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Improving healthcare decisions

When and How Can Health-Preference Measures Be Transferred Between Contexts?

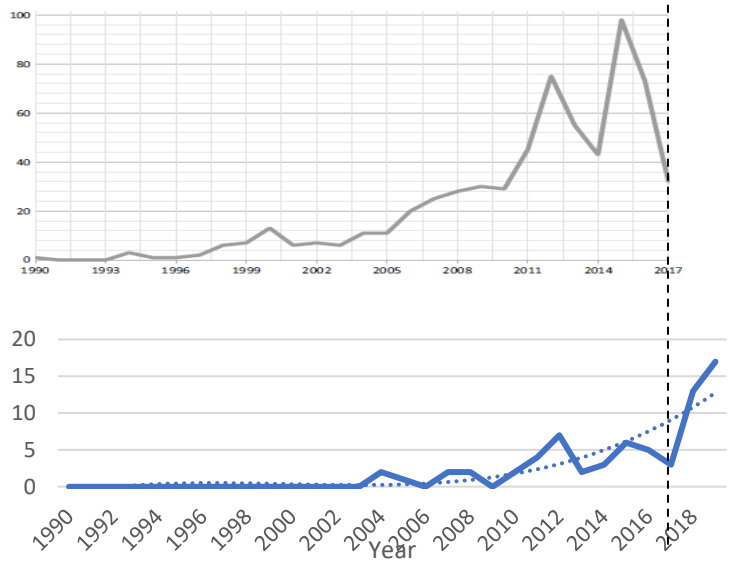
Brought to you by the:
ISPOR Health Preference Research Special Interest Group

Background and forum overview

Moderator
Kevin Marsh, PhD
Executive Director, Evidera

Background

- Quantitative preference data have an increasing role in healthcare decision making.
- Cost / time to collect preference data are barriers to the use of preference data.
- As the evidence base grows, can transferring existing preference data for new applications help to overcome this barrier?



All indications, DCEs[1]

Oncology, any preference method[2]

[1] Soekhai et al 2019
[2] Collacott et al, 2021

Objective

- When and how can health-preference data be transferred?
  - Between countries
  - Between diseases
  - Between indications
  - Between sub-groups

- How should studies be designed and reported with transferability in mind?

- How can the validity and reliability of transfers be assessed?

Outline and Speakers

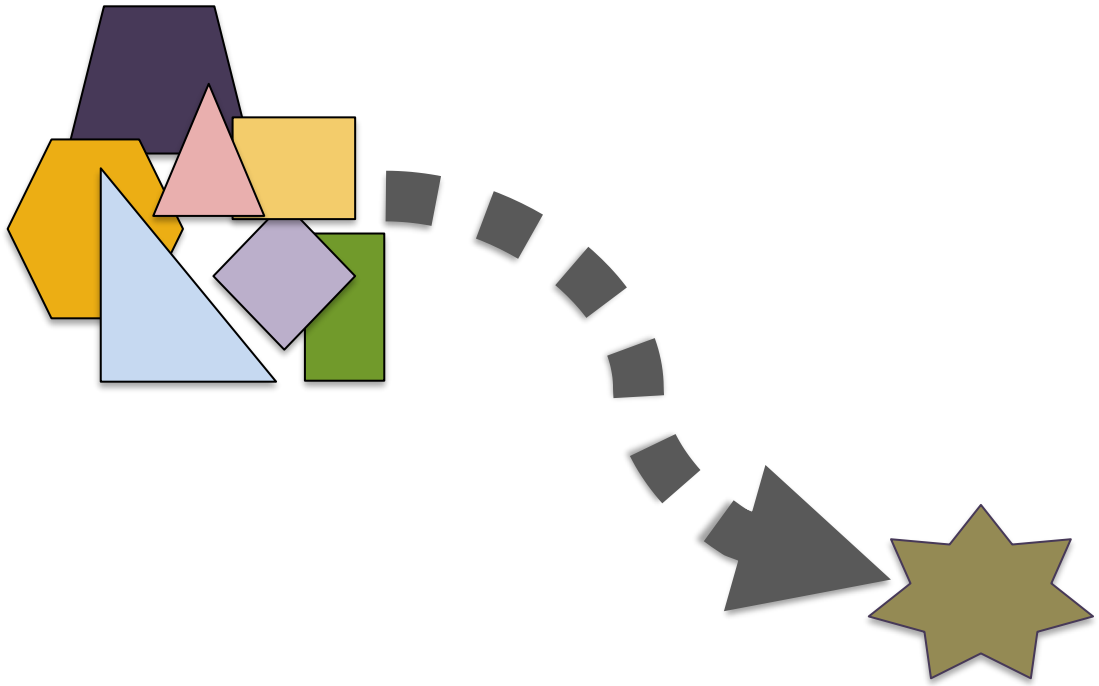
Section		Panellist	Affiliation
1. Lessons from environmental economics		**Reed Johnson, PhD**	Duke Clinical Research Institute, USA
2. IMI PREFER's guidance on transferring preferences		**Ardine de Wit, PhD**	UMC Utrecht, Netherlands
Empirical evidence on transferability ..	3. Between countries	**Bram Roudijk, PhD**	EuroQoL Research Group, Netherlands
	4. Between patients	**Nicolas Krucien, PhD**	Evidera, UK

1

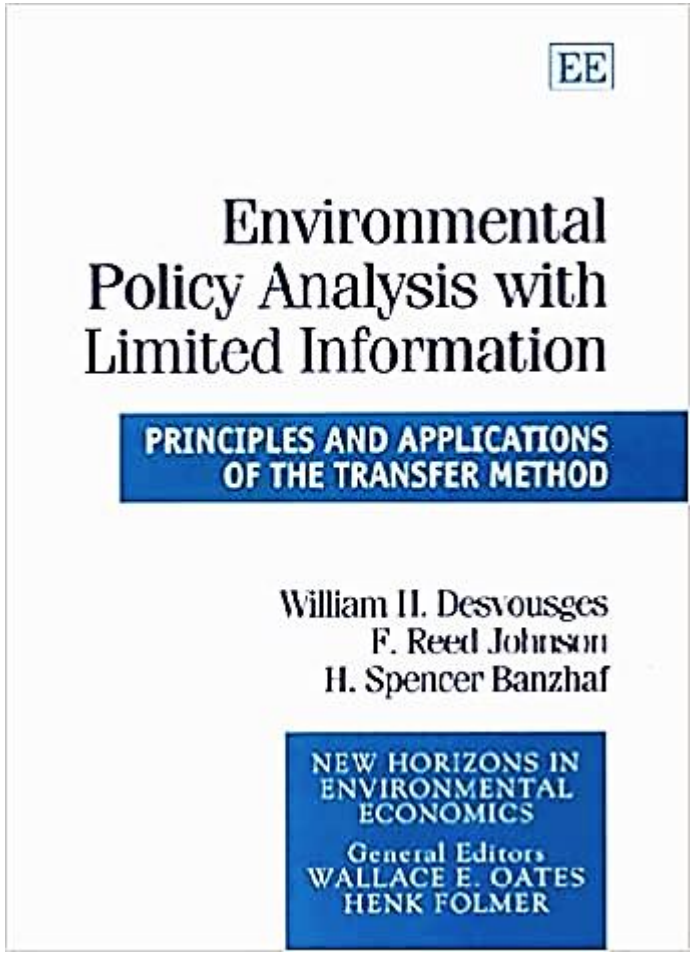
Transferring Benefit-Transfer Methods:
Environmental Non-market Valuation to Health Economics

F. Reed Johnson, PhD
Department of Population Health Sciences
Duke University School of Medicine

40 Years of Environmental Benefit-Transfers



- 1981 Environmental Protection Agency requirement for nonmarket benefit values for air and water pollution-abatement regulations (Executive Order 12291)
- 1992 EPA conference to assess benefit-transfer experience and research needs
- 2000 EPA Guidance for Preparing Economic Analyses
- Active literature subsequent 2 decades
  - Proceedings of EPA workshops 2006, 2016
  - Books: 1999, 2002, 2006, 2007, 2015



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Environmental versus Health Applications

Environmental

- Primarily willingness to pay for cost-benefit analysis
- Also used to define in-kind equivalent restoration for natural-resource damages

Health

- Maximum acceptable risk
- Minimum acceptable benefit
- Healthy-time equivalent
- Willingness to pay

Steps for Benefit Transfers

1. Select study cases based on indicators of internal and external validity

- Degree of similarity among:
  - Outcomes to be valued
  - Baseline levels and quality or quantity changes
  - Characteristics of treatment populations

- Study-design considerations
  - How should valuation method affect study selection?
  - How should quality standards affect study selection?

Steps for Benefit Transfers

2. Derive benefit unit value estimate or value function from previous studies

$v(X)$ Constant value for benefit category X (e.g. reduction in mortality risk)

$v(X_i)$ Value varies by benefit type *i* (e.g. reduction in MI mortality risk)

$v(X_{ij}, Z)$ Value varies by

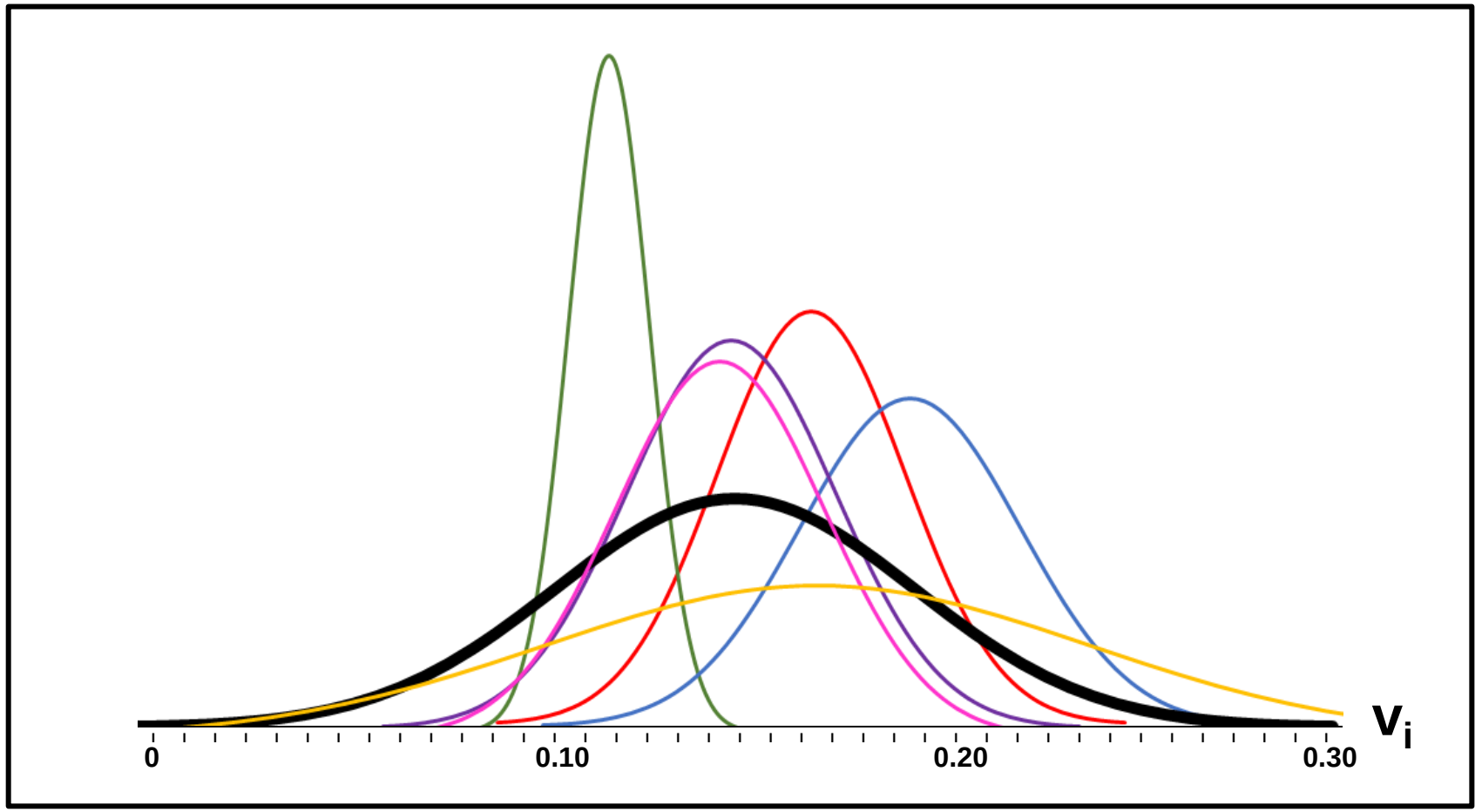
- benefit type ***i***
- patient type ***j*** (age, gender, risk tolerance, health status, …)
- study characteristics ***Z*** (method, N, sample characteristics, journal, …)

DCE Maximum Acceptable Risk Values for Psoriasis

Gonzalez JM. Evaluating Risk Tolerance from a Systematic Review of Preferences: The Case of Patients with Psoriasis. *The Patient* (2018)

- Estimated v(X), v(X_i), and v(X_i,Z) for maximum acceptable risk
- 4 approaches using 61 estimates
  - Select “best”
  - Calculate simple average
  - Derive mother distribution
  - Estimate meta-regression

Mother Distribution for 6 Estimates



Desvousges WH, Johnson FR, Banzhaf HS. Environmental policy analysis with limited information: Principles and applications of the transfer method. 1999.

Meta-Regression for v(X, Z)

- Reduced-form prediction model
  - Allows wide range of explanatory variables
  - Does not ensure theoretical consistency
  - Requires invariant structure
- Structural model (preference calibration)
  - Uses explicit utility-theoretic conceptual framework
  - May not predict well

Steps for Benefit Transfers

2. Reconcile differences between study and new-application contexts.

- X variables among studies and between studies and new application
  - Differences in symptom kinds, severities, and durations
  - Differences in patient treatment experience and demographics

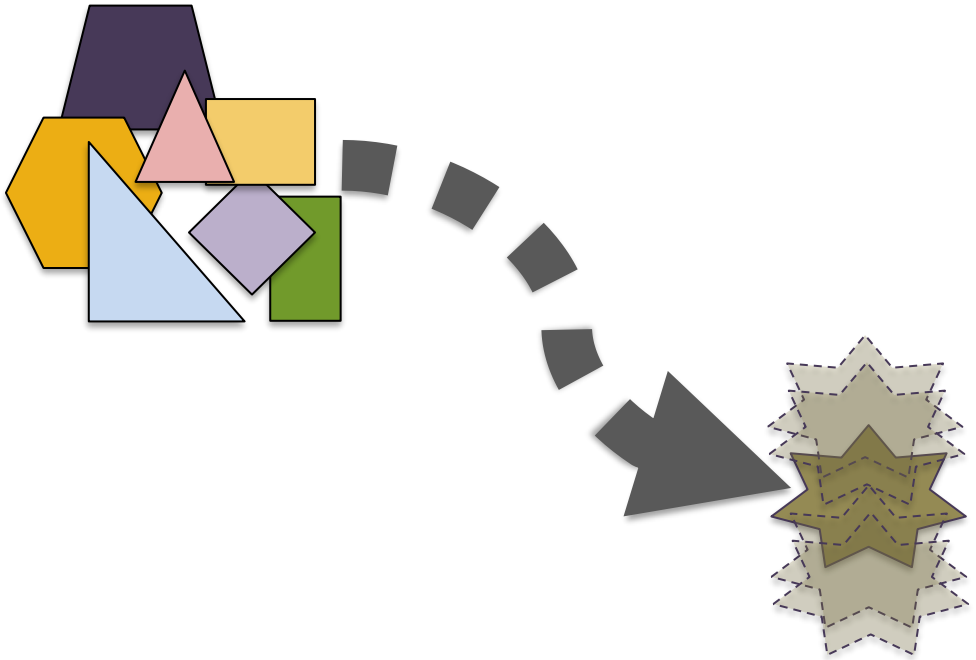
- Z variables
  - Differences in valuation methods
  - Differences in model specifications
  - Differences in sample sizes

Steps for Benefit Transfers

3. Use chosen method to predict or extrapolate study values to new application.

How similar is similar enough?

How good is good enough?



Steps for Benefit Transfers

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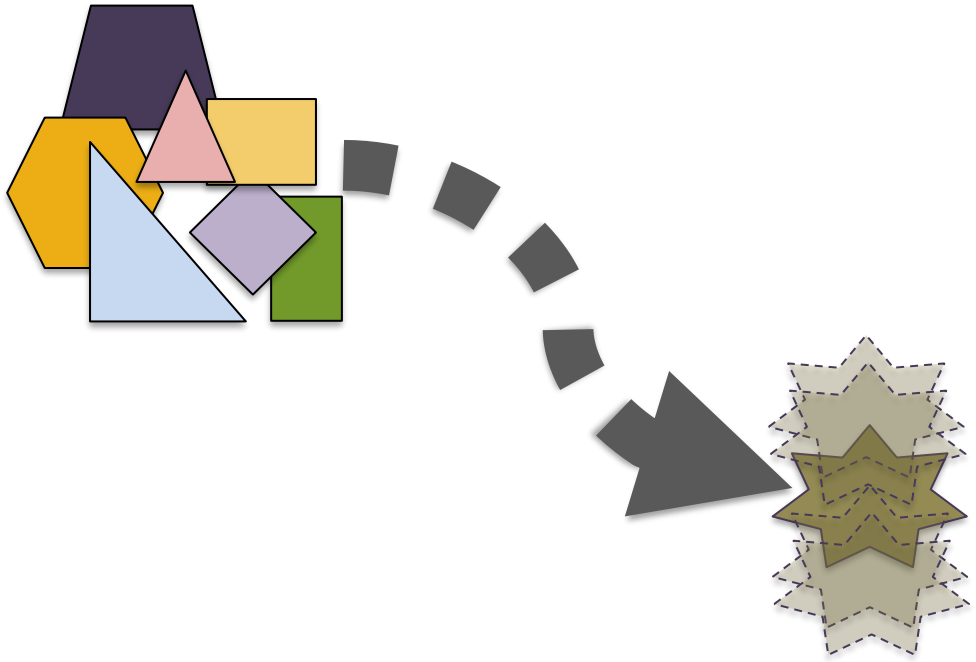


Convergent-validity tests

- Function transfers have smaller errors than value transfers
- Quantity transfers have lower transfer errors than quality transfers
- WTP from contingent valuation has lower errors than other methods
- Combining data from multiple studies reduces transfer errors

Kaul S, et al. What can we learn from benefit-transfer errors? Evidence from 20 years of research on convergent validity. Journal of Environmental Economics and Management 2013;66(1):90-104.

DO NOT IGNORE 4 DECADES OF RESEARCH ON BENEFIT-TRANSFER METHODS IN ENVIRONMENTAL ECONOMICS.

2

Development of a checklist to assess transferability of patient preferences within the IMI-PREFER project

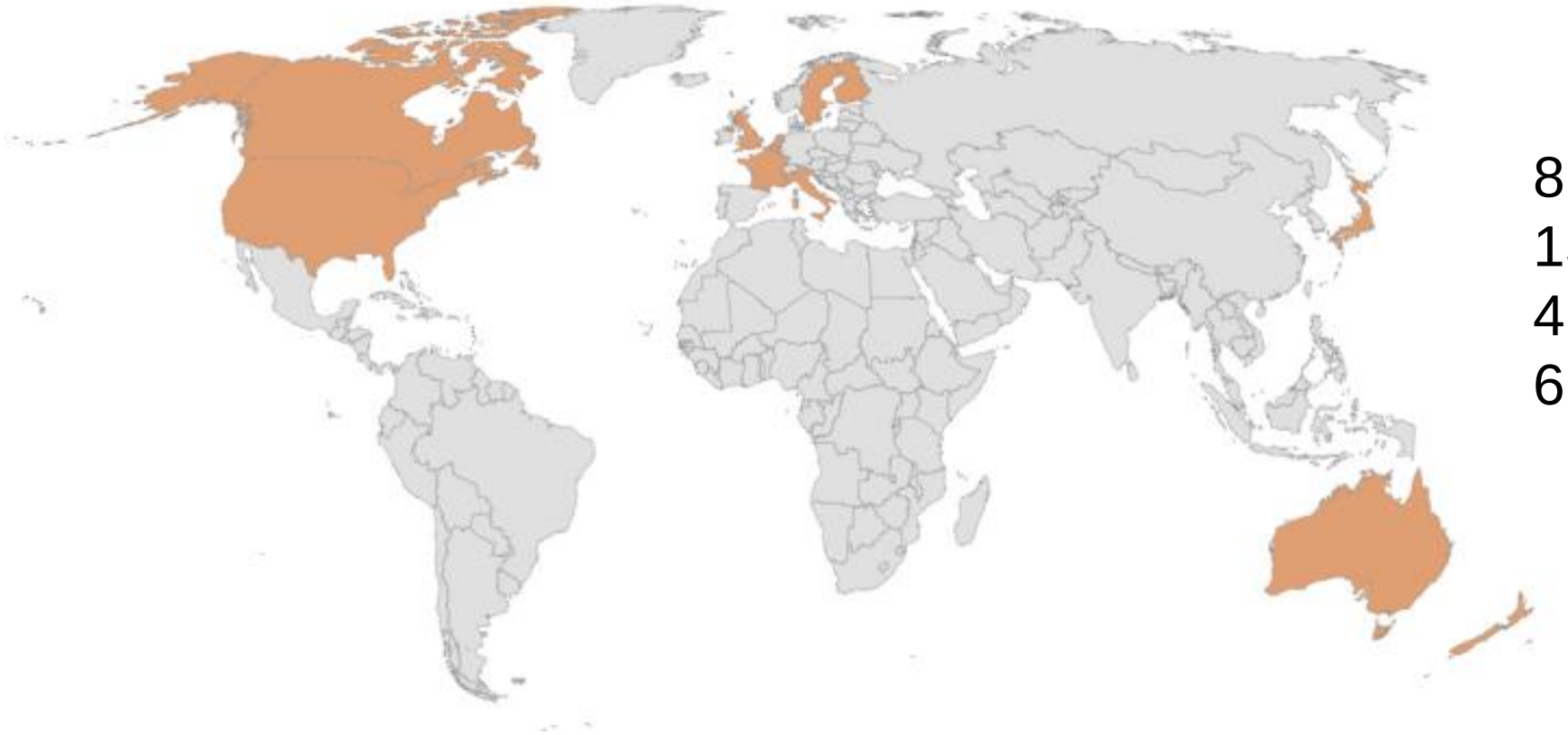
Ardine de Wit
Associate professor of HTA
University Medical Centre Utrecht
The Netherlands

Goal of the IMI PREFER Project

By developing expert and evidence-based **recommendations**, PREFER aims to guide **industry, regulatory authorities and HTA bodies and reimbursement agencies** on how **patient preferences** can be assessed and used to inform medical product **decision making**.

October 2016 – May 2022

11 prospective case studies were performed in a wide range of medical fields and topics



8,589 respondents
15 countries
4 continents
6 preference methods

Transferability, current state of research

- Transferability is not yet widely studied in the field of PPS
- Checklists / frameworks exist in other fields, e.g. economic evaluations / HTA, clinical effectiveness trials (reviews) and health promotion interventions

- One review (*Munthe-Kaas, 2019)* identified 25 checklists related to transferability issues with different intended user groups, such as decision-makers, researchers, authors of systematic reviews, healthcare practitioners
  - Analysis of content of checklists

Munthe-Kaas H, Nøkleby H, Nguyen L. Systematic mapping of checklists for assessing transferability. Syst Rev. 2019 Jan 14;8(1):22. doi: 10.1186/s13643-018-0893-4. PMID: 30642403; PMCID: PMC6330740.

Development of a checklist to assess transferability of patient preferences

- Basis: existing checklists from other fields
- Workshop with 6 PREFER case studies: how transferable are results of this case study
- Development of draft checklist with 2 versions:
  - Transferability from one country to another country
  - Transferability across diseases / indications / sub-groups

- Used checklist for the 11 prospective case studies
- Initial conclusions on transferability of case study results in different transferability situations

Checklist for transferability across countries

- Methodological characteristics of the study
  - Attributes
  - Levels and their range
- Population characteristics
  - Sociodemographic and educational factors
  - Epidemiologic factors
  - Attitudinal issues
  - Cultural and religious issues
- Healthcare context
  - Commercial and financial (reimbursement) availability of medical products
  - Geographical accessibility of medical products
  - Level of experience with use of medical products or adverse health effects
  - Level of trust of patients in treatment with a medical product
  - The standard of care (SoC) for treatment of a certain disease
  - Healthcare and social security system

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Example: lung cancer case study (immuno-chemotherapy)

Levels and their range
Item: Please consider whether the **levels and their ranges** chosen for the country of study would also have been identified as the representative (range of) levels impacting on patient preferences in another country.
Reflections: The levels and ranges were **identified through discussions with patients, oncologists, patient organizations, and stakeholders from different areas** (e.g. oncology research, health economics, drug development, pharmaceutical sciences, etc.) and different countries, to ensure they were relevant and realistic. Since the attributes are **based on common characteristics of the treatments** which are **not country-specific**, the associated levels and ranges are also not a concern and **can be extrapolated to other countries.**

Example: COPD case study (importance of symptom relief)

Cultural and religious beliefs
Item: Please consider whether there are differences regarding **cultural issues or religious beliefs** between countries that may impact patient preferences. Examples are: preferences with regards to extremely sensitive issues such as abortion, sexuality, euthanasia; cultural differences with regard to the importance of health; differences in lifestyle that may be large enough to impact on patient preferences with regard to the subject of the PP study
Reflections: We did not specifically investigate cultural or religious beliefs. However, the five countries in our study (US, UK, Australia, France and Japan) **are quite culturally diverse and this did not lead to relevant differences in expressed preferences**, so it is unlikely that cultural (or religious beliefs) are likely to influence the results.

Transferability to other countries, initial findings from applying the checklist

- Methodological characteristics
  - If a cost attribute is included: in general not transferable
  - Only treatment characteristics or symptoms: better transferable
    - not to countries where out-of-pocket cost is important!
- Population characteristics
  - Sociodemographic and educational differences were mentioned most often as hampering transferability
- Health care context
  - If there are **attributes** on health care context then transferability could be problematic, unless similar standard healthcare system in other countries

Conclusion

- Checklist is useful when a specific transferability question is at stake **for a well designed and performed PP study**.
- The usability of the checklist should be tested in specific transferability situations
- Checklist can also be used in design phase of study to include relevant (patient) characteristics in the survey to increase future transferability
  - However, unsure if the current list covers all aspects for this purpose

About the PREFER project

The Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER) is a five year project that has received funding from the **Innovative Medicines Initiative** 2 Joint Undertaking under grant agreement No 115966. This Joint Undertaking receives support from the European Union's **Horizon 2020** research and innovation programme and **EFPIA**.

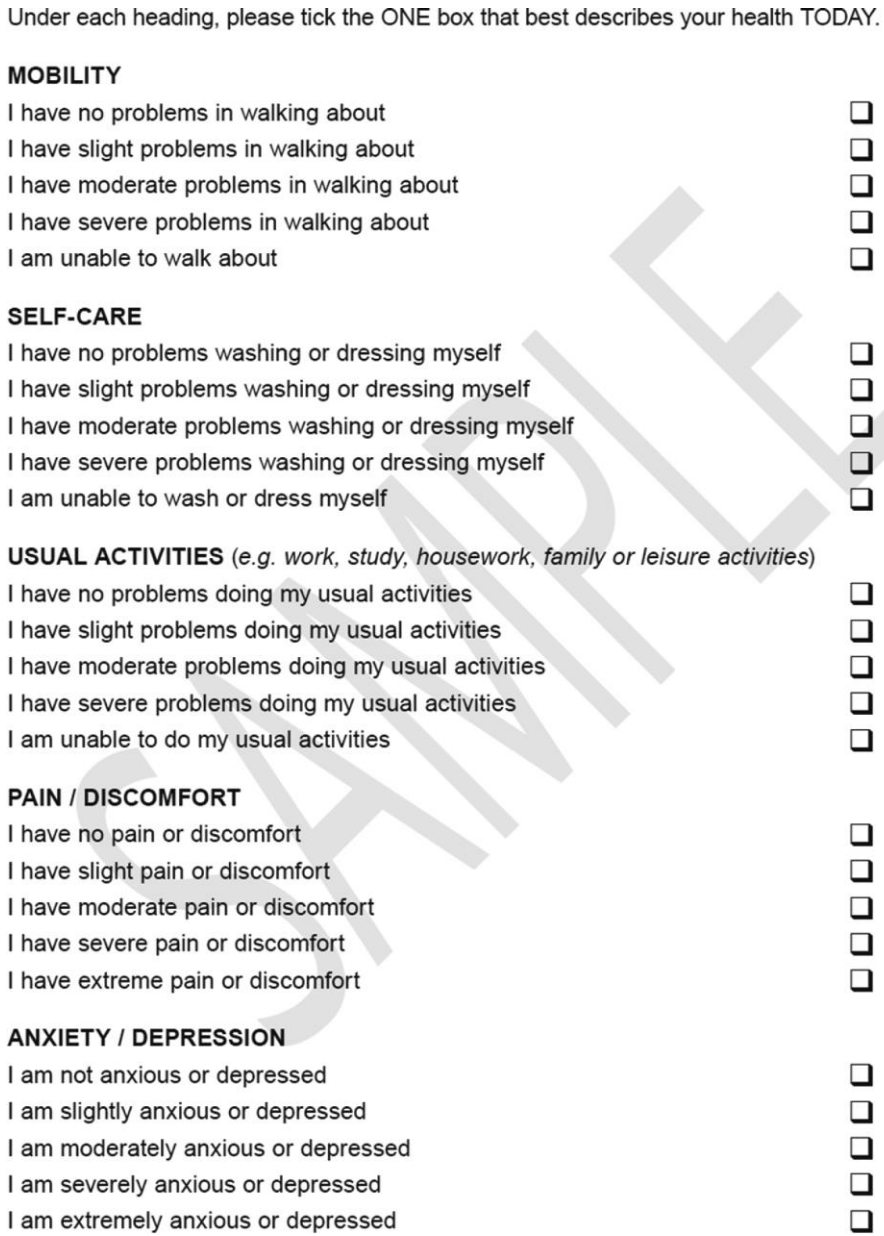
3

Differences in health state values between countries: the case of the EQ-5D

Bram Roudijk, PhD
EuroQol Research Foundation

What is EQ-5D and how is it valued?

- EQ-5D: family of HRQoL instruments
- 5 health domains:Mobility, Self-care, Usual Activities, Pain/Discomfort and Anxiety/Depression.
- The EQ-5D-3L: 3 levels of severity
- The EQ-5D-5L: 5 levels of severity
- Valued using cTTO and DCE



Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES (*e.g. work, study, housework, family or leisure activities*)

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

EQ-5D value sets

- For EQ-5D-3L: value sets available for 35 countries.
- For EQ-5D-5L: value sets available for 28 countries.

- EQ-5D-3L value sets: no standardized valuation protocol

- For EQ-5D-5L: standardized valuation study protocol; methodological differences between studies are minimized.

Why may utilities then still differ between countries?

Quick recap from PREFER checklist:

- Methodological differences
- Population characteristics
- Healthcare context

How may utilities differ between countries?

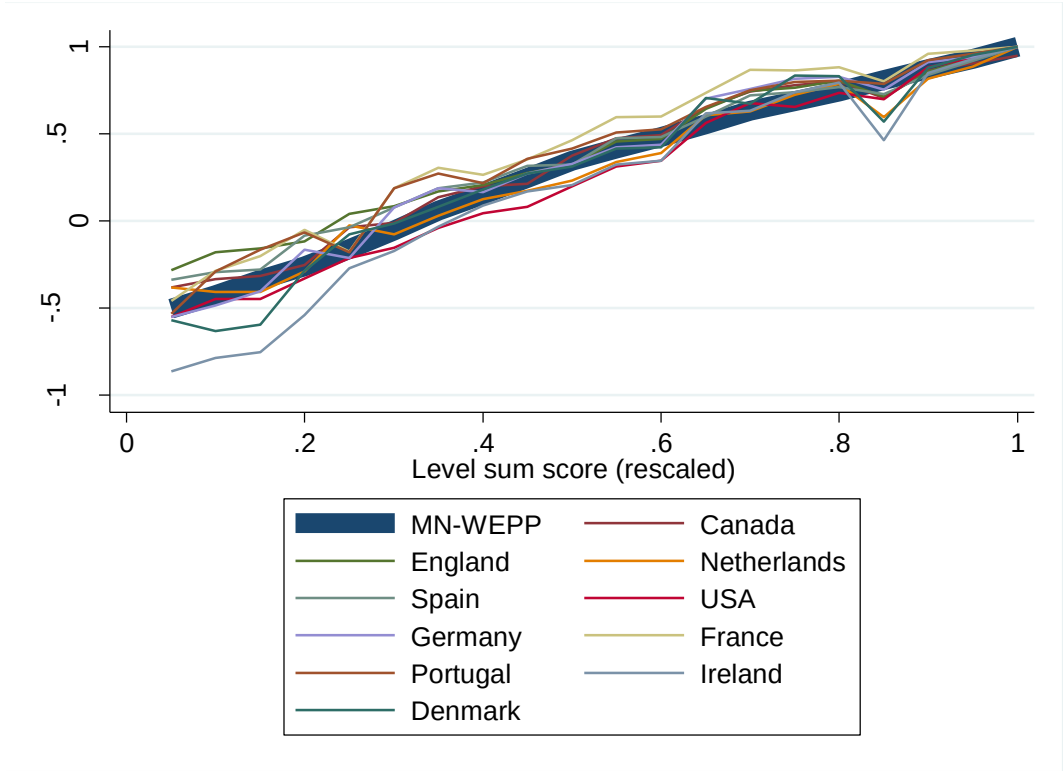
- Relative importance of different health domains may differ between countries.
- Willingness to trade life years for quality of life. This affects the scale length of a value set.
- Marginal difference of moving from one level of severity to another.

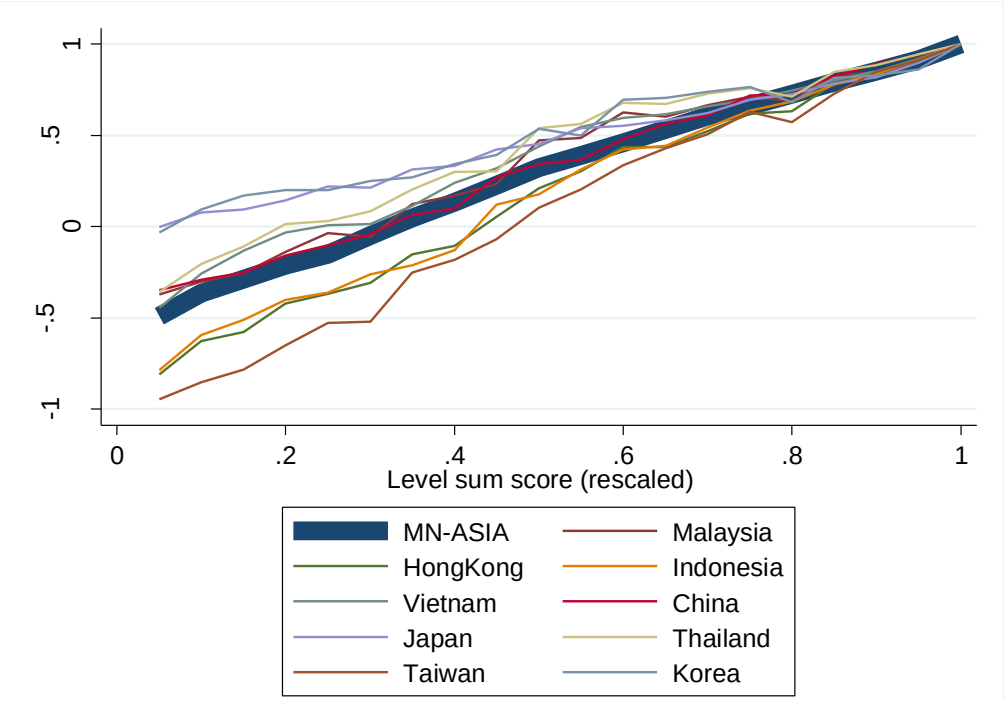
Evidence from multi-country study (EQ-5D-5L only, Roudijk et al, 2022)

- Utilities from countries that are geographically more typically are more similar to each other as compared to utilities that are more geographically distant. (e.g. Europe versus Asia)
- However, differences between countries within a certain region can still be substantial.
- For example, being in extreme pain for a year in France would yield 0.558 QALY's, while this would be 0.388 in Germany.

Roudijk, B., Janssen, M.F. & Olsen, J.A.(2022) How do EQ-5D-5L value sets differ? Book chapter from Devlin, N., Roudijk, B., Ludwig, K. (2022) EQ-5D-5L value sets: compendium, comparative review and user guide (forthcoming)

EQ-5D-5L values applied to patient data





Role of cultural values

- Relative importance of domains correlates to cultural variables (Bailey & Kind, 2010)
- Propensity to trade life years for quality of life is not related to cultural variables (Roudijk et al, 2019)
- Substantial variation remains after correcting health state valuations for cultural variables.

Bailey, H., & Kind, P. (2010). Preliminary findings of an investigation into the relationship between national culture and EQ-5D value sets. Quality of Life Research, 19(8), 1145-1154.
Roudijk, B., Donders, A. R. T., & Stalmeier, P. F. (2019). Cultural values: can they explain differences in health utilities between countries?. *Medical Decision Making*, *39*(5), 605-616.

Summary

- EQ-5D utilities differ between countries.
- For the EQ-5D-5L, which uses a standardized protocol to collect valuation data, differences between countries persist.
- Difference between countries are smaller between countries that share geographical and cultural similarities, but persist.
- The role of cultural values on utilities is ambiguous. Importance of health domains related to culture, but not scale length.

4

Consistency of Benefit-Risk Trade-Off Across Studies

Nicolas Krucien, PhD
Lead data analyst in stated preferences
Evidera by PPD

Transferability across diseases

- X: Benefit measure
- Xi: Benefit characteristics
- Xj: Patient characteristics
- Z: Study characteristics

$$v(X_{ij}, Z)$$

- Two main cases:
  - To assess the relative value of treatments for different diseases
  - To compensate for insufficient evidence in some contexts (limited evidence, difficulty to run PP studies)

Objective

- Practically difficult due to important variability in study design
  - Only 1 meta-analysis of risk tolerance in patients with psoriasis (Gonzalez, 2018)

- Different approach: Consistency of preferences across indications (Xi) while controlling for several study features (Z)
  - Meta-analysis of studies that assessed the same benefit-risk trade-off regardless of the patient group (Ignore Xj)
  - Marginal rate of substitution (MRS) between improvements in survival ("benefits") and risk of moderate-severe adverse events ("risks")

Heterogeneity in study design

- Studies identified from 3 reviews (General DCE review; review of PP studies in CVD; review of PP studies in Cancer)
  - 23 studies included both survival and adverse event attributes
- Due to lack of details in reported results or issues with preference estimates (eg unsignificant risk estimate), 11 studies were excluded

Participants	Studies
Disease group	
Cancer	9 (75)
Cardiovascular	3 (25)
Participants	
Average age, years	
< 18	1 (8)
18–50	1 (8)
50–60	3 (25)
60–70	3 (25)
≥ 70	2 (17
Not reported	2 (17)
Methods	
Definition of survival attribute	
Length of time will survive	5 (42)
Probability of being alive/dead at a defined timepoint	7 (58)
Reporting of the survival partial value function	
Parameters for categorical levels	4 (33)
Linear continuous (confirmed)	4 (33)
Linear continuous (not confirmed)	4 (33)

Data are presented as *N* (%)

Model specification

- Outcome: Reduction in AE risk that gave same utility as 1-month increase in survival
  - Computed from each level of the survival attribute and for each patient subgroup
  - 42 MRS measures
- Predictors:
  - Indication (CVD vs Cancer)
  - Format of survival information (Time vs %)
  - AE severity (Moderate vs severe)
  - Life expectancy without disease (in years)
  - Expected survival with disease (in years)
  - LE shortfall
- Model: Reweighted log-linear model of ln(MRS) with random effects

Results (1)

- Average MRS = 2.3%.
- However, important variation across the studies (Min=0.002%; Max=13.5%).

- A 1-year increase in the expected survival was associated with a 9.8% decrease in MRS value.

Parameters	MLE (SE)
Model parameters	
Constant	2.136 (0.908)*
Expected survival	− 0.103 (0.014)***
Life expectancy without disease	− 0.001 (0.03)
Severe adverse events (moderate)	− 0.921 (0.239)***
Cardiovascular area (cancer)	− 0.85 (1.104)
Survival type in % (time)	− 0.489 (1.088)
Variance parameters	
Between-study variance	1.559
Within-study variance	93.793

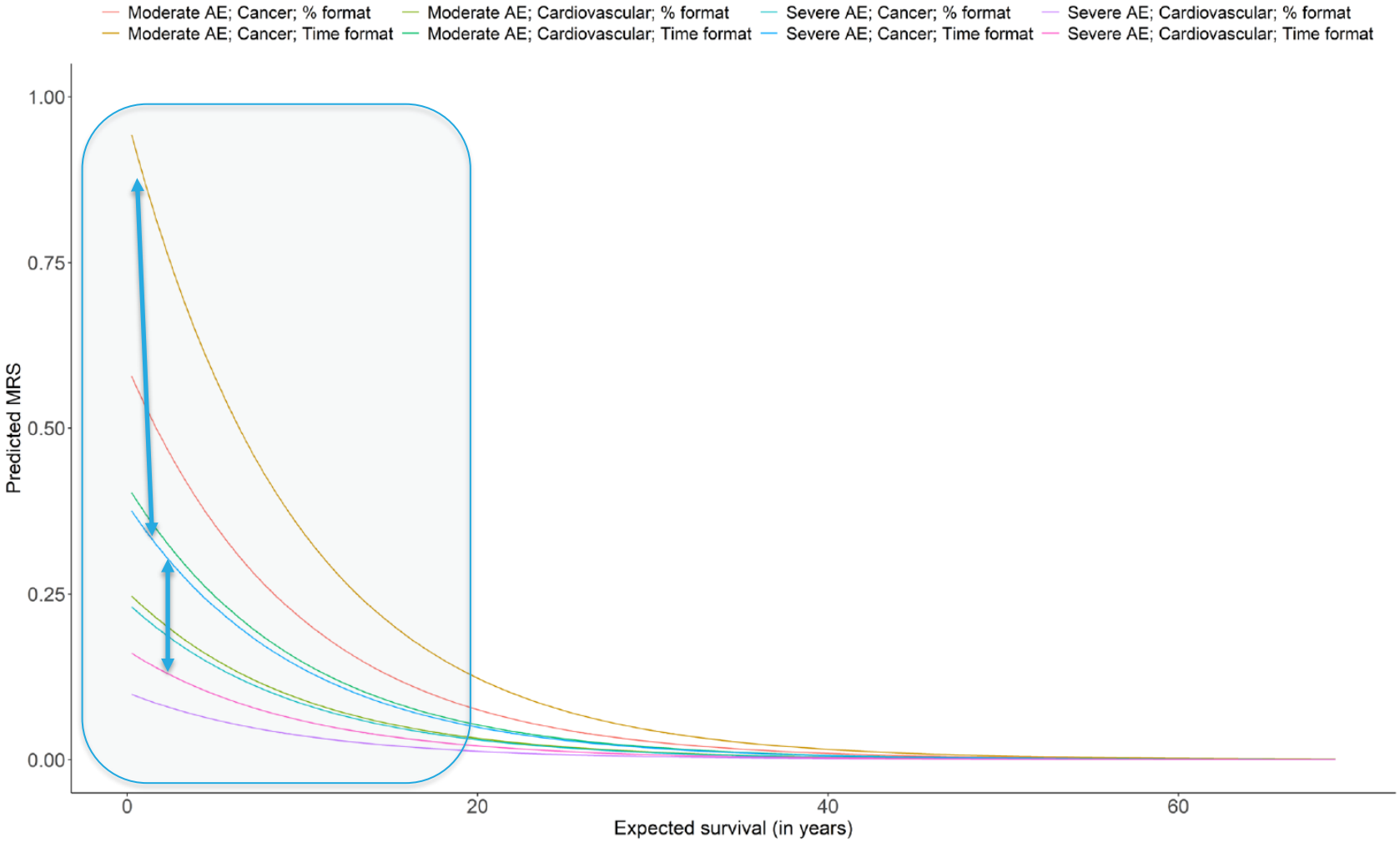
Analysis information: Observations= 42; Log-likelihood= − 61.9

MLE maximum likelihood estimate, *MRS* marginal rate of substitution, *SE* standard error

***$p < 0.1\%$; **$p < 1\%$; *$p < 5\%$

Results (2)

- MRS started to increase only when expected survival was < 20 years.
- Results differed across situations only for a low level of expected survival (i.e., < 10
- years).
- Differences largely driven by type of AE



Discussion

- Absence of effect of therapeutic area (CVD vs Cancer) is a first step in supporting values transfer.
- Heterogeneity in study design and/or results reporting remains an important issue:
  - Almost half of the studies identified were excluded from the analysis because there was insufficient detail in the publication
  - Transformations were required to ensure the comparability of the survival preferences across studies
- Limitations: Small number of observations (n=42); some potentially key variables (eg HRQoL) missing
- Need to replicate this study on other benefit measures (eg MRS for mode of administration)

5

Discussion

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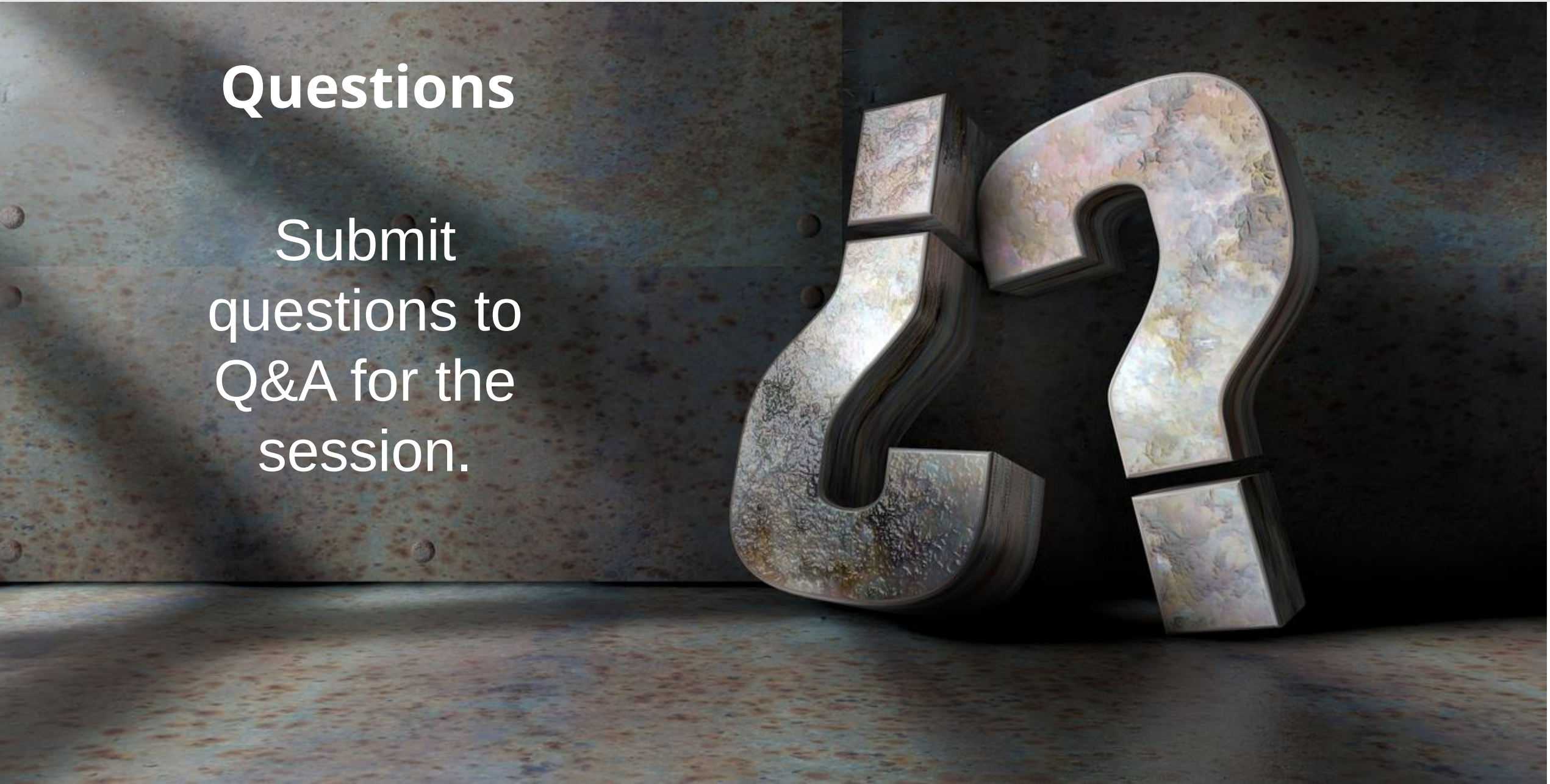
Questions

Submit questions to Q&A for the session.



Health Preference Related Sessions at ISPOR Europe 2021

Thursday, 2 December 2021 from 11:00 – 12:00 CET

- How and When Should Evidence from Patient Preference Studies Be Integrated into HTA: Aligning Methodology, Agency and Industry Perspectives *[Issue Panel]*

Thursday, 2 December 2021 from 12:30 – 13:30 CET

- Novel Approaches to Identify and Quantify Patient Input for (HTA) [*Workshop*]

Thursday, 2 December 2021 from 16:00 – 17:00

- Quantitative Benefit Risk Assessment Emerging Good Practices Task Force: A Roadmap *[Task Force Forum]*

Pre-recorded: See Program for Monday, 22 November

- Evaluating Individuals and Patients Preferences: Discrete Choice Experiments and Beyond [*4 Podium Presentations*]
- The EQ-5D-5L in Practice in Europe and Beyond: Advantages and Limitations [*4 Podium Presentations*]

ISPOR Good Practices Task Force Reports

- **Conjoint Analysis Applications in Health - A Checklist** (Bridges et al, 2011) #5 most cited article in *Value in Health*
- **Constructing Experimental Designs for Discrete-Choice Experiments** (Johnson et al, 2013) # 8 most cited article in *Value in Health*
- **Statistical Methods for the Analysis of Discrete-Choice Experiments** (Hauber et al, 2016 # 37 most cited article in *Value in Health*

In development:

- **Using Patient Preferences in Decision Making**
- **Quantitative Benefit Risk Assessment**

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Current Health Preference Research SIG Key Project

Accounting for preference heterogeneity in discrete-choice experiments - A review of the state of practice: Report of the ISPOR Health Preference Research Special Interest Group

Submitted to *Value in Health* September 2021

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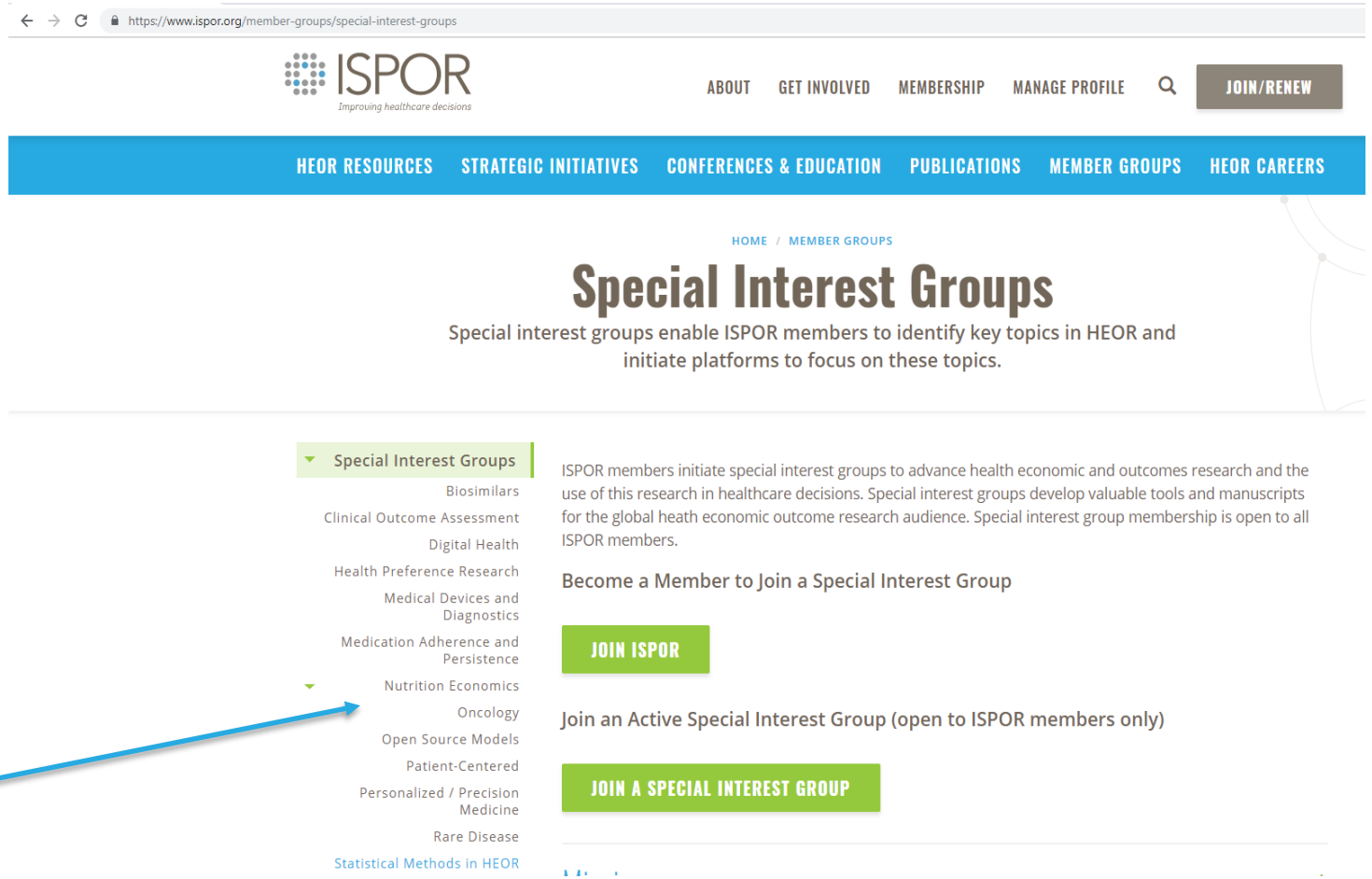

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Thank you!

For questions:

healthpreference@ispor.org