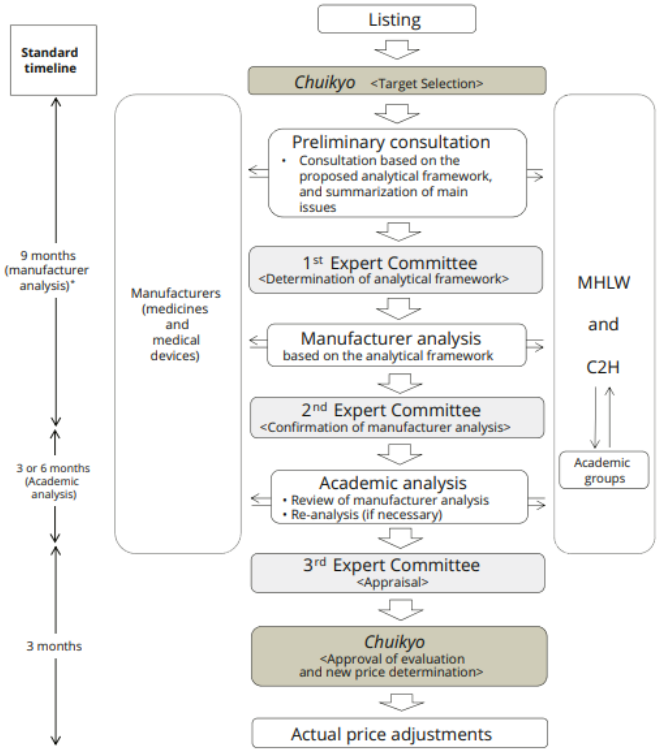
China (Cont'd)

- Gaps in applying PROs in HTA
  - Guidelines are not strictly followed
  - Lack of data on PROs
    - Less than one third of the clinical trials conducted in China from 2010 to 2020 included PROs as endpoints
  - QoL instruments that have not been mapped to utility values
- Future trend
  - PROs become more recognized by academics and government in China
    - The Centers for Drug Evaluation published the draft guidelines for applying PROs in clinical studies of pharmaceutical products in 2021
    - A value set for SF-6Dv2 in the China population was published by Wu et al. in 2021
  - More PRO data will likely be available in clinical trials
  - PRO information in the real-world data is expected to increase, especially with the development of ePRO
  - More HTA submissions with high-quality CUA

References:
Yue X, Li Y, Wu J, Guo JJ. Current Development and Practice of Pharmacoeconomic Evaluation Guidelines for Universal Health Coverage in China. Value Health Reg Issues. 2021 May;24:1-5.
https://www.ccfdie.org/cn/yjxx/yphzp/webinfo/2022/01/1640591393226969.htm
Wu, J., Xie, S., He, X. et al. Valuation of SF-6Dv2 Health States in China Using Time Trade-off and Discrete-Choice Experiment with a Duration Dimension. PharmacoEconomics ***39,*** *521–535 (2021).*
PRO=patient-reported outcome, QoL=quality of lie, HTA=health technology assessment, CUA=cost-utility analysis.

Japan

- HTA in Japan
  - The MHLW started a 3-year pilot HTA program in 2016
  - The first official guideline for the economic evaluation of drugs/medical devices was developed in the same year
  - The HTA process was formally implemented in April 2019
- *Guideline for Preparing Cost-Effectiveness Evaluation to the Central Social Insurance Medical Council version 3 2022* recommends
  - Evidence based on CUA with QALY as the preferred outcome measure; if QALY is not available, others, such as cost-minimization analysis, may be considered
  - QoL score should be measured by a preference-based measure, with EQ-5D-5L as the first choice, and should be responded by patients, when possible
  - Mapping is acceptable if a preference-based measure is not available
  - If QoL scores from patients cannot be collected, direct methods, such as SG, TTO and DCE, in the general population are acceptable
  - Use of Japanese data on QoL is preferred; if Japanese data is unavailable, high-quality data outside Japan is acceptable



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Hasegawa M, Komoto S, Shiroiwa T, Fukuda T. Formal Implementation of Cost-Effectiveness Evaluations in Japan: A Unique Health Technology Assessment System. Value in Health. 2020;23(1): 43-51.
https://c2h.niph.go.jp/tools/guideline/guideline_en.pdf
MHLW= Ministry of Health, Labor, and Welfare, C2H= Center for Outcomes Research and Economic Evaluation for Health, Chuikyo=Central Social Insurance Medical Council.
CUA= cost-utility analysis, QALY= quality-adjusted life year, QoL=quality of life, EQ-5D-5L= European quality of life five dimensions -5 levels, SG=standard gamble, TTO=time-trade off, DCE=discrete choice experiment

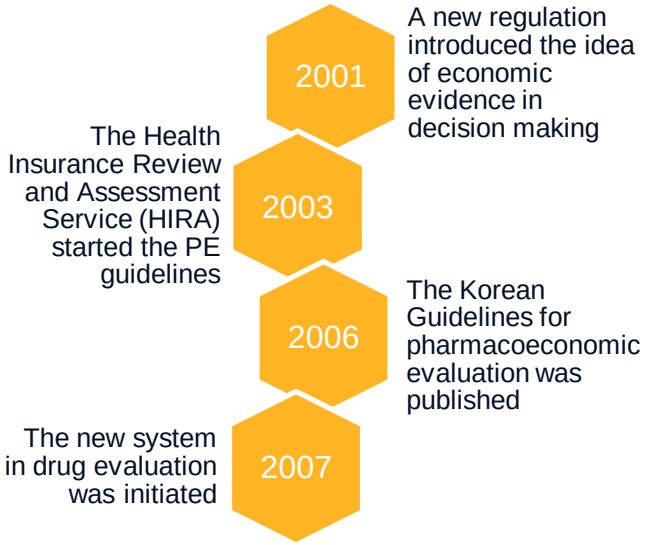
Japan (Cont'd)

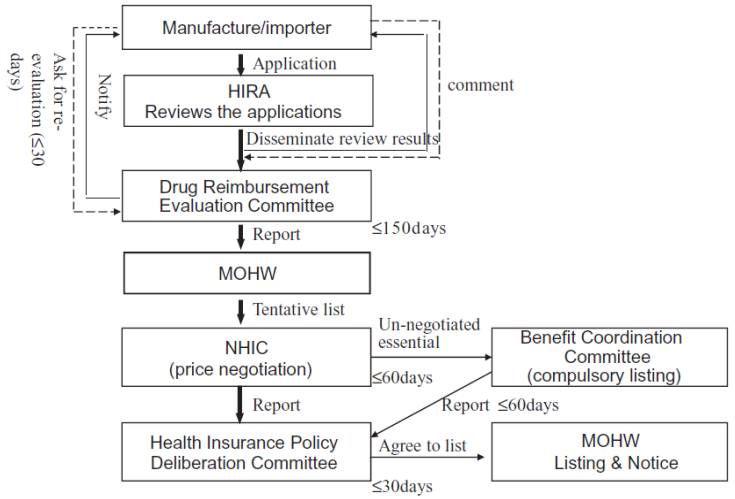
- Challenges
  - Many clinical trials in Japan do not include PROs as endpoints
  - Companies lack expertise in generating and collecting PRO data
  - EQ-5D is the only measure with a valid value set in Japan
- Opportunities
  - Professional organizations take initiatives in better understanding and implementing PROs in clinical trials and real-world practice, e.g., the collaboration of the Japan Clinical Oncology Group and the European Organization for Research and Treatment of Cancer
  - The establishment of the new HTA system is likely to increase the demand for QoL data, which may facilitate incorporation of PROs in clinical trials for innovative drugs

References:
Kamae I, Thwaites R, Hamada A, Fernandez JL. Health technology assessment in Japan: a work in progress. J Med Econ. 2020 Apr;23(4):317-322.
Terada M, Nakamura K, Martinelli F, Pe M, Mizusawa J, Eba J, Fukuda H, Kiyota N, Gatellier L, Majima Y, Velikova G, Bottomley A. Results from a 1-day workshop on the assessment of quality of life in cancer patients: a joint initiative of the Japan Clinical Oncology Group and the European Organisation for Research and Treatment of Cancer. Jpn J Clin Oncol. 2020 Oct 22;50(11):1333-1341.
PRO=patient-reported outcome, EQ-5D=European quality of life five dimensions, QoL=quality of lie, HTA=health technology assessment.

South Korea

- History of HTA in South Korea



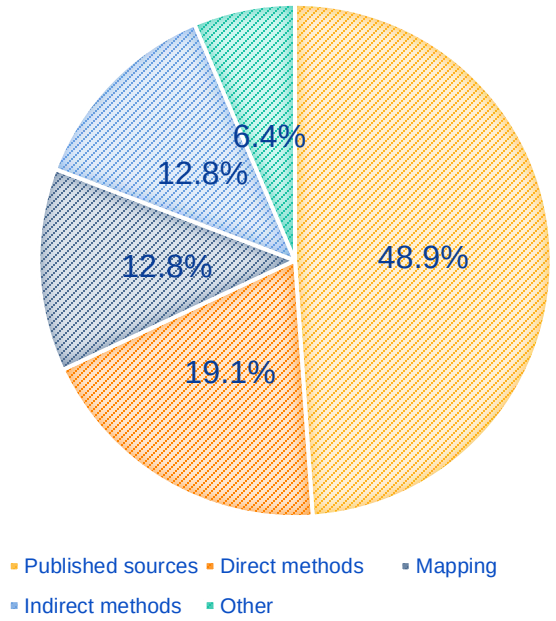


- *Guidelines for Economic Evaluation for Pharmaceuticals, Version 3, 2021*
  - CUA with QALY is preferred
  - Utility values from indirect methods using a generic preference-based measure from clinical trials are preferred
  - The value set should reflect the preference of a representative Korean general population
  - Direct methods, mapping and using published sources are acceptable when data based on indirect methods were not available
  - Do not recommend disease-specific QoL measures
  - Utility values from multiple sources in the same evaluation should be avoided

References:
Bae EY, Lee EK. Pharmacoeconomic guidelines and their implementation in the positive list system in South Korea. Value Health. 2009 Nov-Dec;12 Suppl 3:S36-41.
Bae EY, Hong J, Bae S, Hahn S, An H, Hwang EJ, Lee SM, Lee TJ. Korean Guidelines for Pharmacoeconomic Evaluations: Updates in the Third Version. Appl Health Econ Health Policy. 2022 Jul;20(4):467-477.
HIRA=Health Insurance Review and Assessment Service, MOHW=Ministry of Health and Welfare, NHIC=National Health Insurance Corporations.
CUA= cost-utility analysis, QALY= quality-adjusted life year, QoL=quality of life.

South Korea (Cont'd)

- Review of utility measurement methods in HIRA submissions 2014-2018
  - 47 out of 50 employed CUA
  - Utility measurement methods vary substantially and are not consistent with the recommendations by the guidelines
- Similar challenges exist in South Korea as in China and Japan
  - Lack of PRO data in clinical trials, particularly preference-based utility measures
  - Use of foreign values from the literature ignores the cultural differences across countries
- Constantly improving and reinforcing the guidelines present the opportunities to generate high-quality PRO data for HTA review



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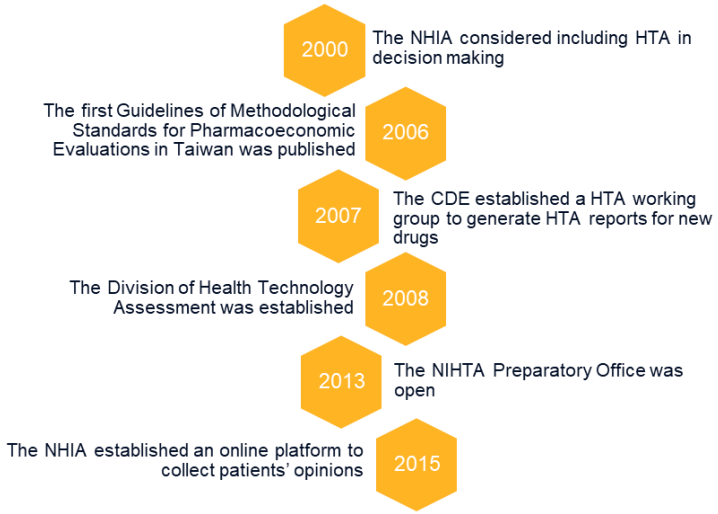
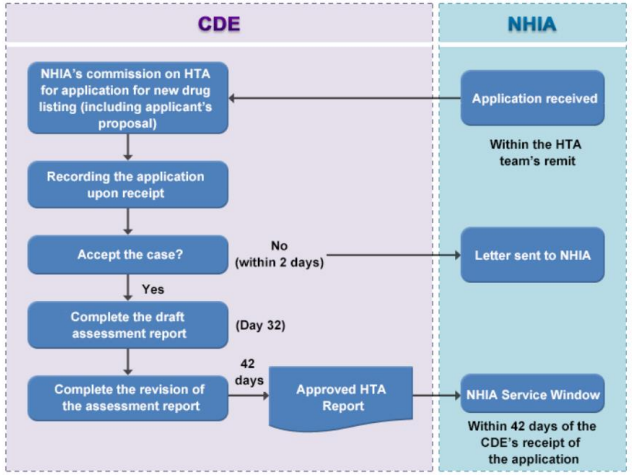
Hong J, Bae EY. A Review of Utility Measurement Methods Used in Pharmacoeconomic Submissions to HIRA in South Korea: Methodological Consistency and Areas for Improvement. Pharmacoeconomics. 2021 Oct;39(10):1109-1121.
HIRA=Health Insurance Review and Assessment Service, CUA= cost-utility analysis, PRO=patient-reported outcome, HTA=health technology assessment.

Taiwan

- History of HTA in Taiwan





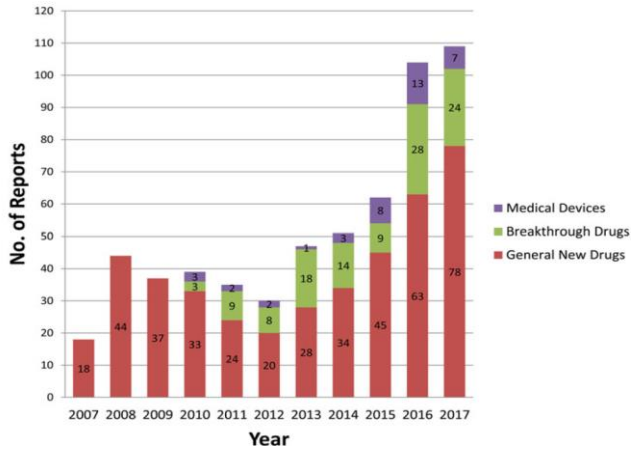
The Process of HTA Assessment for Applications of NHI New Drug Listing

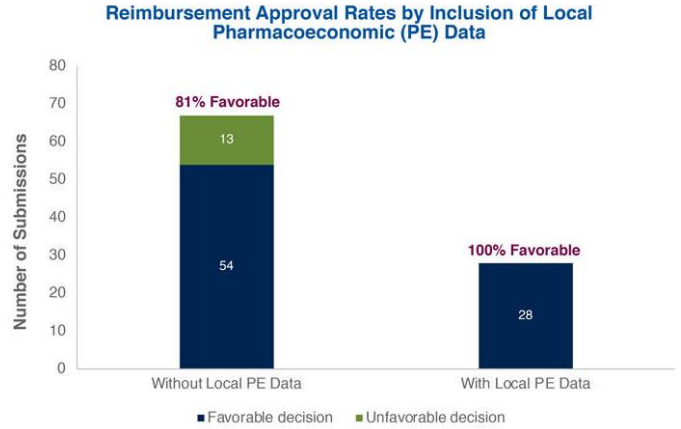
- *Guidelines of Methodological Standards for Pharmacoeconomic Evaluations, 2014*
  - CUA with QALY as the effectiveness outcome is preferred; if CUA is not feasible, CEA can be conducted using final treatment outcomes, such as life-years
  - Utility values should be based on a representative Taiwan population
  - A value set reflecting the preference of the Taiwan population should be used
  - Multiple methods, direct, indirect, mapping and literature review, are acceptable to generate utility values
  - If utility values for the Taiwan population are not available, data from neighboring countries may be used. Details should be provided whether the utility source can reflect the scenario in Taiwan

References:
https://www.cde.org.tw/eng/HTA/
https://www.cde.org.tw/eng/HTA/business
http://www.taspor.org.tw/
HTA=health technology assessment, NHIA= National Health Insurance Administration, CDE= Center for Drug Evaluation, NIHTA= National Institute for Health Technology Assessment. CUA= cost-utility analysis, QALY= quality-adjusted life year, CEA=cost-effectiveness analysis.

Taiwan (Cont'd)

- HTA catalyzed PE research in Taiwan
  - 576 assessment reports were generated in the first 10 years of HTA implementation
  - A Taiwan value set was generated for EQ-5D-5L
  - A pilot study of MCDA in prostate cancer was conducted in 2017
- Preference of local PE data in decision making
  - Review of 95 drug evaluations in 2011-2017 showed a higher percentage of favorable review when local PE data is included in the submission





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Lin HW, Li CI, Lin FJ, Chang JY, Gau CS, Luo N, Pickard AS, Ramos Goñi JM, Tang CH, Hsu CN. Valuation of the EQ-5D-5L in Taiwan. PLoS One. 2018 Dec 26;13(12):e0209344.
HTA=health technology assessment, PE=pharmacoeconomics, EQ-5D-5L= European quality of life five dimensions -5 levels, MCDA= multiple-criteria decision analysis

Summary of PE/HTA Guidelines on PROs

- CUA with QALY is preferred by all four countries/regions thus the guidelines focus on utility measurements in economic evaluations

	China	Japan	South Korea	Taiwan
Methodology	Indirect methods preferred	Indirect methods preferred	Indirect methods preferred	All acceptable
Utility instrument	EQ-5D	EQ-5D	Not specified	Not specified
Value set availability	EQ-5D SF-6D	EQ-5D*	EQ-5D	EQ-5D
Cultural preference	• Data based on the representative local general population are preferred • Local value set should be used, if available • If utility values based on the local population are not available, literature from other countries may be used but details should be provided on selection of the utility values			

* SF-6D value set is available for Japan but has issues of inconsistencies and prediction errors (Joelson, 2021)

References:
https://www.ispor.org/docs/default-source/heor-resources-documents/pe-guidelines/china-guidelines-for-pharmacoeconomic-evaluations-2020.pdf?sfvrsn=446b6f6_3
https://c2h.niph.go.jp/tools/guideline/guideline_en.pdf
Bae EY, Hong J, Bae S, Hahn S, An H, Hwang EJ, Lee SM, Lee TJ. Korean Guidelines for Pharmacoeconomic Evaluations: Updates in the Third Version. Appl Health Econ Health Policy. 2022 Jul;20(4):467-477.
http://www.taspor.org.tw/
HTA=health technology assessment, PE=pharmacoeconomics, CUA= cost-utility analysis, QALY= quality-adjusted life year, EQ-5D=European quality of life five dimensions, SF-6D=short form six dimensions

Gaps and Future Directions in Incorporating PROs in HTA in Asia

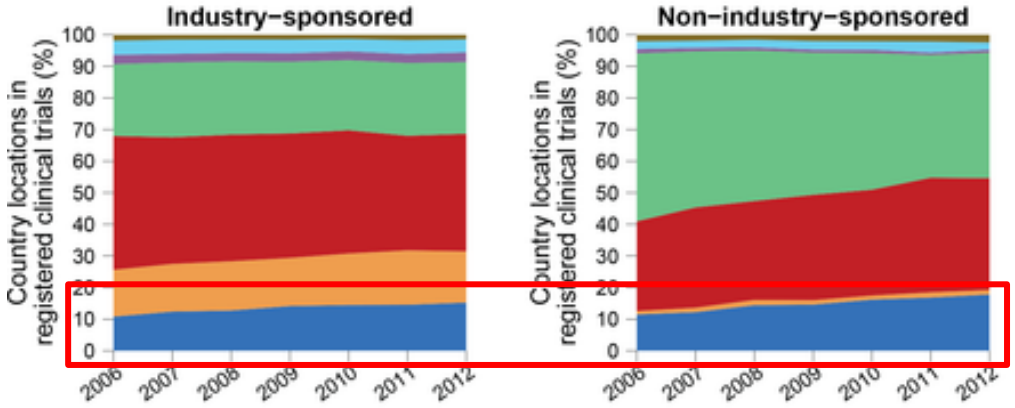
- Gaps
  - Availability of data
  - Quality of data
  - Lack of local validation of instruments
  - Lack of professionals who can evaluate PROs and have deep understanding of HTA
  - Limited to the use of utility in the HTA process
- Future directions
  - Continue to develop PRO data through clinical trials and real-world data collections
  - Address cultural differences when adapting existing instruments from Western countries
    - Translation
    - Ways of application (paper-and-pencil, face-to-face interview, online survey, etc.)
    - Validation
  - Develop new and culturally-appropriate PRO instruments in Asia
  - Leverage the best data at hand and address uncertainties in utility in HTA
  - Evaluate the value of the innovative medical treatments beyond ICER

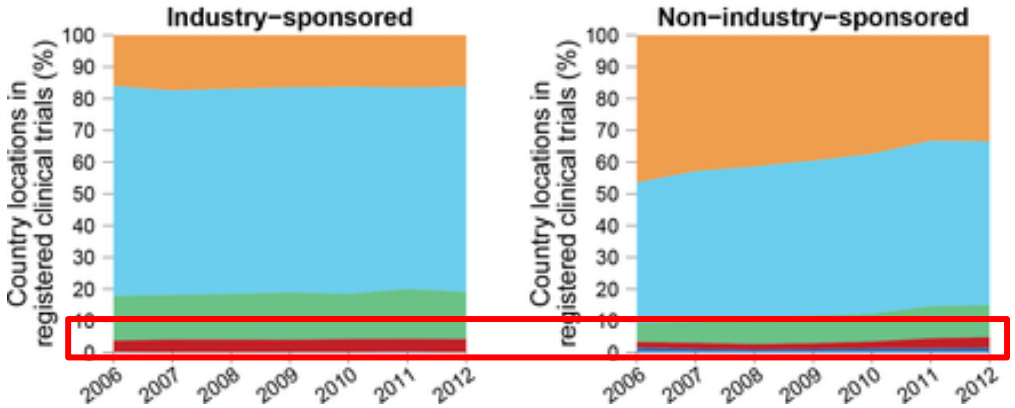
PRO=patient-reported outcome, HTA=health technology assessment, ICER=incremental cost-effectiveness ratio

Methods and Solutions to Recognize Cultural Differences

Andrea Latour
PRMA Consulting

Clinical trials have been unequally distributed across countries and income level. Industry sponsorship has had a major influence in this unequal mapping





Income level	Median number of trials per 1M inhabitants
High	116.0
Upper-middle	13.8
Lower-middle	1.8
Low	1.1

Atal I, Trinquart L, Porcher R, Ravaud P. Differential globalization of industry-and non-industry–sponsored clinical trials. PloS one. 2015 Dec 14;10(12):e0145122.

One of the reasons can be attributed to the mistrust in the system..

Over 100 African Americans died in the Tuskegee syphilis study

Image: Wikipedia

Mistrust of the health care system emerged as a primary barrier to participation in medical research among participants in a 2010 study among African American adults

Scharff DP, Mathews KJ, Jackson P, Hoffsuemmer J, Martin E, Edwards D. More than Tuskegee: understanding mistrust about research participation. Journal of health care for the poor and underserved. 2010 Aug;21(3):879.

The US FDA has recently (April 2022) developed Industry guidance to improve enrolment from underrepresented racial and ethnic populations in clinical trials

Sponsors of medical products are now advised to develop and submit a "**Race and Ethnicity Diversity Plan**

I. **site location and access** (e.g., language assistance for persons with limited English proficiency, reasonable modifications for persons with disabilities, and other issues such as transportation);

II. **sustained community engagement** (e.g., community advisory boards and navigators, community health workers, patient advocacy groups, local healthcare providers, etc.);

III. **reducing burdens due to trial/ study design/ conduct** (e.g., number/frequency of study-related procedures, use of local laboratory/imaging, telehealth)

FDA. Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials Guidance for Industry U.S. Department of Health and Human Services Food and Drug Administration. April 2022

It is not only demographics. Cultural beliefs play a critical role in PROs, and consequently, HTA (1/3)

Table 1: Percentage of Australian and Japanese respondents who 'agree' or 'strongly agree' with each statement from the Personal stigma scale†

Statement	Depression Vignette	Depression/Suicidal Vignette	Early Schizophrenia Vignette	Chronic Schizophrenia Vignette
Person could snap out of the problem				
Australian	24.7 (21.7%–27.9%)	22.7 (19.9%–25.7%)	18.3 (15.6%–21.3%)	17.9 (15.0%–21.2%)
Japanese	47.2 * d (42.8%–51.6%)	49.4 * d (45.0%–53.8%)	41.2* (36.9%–45.5%)	36.4 * a,b (32.2%–40.6%)
Problem is a sign of personal weakness				
Australian	13.4 (11.0%–16.2%)	16.9 (14.4%–19.6%)	19.3 (16.6%–22.4%)	14.0 (11.7%–16.7%)
Japanese	45.4* (41.0%–49.8%)	45.0* (40.6%–49.4%)	46.6* (42.2%–51.0%)	46.0* (41.6%–50.4%)
Problem is not a real medical illness				
Australian	14.6 (12.3%–17.1%)	15.2 (13.0%–17.8%)	14.9 (12.7%–17.4%)	13.9 (11.7%–16.6%)
Japanese	40.2* (35.9%–44.5%)	38.4* (34.1%–42.7%)	31.4* (27.3%–35.5%)	35.8* (31.6%–40.0%)
People with this problem are dangerous				
Australian	11.9 c,d (9.8%–14.3%)	18.3 c (15.7%–21.2%)	24.9 a,b (22.2%–27.8%)	22.5 a (19.6%–25.7%)
Japanese	14.6 d (11.5%–17.7%)	16.0 d (12.8%–19.2%)	20.4 d (16.9%–23.9%)	37.6 * a,b,c (33.3%–41.9%)
Avoid people with this problem				
Australian	6.9 (5.3%–9.0%)	4.7 (3.5%–6.4%)	4.9 (3.6%–6.6%)	5.2 (3.9%–7.0%)
Japanese	7.8 d (5.4%–10.2%)	5.8 c,d (3.7%–7.9%)	11.8 *,b (9.0%–14.6%)	17.8 * a,b (14.4%–21.2%)
People with this problem are unpredictable				
Australian	42.2 c,d (38.8%–45.6%)	51.1 c,d (47.6%–54.5%)	67.1 a,b (63.9%–70.1%)	67.5 a,b (64.1%–70.7%)
Japanese	18.6 * c,d (15.2%–22.0%)	20.0 * c,d (16.5%–23.5%)	31.0 * a,b,d (26.9%–35.1%)	45.6 * a,b,c (41.2%–50.0%)
If I had this problem I wouldn't tell anyone				
Australian	17.0 c,d (14.5%–19.9%)	21.5 d (18.8%–24.3%)	26.7 a (23.8%–29.8%)	31.1 a,b (28.1%–34.3%)
Japanese	26.8 * d (22.9%–30.7%)	24.8 c,d (21.0%–28.6%)	35.0 b (30.8%–39.2%)	37.2 a,b (32.9%–41.5%)
I would not employ someone with this problem				
Australian	21.6 d (19.2%–24.3%)	22.5 d (19.8%–25.4%)	24.8 (22.0%–27.9%)	32.4 a,b (29.2%–35.8%)
Japanese	38.6 * d (34.3%–42.9%)	38.6 * d (34.3%–42.9%)	47.6 * d (43.2%–52.0%)	61.2 * a,b,c (56.9%–65.5%)
I would not vote for a politician with this problem				
Australian	30.1 d (26.9%–33.4%)	32.5 d (29.4%–35.8%)	35.3 d (32.2%–38.5%)	45.7 a,b,c (42.5%–49.0%)
Japanese	58.0 * d (53.7%–62.3%)	53.8 * d (49.4%–58.2%)	58.0 * d (53.7%–62.3%)	73.8 * a,b,c (69.9%–77.7%)

Griffiths KM, Nakane Y, Christensen H, Yoshioka K, Jorm AF, Nakane H. Stigma in response to mental disorders: a comparison of Australia and Japan. BMC psychiatry. 2006 Dec;6(1):1-2.

It is not only demographics. Cultural beliefs play a critical role in PROs, and consequently, HTA (2/3)

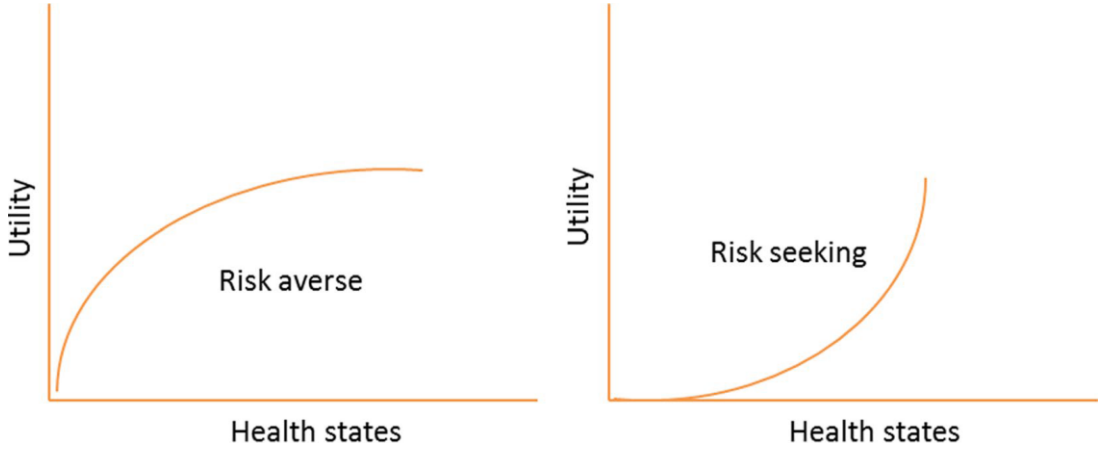
Time Trade Off

- Concept: willingness to trade lengths of life for QoL reflects a person's time preference, which in turn is a **cultural value**.
- Geert Hofstede: long-term orientation (China, Hong Kong, Taiwan and Japan) → less willing to trade lengths of life for QoL
- A medical intervention likely to restore perfect health **in an Asian context will not create as much value**

Standard Gamble

- Concept: gambling P of death vs perfect health
- US and UK → risk taking
- Japan, Korea, Italy → risk averse.
- Risk averse hesitate to engage in gambling, meaning they would assign **high utility** to any given health state

Utility functions according to risk preference



Mahlich J, Dilokthornsakul P, Sruamsiri R, Chaiyakunapruk N. Cultural beliefs, utility values, and health technology assessment. Cost Effectiveness and Resource Allocation. 2018 Dec;16(1):1-8.

It is not only demographics. Cultural beliefs play a critical role in PROs, and consequently, HTA (3/3)

- Based on lit review the authors tested country-specific utility sets
- ICER for Japan was twice that of the UK, or 37% higher than that of the US
- → drugs **would then sell at lower prices** in Japan than in the UK
- Short term TH correlated with lower education and unhealthy behaviour e.g. smoking
- Long term TH correlated with higher education and healthier lifestyle
- **No one-size-fits-all cost-effectiveness approach**

	Germany	Japan	UK	US
Break through innovation				
Incremental cost (JPY)	1,000,000	1,000,000	1,000,000	1,000,000
Incremental QALY	0.506	0.289	0.575	0.400
ICER (JPY per QALY)	1,976,121	3,463,208	1,738,434	2,499,378
Incremental innovation				
Incremental cost (JPY)	1,000,000	1,000,000	1,000,000	1,000,000
Incremental QALY	0.340	0.194	0.387	0.269
ICER (JPY per QALY)	2,939,257	5,151,130	2,585,724	3,717,543

UK United Kingdom, *US* United States; *QALY* quality-adjusted life year, *ICER* incremental cost-effectiveness ratio, *JPY* Japanese Yen

Mahlich J, Dilokthornsakul P, Sruamsiri R, Chaiyakunapruk N. Cultural beliefs, utility values, and health technology assessment. Cost Effectiveness and Resource Allocation. 2018 Dec;16(1):1-8.

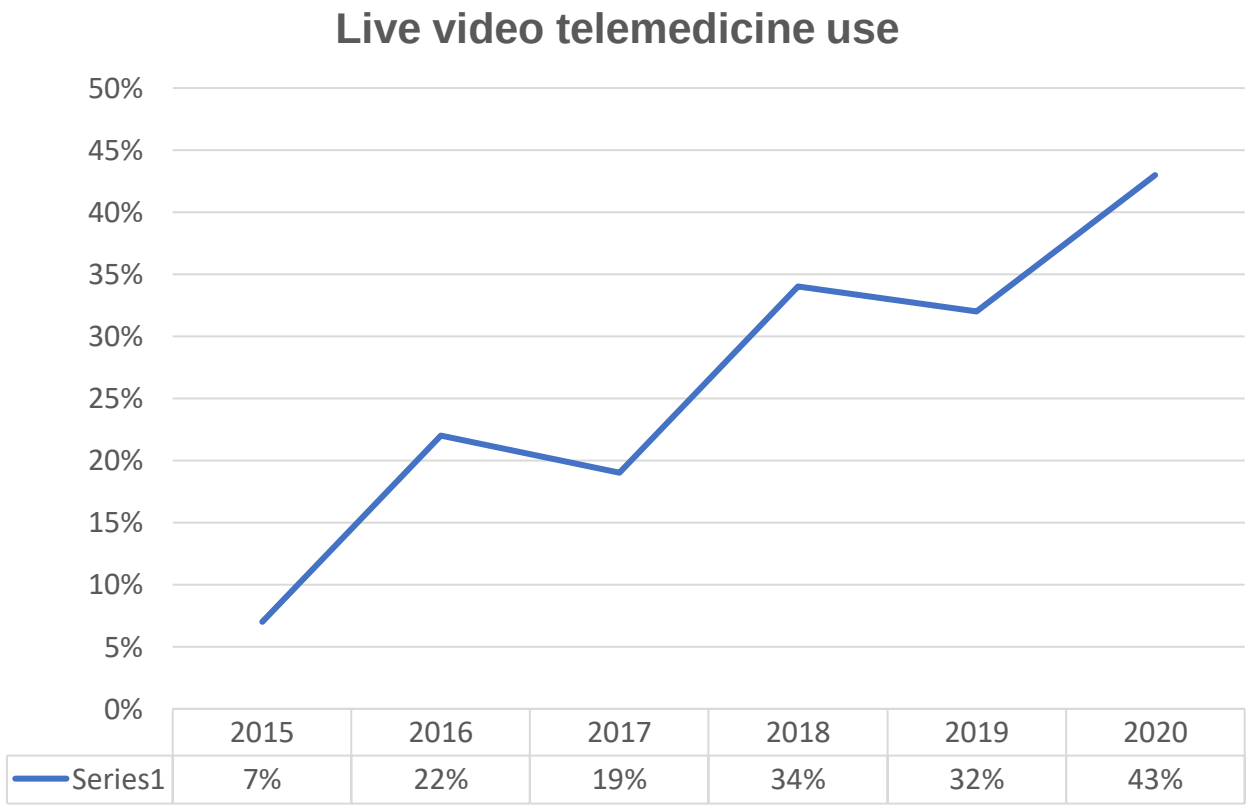
Cultural adaptation of PRO measures

Cross-cultural adaptation (CCA) should involve:

1. "*investigating the extent to which the instrument measures the underlying concept and the parameters of latent trait in the target culture as well as it did in source culture and;*
2. *ensuring the transfer of meaning across languages to achieve a similar effect on respondents who speak different languages*"

Prakash V, Shah S, Hariohm K. Cross-cultural adaptation of patient-reported outcome measures: a solution or a problem?. Annals of Physical and Rehabilitation Medicine. 2019 Feb 10;62(3):174-7.

Telemedicine (and other digital solutions)



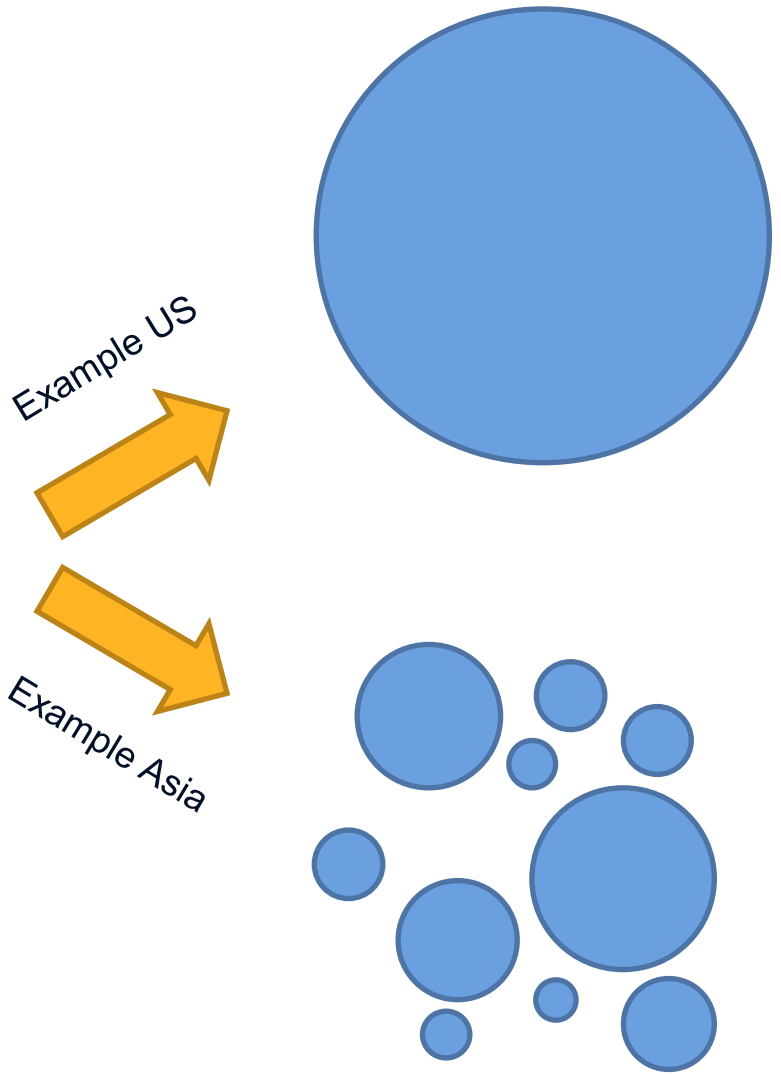
https://rockhealth.com/insights/digital-health-consumer-adoption-report-2020/

- Remote patient monitoring (RPM)
- Teleconsultations
- Acute care
- Wearables
- Etc

- Fosters inclusion, e.g. age, gender, race, geography, etc
- BUT barriers to digital access and literacy

Evidence synthesis

- Regulatory and HTA bodies require evidence on a large sample size to detect a clinically meaningful and statistically significant benefit
- In some disease areas sample sizes required may be very large
- E.g. study in T2D that requires 10,000 patients



- Large multicentre comparative RCT
- Developed for US
- Tot = 10,000 patients

- Several smaller trials pooled
- Tot = 10,000 (or maybe 5,000)
- Important to understand design differences and adjust

PRO adaptations and country-specific co-creation

PRO instruments developed for US and UK → Can be cross-culturally adapted → But may still face issues with cultural equivalence → **Solution: Country-specific co-creation**

Stakeholders in co-creation [1]

- Patients
- Caregivers
- Patient advocacy groups
- Regulators
- HTA agencies
- Clinicians

Benefits of co-creation [2]

- Improve patient autonomy and engagement
- Promote shared decision making
- Improve health literacy and trust
- Capture the right PROs
- Culturally appropriate PRO tools

1. Yang Z, Purba FD, Shafie AA, Igarashi A, Wong EL, Lam H, Van Minh H, Lin HW, Ahn J, Pattanaphesaj J, Jo MW. Do health preferences differ among Asian populations? A comparison of EQ-5D-5L discrete choice experiments data from 11 Asian studies. Quality of Life Research. 2022 Feb 18:1-3.
2. Israilov S, Hyung J. How Co-Creation Helped Address Hierarchy, Overwhelmed Patients, and Conflicts of Interest in Health Care Quality and Safety. November 2017, Volume 19, Number 11: 1139-1145

But are these technical and complex solutions always needed?

Reimbursement status of the 5 highest selling cancer medicines in 2022 (latest data point available)

Country/ Source	Lenalidomide (Revlimid)	Nivolumab (Opdivo)	Ibrutinib (Imbruvica)	Pembrolizumab (Keytruda)	Palbociclib (Ibrance)
UK/ CDF 2022	√	√	√	√	√
Australia/ PBS 2022	√	√	√	√	√
Singapore/ MAF 2022	√	√	×	√	√
Indonesia/ NF 2019	×	×	×	×	×
Thailand/ NLEM List 2021	×	×	×	×	×
The Philippines/ DPRI 2020	×	×	×	×	×

√ Subsidized
× Not subsidized

CDF: cancer drug fund; DPRI: drug price reference index; MAF: medication assistance fund; NF: National Formulary; NLEM: National List of Essential Medicines; PBS: Pharmaceutical Benefits Scheme; RDL: reimbursement drug list
Source for 5 highest selling cancer medicines in 2022: Fierce Pharma

Conclusion

- PROs focused on US/ Europe/ high income
- Underserved communities LESS inclusion in research but MORE clinical need/ disease prevalence
- Cultural aspects are important, even across Asia
- Can adapt PRO instruments, but with limitations
- Solutions: telemedicine, pooling, etc
- Not every country needs the same solution

Q&A

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Thank you!