BBS Workshop on

Patient-Focused Drug Development: The Role of Patient Preference Studies

October 22nd, 2024

Organizers:
Conny Berlin & Byron Jones, Novartis
Lilla Di Scala, BBS President; J&J
Marisa Bacchi, BBS
Bibiana Blatna, Novartis

Agenda

Moderator: Conny Berlin (Novartis)

Welcome	Lilla Di Scala (President of BBS; J&J)	2:00 – 2:05
Introduction to patient preference studies, IMI PREFER and ICH E22 guidance	Sheila Dickinson (Novartis, ICH E22 member)	2:05 – 2:30
Do we always need a new Patient Preference Study? Transferability of Patient Preference Information. Results of a systematic literature review on patient preference studies.	Michael Bui (University of Twente)	2:30 – 2:55
Regulatory and HTA perspectives on Patient Preference Studies	Tommi Tervonen (KIELO Research)	2:55 – 3:20
Break		3:20 – 3:30
Case study 1: Patient Benefit-Risk Trade-off Preferences for NDMM Treatment Options	Ellen Janssen (J&J)	3:30 – 3:55
Case study 2: PAUSe - PAtient preference stUdy in inSomnia: implementing a preference study in a pivotal trial	Andrea Phillips-Beyer (Innovus Consulting Ltd)	3:55 – 4:20
How to make patient-centred approaches a reality?	Conny Berlin (Novartis, moderator), Laura Lee Johnson (FDA, ICH E22 member), Brett Hauber (Pfizer, ICH E22 member), Ellen Janssen (J&J, BIO PFDD Task Force Lead on Preference Studies)	4:20 – 5:00

Welcome

Lilla Di Scala, BBS President

BBS Workshop on

Patient-Focused Drug Development:
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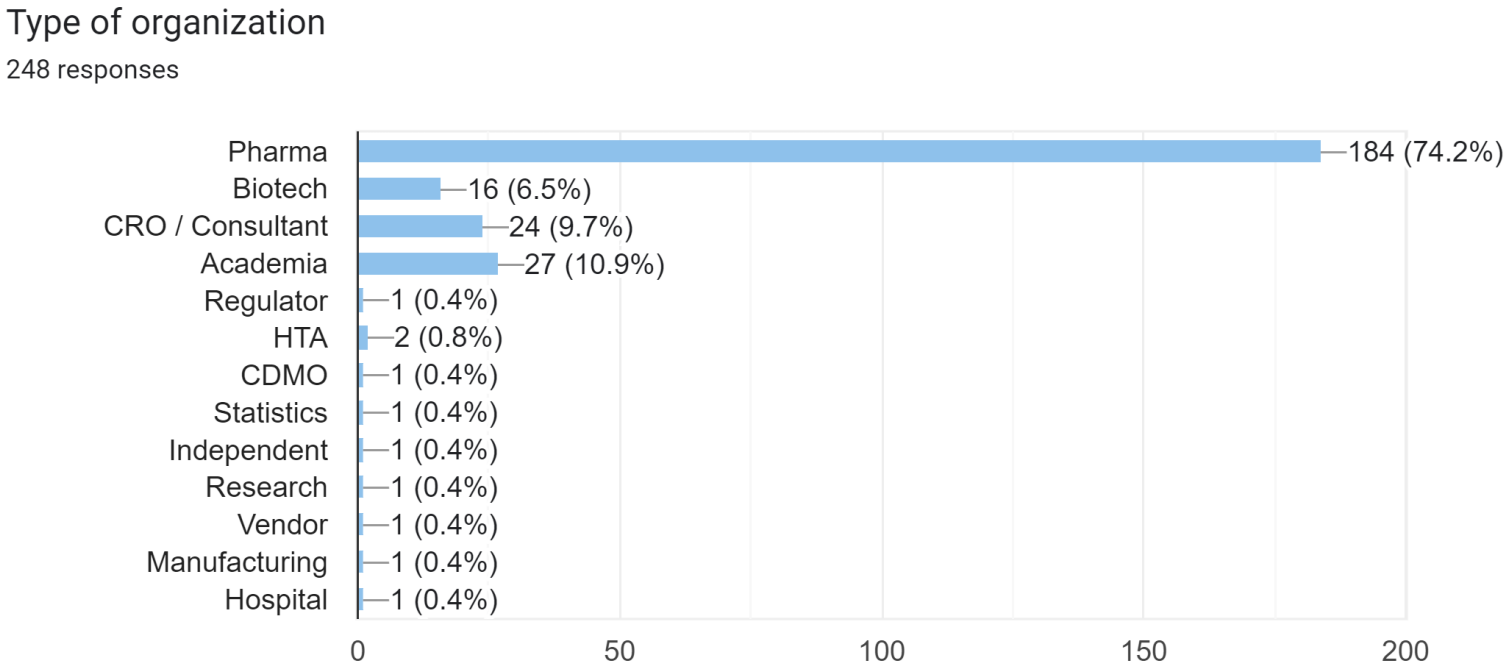

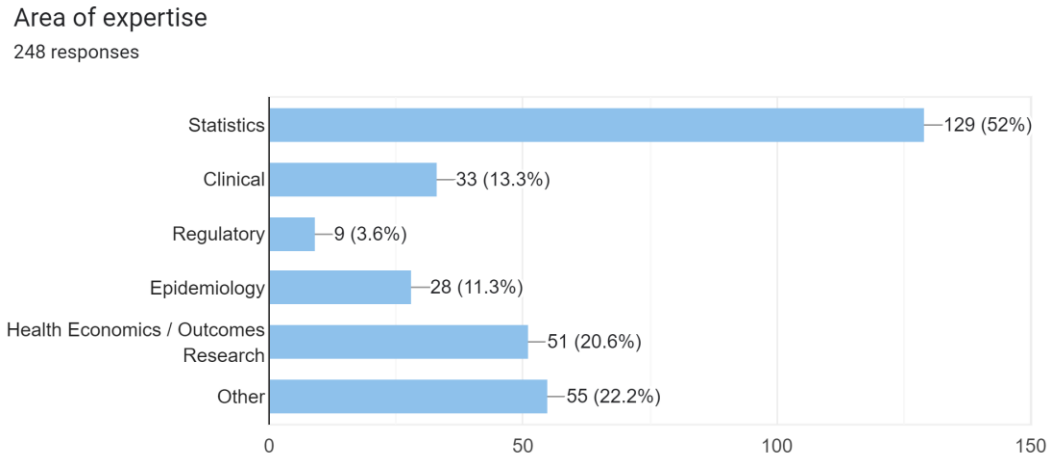

Looking back at January-September 2024

7 events and counting!

- February 12th **Causal thinking in clinical trials**
  Novartis; organizers: Giusi Moffa, Achim Güttner, Fred Sorenson, Bibiana Blatna and Frank Bretz
- April 12th: **Reproducibility in biomedical research**
  University of Basel; organizers Valentin Amrhein, Daniel Sabanés Bové and Andreas Ziegler
- April 17th: **Next Generation event on visualization**
  Swiss TPH; organizers: Joana Marques Barros, Muriel Buri, Kristina Weber and Ottavia Prunas
- May 16th: **Essentials of Medical Data Sharing and Privacy – Maximize the use of data**
  University of Basel; organizers: Dominik Heinzmann, Peter Krusche and Giusi Moffa
- August 29th: **Controlling the chances of false discoveries in exploratory analysis of clinical trials**
  Virtual; organizers: Kostas Sechidis and Frank Bretz
- September 20th: **Next Generation event on Thriving Careers**
  Roche; organizers: Antonella Mazzei, Lukas Widmer, Muriel Buri, Olympia Papachristofi and Youyo Hu
- September 25th: **AI in Clinical Research and Drug Development and BBS General Assembly**
  D-BSSE (ETH); organizers: Marcel Wolbers, Jenny Devenport, Dominik Heinzmann, Kristina Weber, Lilla Di Scala, Marco Cattaneo, Andreas Ziegler, Jack Kuipers and Giusi Moffa

Upcoming events in 24-25

Already 7 events in 2024, last of which the Annual meeting on AI in Clinical Development (September 25th)

- October 22nd: **Patient-Focused Drug Development**: The Role of Patient Preference Studies
- November/December: **Do you speak statistics?**

  TBD; Organizers: Julie Jones, Achim Güttner
- **Essentials of IDMC**
- **Innovative statistics for HTA**
- **NextGen Mentoring Program**

ISCB25 Basel

- Coming to Basel
  24th to 28th August 2025!
- BBS will **be jointly organizing the ISCB25** conference and is greatly supporting the Local Organizing Committee to gear up for the event
- BBS will also host one of the ISCB25 invited sessions on the topic of “AI in drug development”
- More to come in the next months….
- In the meantime, see https://iscb2025.info/ as well as the dedicated video.

Introduction to patient preference studies, IMI PREFER and ICH E22 guidance

Sheila Dickinson
BBS Seminar
Oct 2024

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Overview

- **Patient preference studies:** a brief introduction
- **IMI PREFER recommendations:** a resource about how and when to do a preference study
- **ICH E22 “General Considerations for patient preference studies”:** what’s coming soon(ish) from ICH about how & when to do a preference study

Patient-focused drug development – what does this mean?

FDA glossary:

“A systematic approach to help ensure that patients’ experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into the development and evaluation of medical products throughout the medical product life cycle.”

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“A systematic approach to help ensure that patients’ experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into the development and evaluation of medical products throughout the medical product life cycle.”

Patient preference studies are a tool to help us learn about patients’ perspectives, needs and priorities

A very brief introduction to patient preference studies

What is meant by patient preference information:

- Assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions. (FDA glossary)

What is a patient preference study:

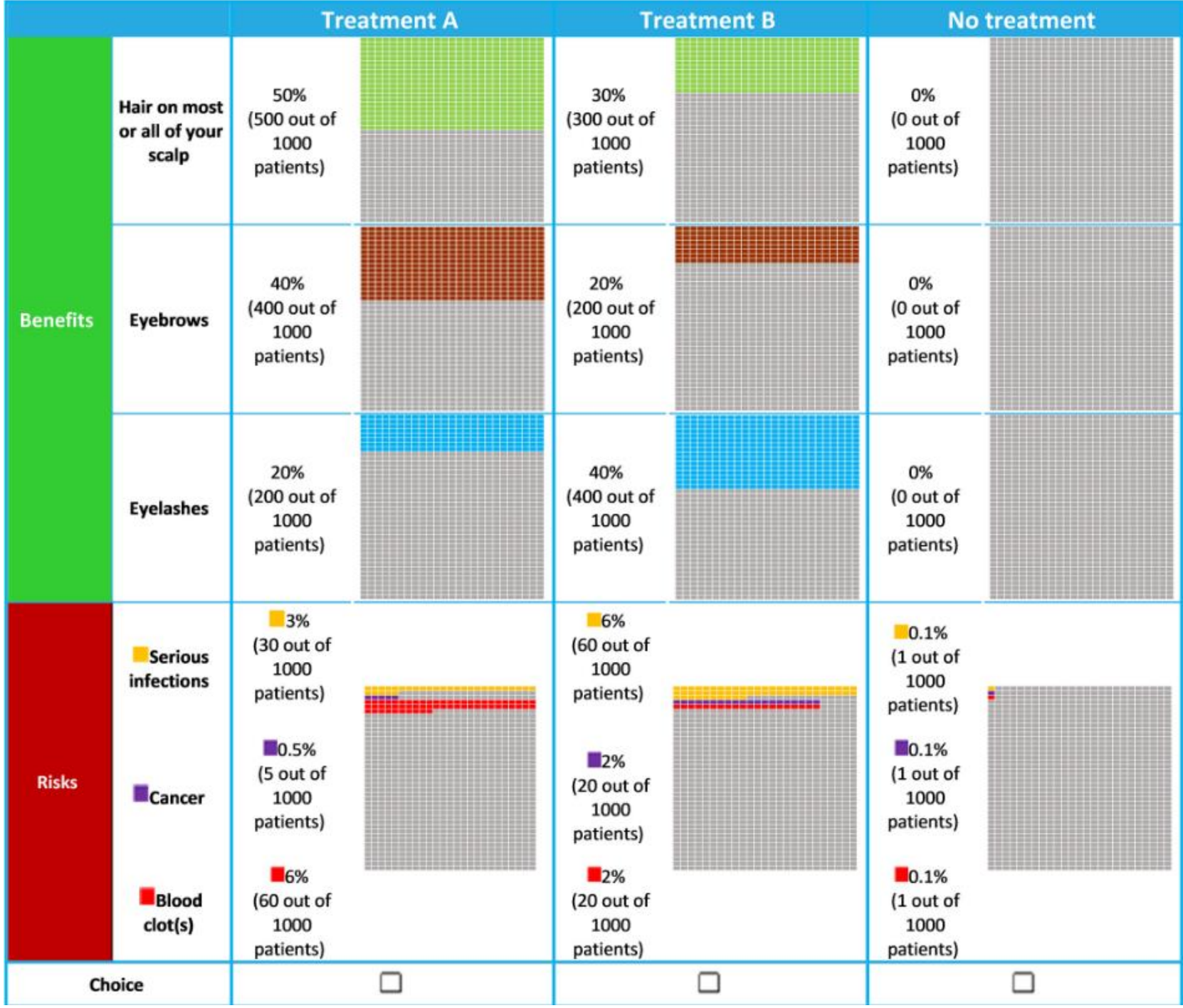
- Typically, a non-interventional study in which patients complete an online survey

Preference methodologies:

- Many preference methodologies are available!
- One frequently-used methodology is Discrete Choice Experiment

Example DCE question – alopecia study

Tervonen et al, 2023, Treatment preferences of adults and adolescents with alopecia areata: A discrete choice experiment, The Journal of Dermatology



DCE Discrete Choice Experiment

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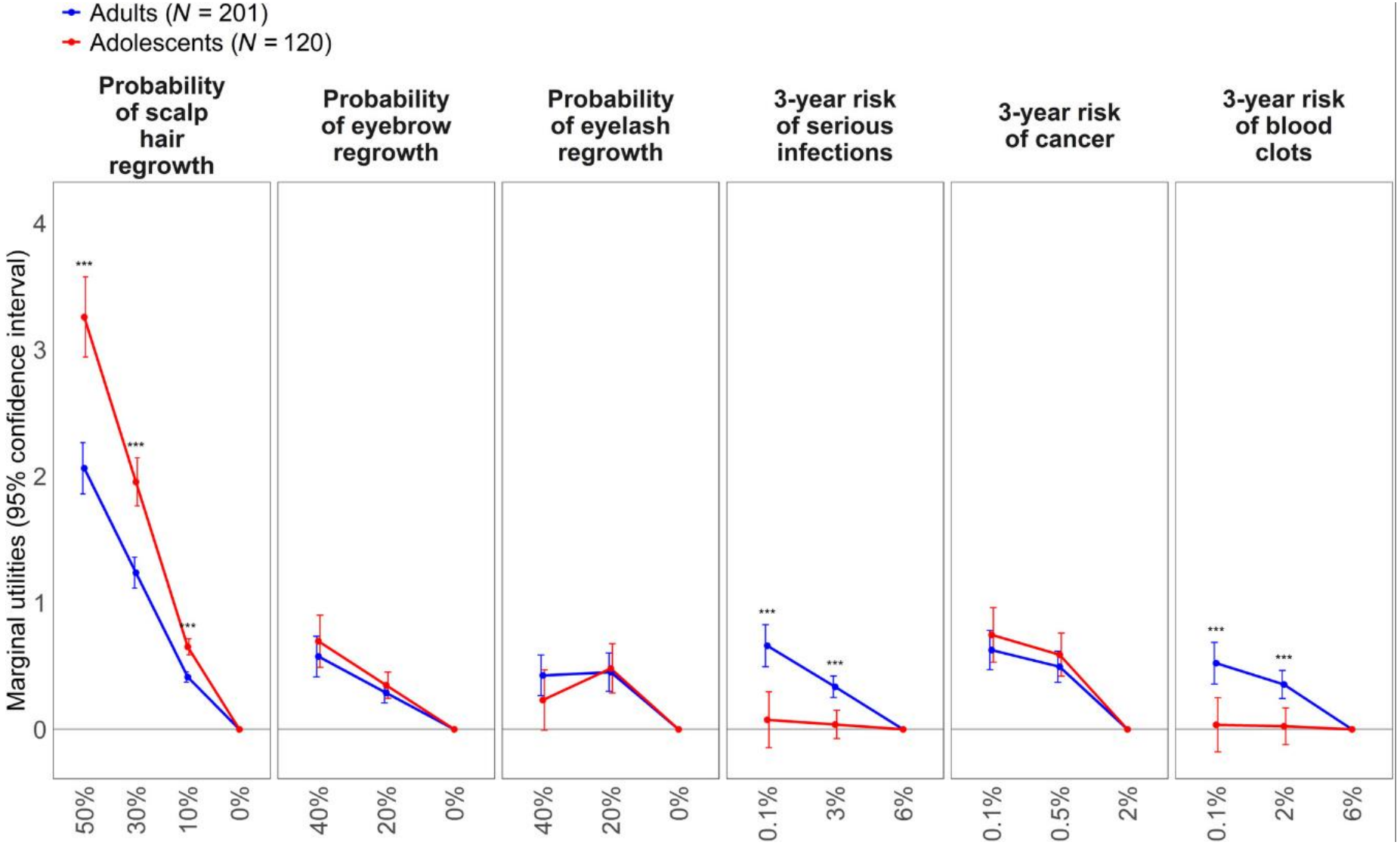
Alopecia preference study results



Tervonen et al, 2023, Treatment preferences of adults and adolescents with alopecia areata: A discrete choice experiment, The Journal of Dermatology

Quotes from EMA public assessment report about alopecia preference study

Quotes from the EMA Public Assessment Report:

“Given the high value that patients with severe AA place on scalp hair regrowth ... the net B/R for ritlecitinib 50 mg, as compared to no treatment, is positive from the patient perspective.”

“The performance of studies to acquire patient preferences for AA treatments in adults and adolescents is appreciated.”

AA: Alopecia areata
B/R: Benefit/Risk

So … if you're now thinking that you'd like more info on preference studies:

Existing resources

- Recommendations from **IMI PREFER** (*details in the next section)*
- **CDRH guidance** on patient preference information
- **MDIC patient-centered benefit-risk framework**

Upcoming resource

- New **ICH guidance**: E22 (*covered in the final section of today's presentation)*

CDRH: Center for Devices and Radiological Health (FDA division)
MDIC: Medical Device Innovation Consortium

IMI PREFER

Why, when and how to assess and use patient preferences in medical product decision-making

Introduction to IMI PREFER

Who was involved in IMI PREFER:	• Public-private partnership, involving **8 academic institutions**, **4 patient organisations**, **1 HTA body**, **16 pharmaceutical companies** • **Industry lead:** Conny Berlin (Novartis); **Academic lead**: Mats Hanson (Uppsala university)
IMI PREFER objective:	• <<PREFER aims to guide industry, regulatory authorities and HTA bodies and reimbursement agencies on **how and when patient preferences can be assessed and used to inform medical product decision-making**.>>
PREFER deliverables:	• PREFER recommendations • CHMP qualification • And more! E.g. case studies, templates, publications....

CHMP: Committee for Medicinal Products for Human Use
HTA: Health Technology Assessment
IMI: Innovative Medicines Initiative

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PREFER deliverables:

- PREFER recommenda
- CHMP qualification
- And more! E.g. case studies, templates, publications....

A CHMP Qualification Opinion describes the acceptability of a specific use of the proposed method (e.g. use of a novel methodology)

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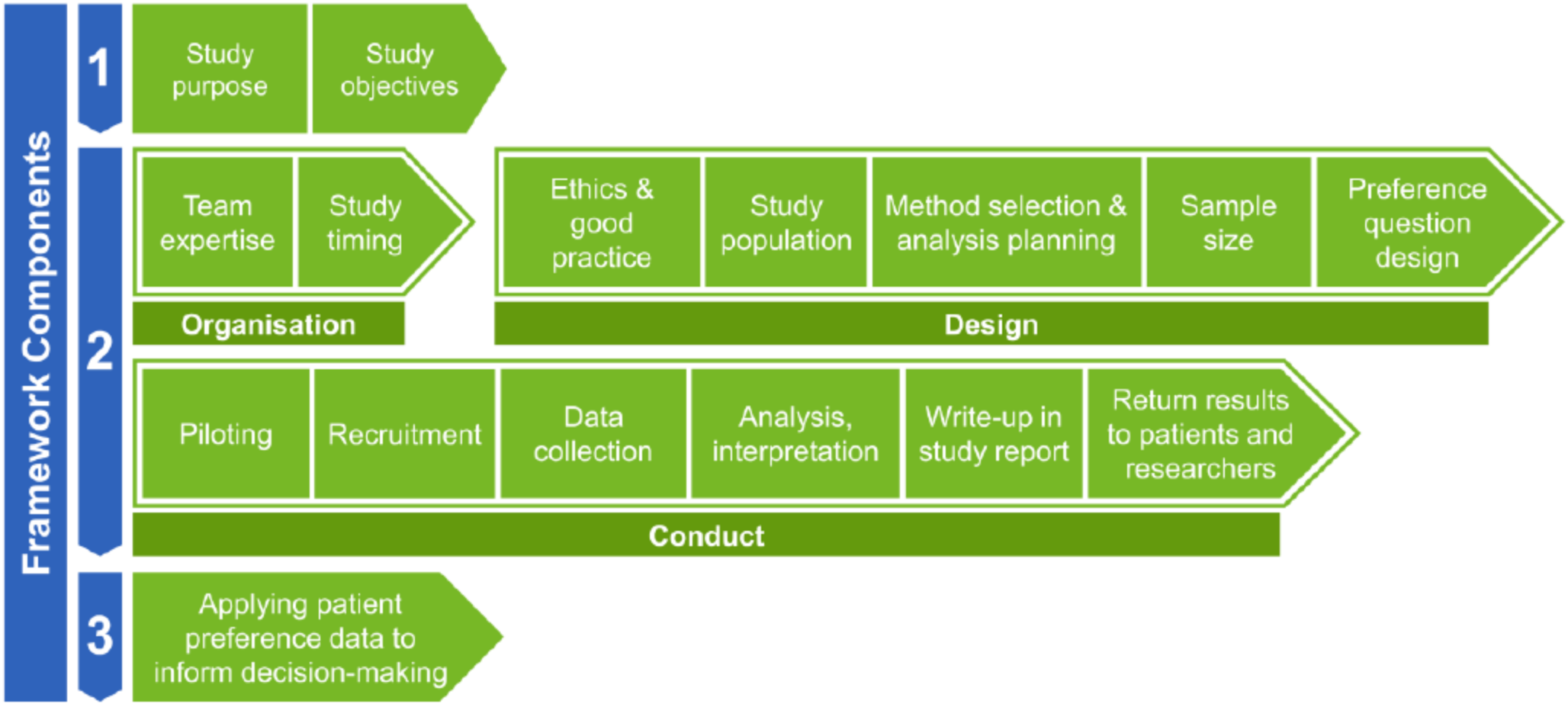
PREFER deliverables:

- PREFER recommendations
- CHMP qualification
- And more! E.g. case studies, templates, publications....

Number of downloads (as of early Oct): >5,000

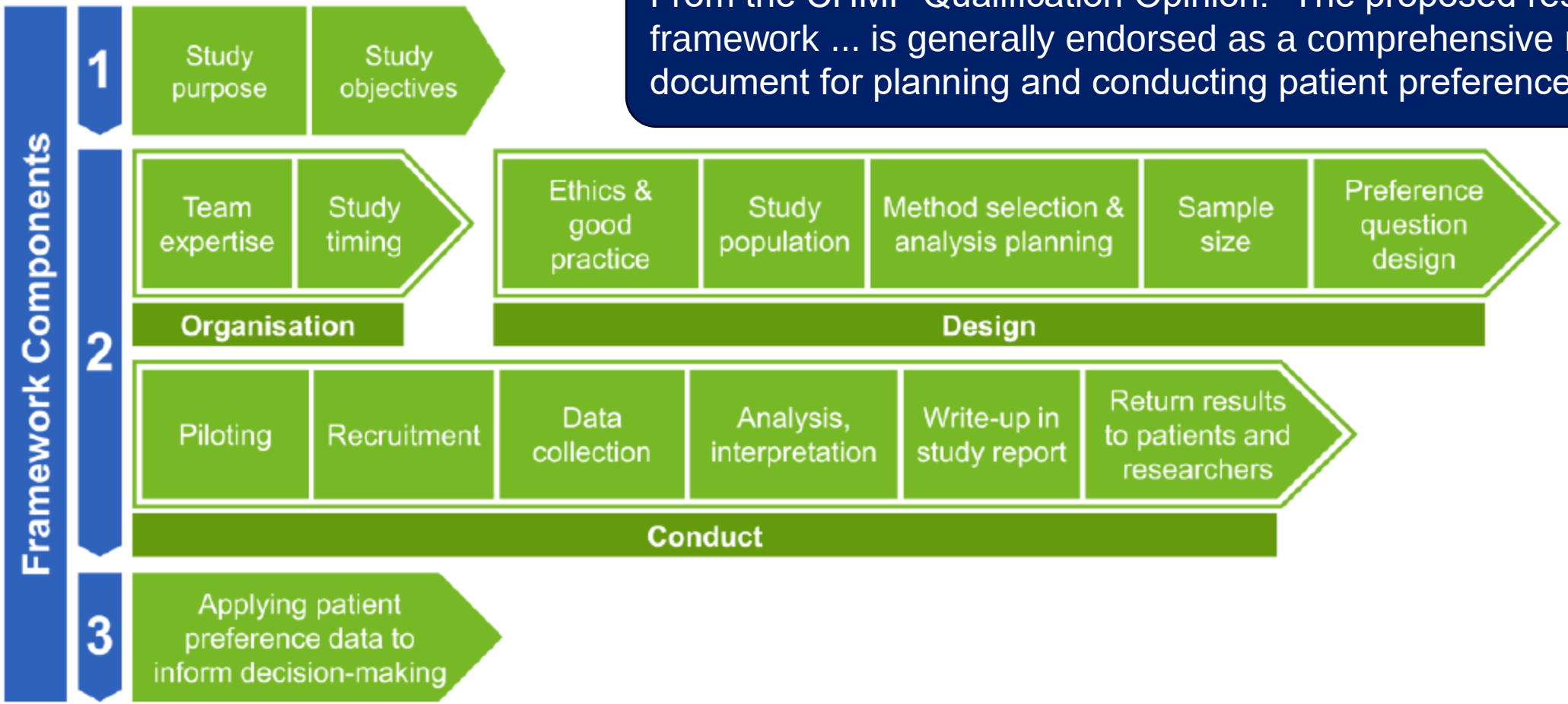
CHMP: Committee for Medicinal Products for Human Use
HTA: Health Technology Assessment
IMI: Innovative Medicines Initiative

From the PREFER recommendations: a framework for preference studies



From the PREFER recommendations: a framework for preference studies

From the CHMP Qualification Opinion: “The proposed research framework ... is generally endorsed as a comprehensive reference document for planning and conducting patient preference studies.”



PREFER framework component 1: how to consider the study purpose

What's the preference-sensitive situation?

- e.g. understanding patients' views on **acceptability of benefit-risk trade-offs**

For which population?

- e.g. adult patients with indication X

For which decision(s) by which decision-maker(s)?

- e.g. **regulatory decision** about approval of a new drug; **industry decision** about choice of endpoints

Preference-sensitive situations

Definition from PREFER (adapted from FDA):

- it is unclear what are the most important disease or medical product characteristics to patients; these can include existing or potential future characteristics (e.g. actual/hypothetical outcomes, and mode of treatment administration)
- there are multiple treatment options and no option is clearly superior or has a clear added value for all patients
- the evidence supporting one option over another is very uncertain or variable, and patients' tolerance for this uncertainty might impact their decisions
- there is potential for considerable heterogeneity in views between patients or between patients and other stakeholders.

Overview of content in the PREFER recommendations

- Section 1 outlines the objective of the recommendations and introduces the different aspects and considerations for designing and conducting patient preference studies.
- Section 2 explains what information can be obtained from patient preference studies, and why and when these studies can be conducted and applied to medical product decision-making by industry, regulators, and HTA bodies and payers.
- Section 3 describes the PREFER framework for patient preference studies. The PREFER framework aims to inform study research teams on key considerations when designing, conducting, and applying the results of a fit-for-purpose preference study, and guide decision-makers when assessing and using preference study results to inform medical product decision-making.
- Section 4 focuses on the involvement of patients and other stakeholders, such as regulators and HTA bodies, in the design, conduct, and analysis of these studies so that the information they generate is meaningful for the patient population and useful for decision-makers.
- Section 5 focuses on different qualitative and quantitative preference methods and describes how stakeholders can select an appropriate method for a given context.
- Section 6 offers insights into when and how the psychological characteristics of participants, in addition to demographic and clinical variables, should be investigated so that preference heterogeneity among patients can be explored and understood.
- Section 7 provides information on how to develop supporting materials so that patients can be educated about the questions and elements they are asked to evaluate and can make informed choices that will ensure validity and meaningfulness of the results.
- Section 8 provides insights into important avenues for further research, including recommendations for which topics and research questions should be explored and incentivised to further increase the quality of patient preference studies and gain wider consensus by all stakeholders involved.

ICH E22

What is ICH (International Conference for Harmonisation)?

ICH mission: “ ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner.”

ICH members:

- **Regulators**: EMA, FDA, PMDA (Japan), NMPA (China) and others
- **Pharmaceutical associations**: PhRMA, EFPIA, BIO and others

Examples of ICH guidelines:

- **ICH M4E(R2)** describes the expected content of all the regulatory submission documents, including the expected content of the Clinical Overview benefit-risk section.
- ICH also has guidances about **clinical study reports** (ICH E3), **statistical principles for clinical trials** (ICH E9) and much more....

What is ICH E22?

What E22 will cover:

- "General considerations for patient preference studies"
- *More info in coming slide*

Who's working on it:

- **Rapporteur**: Francesco Pignatti (EMA)
- **Regulatory lead**: Robyn Bent (FDA)
- **Other working group members**: see next slide

When will it be available:

- **Target for adoption of the guideline:** Dec 2026

ICH E22 expert working group members

Rapporteur

Dr. Francesco Pignatti (EC, Europe)

Regulatory Chair

Ms. Robyn Bent (FDA, United States)

Experts

ANVISA, Brazil
Ms. Kalinka de Melo Carrijo

BIO
Ms. Allison Martin

EC, Europe
Dr. Douwe Postmus

EDA, Egypt
Dr. Dalia Kamal

EFPIA
Ms. Sheila Dickinson

FDA, United States
Dr. Laura Lee Johnson
Dr. Xinyi Ng

IFPMA
Ms. Lizis Kimura Lopes

IGBA
Dr. Ravi Shankar

JPMA
Ms. Inaha Okuda
Dr. Yasuo Sugitani

MHLW/PMDA, Japan
Dr. Madoka Inoue
Dr. Shun Tezuka

NMPA, China
Ms. Cong Zhao

National Center, Kazakhstan
Dr. Elmira Tulentayeva

PhRMA
Dr. Brett Hauber
Dr. Bennett Levitan

SFDA, Saudi Arabia
Dr. Shatha Almuhaidib

Swissmedic, Switzerland
Dr. Justyna Kozik-Jaromin

TFDA, Chinese Taipei
Dr. Kuan Ting Chen

ICH E22: expected content (per the concept paper)

Link to E22 concept paper

3. Issues to be resolved and expected deliverable(s)

The proposed guideline intends to provide high level principles and practical guidance for regulatory implementation, in the following areas:

- Describe situations where PPS could be informative to pharmaceutical product development;
- Study design and methodological considerations, including:
  - Objectives, preference-elicitation method(s), and application of preference data;
  - Population(s) to be studied;
  - Attributes and attribute levels;
  - Plans for instrument development, pretesting, internal validity checks, and testing;
  - Statistical analyses;
  - Consideration of preference heterogeneity;
- Study documentation;
- Operational aspects and additional considerations, including:
  - Global applicability and cross-cultural context;
  - Good practices including quality checks;
  - Reporting and submission including impact on CTD Modules 2 and 5.

CTD: Common Technical Document PPS: Patient Preference Study

ICH E22: expected content (per the concept paper)

Link to E22 concept paper

However, note that preference data in the label is out-of-scope!

> The placement of PPS data in labelling is considered a regional matter outside the scope of this guideline.

ICH E22: expected content

Link to Francesco Pignatti's EFSPI presentation

Harmonisation of Regulatory "Requirements" for Patient Preference Studies (E22)

Key regulatory guidance:

- PREFER recommendations / EMA Qualification
- MDIC Benefit-Risk Framework and Compendium of Methods
- FDA CDRH Guidance on Patient Preference Information; CDRH/CBER Draft Guidance on Patient Incorporating Voluntary Patient Preference Information over the Total Product Life Cycle (NEW)
- FDA CDER Guidance on Collecting Patient Input
- Other: E.g., ISPOR Good Research Practices

4

Note the mention of PREFER!

FDA CDRH guideline on patient preference information was updated in Sept 2024

In conclusion

Preference studies are one tool to implement patient-focused drug development

Many resources are available to support doing patient preference studies, including IMI PREFER recommendations

Plus – in future – an ICH guideline (E22)

Contact Name
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Thank you

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Transferability of Patient Preference Information in Medical Product Decision-Making

BASEL BIOMETRICS SOCIETY 2024

MICHAEL BUI[1]

[1] Department of Health Technology and Services Research, Technical Medical Centre, University of Twente (m.bui@utwente.nl)

Background

Patient preference studies

- Major growth in published studies[1]
- Inform drug development decisions[2]
- Time-consuming and expensive
- Findings not used beyond purpose of original study
- More research on transferability needed[3]
- Aim: find promising area for methodological research

1 Soekhai V, de Bekker-Grob EW, Ellis AR, Vass CM. Discrete Choice Experiments in Health Economics: Past, Present and Future. Pharmacoeconomics. 2019;37(2):201-226. doi:10.1007/s40273-018-0734-2

2 Breckenridge A. Patient opinions and preferences in drug development and regulatory decision making. Drug Discovery Today: Technologies. 2011;8(1):e11-e14. doi:10.1016/j.ddtec.2011.03.002

3 DiSantostefano RL, Smith IP, Falahee M, et al. Research Priorities to Increase Confidence in and Acceptance of Health Preference Research: What Questions Should be Prioritized Now? Patient. Published online December 16, 2023. doi:10.1007/s40271-023-00650-x

Definition of Promising Area

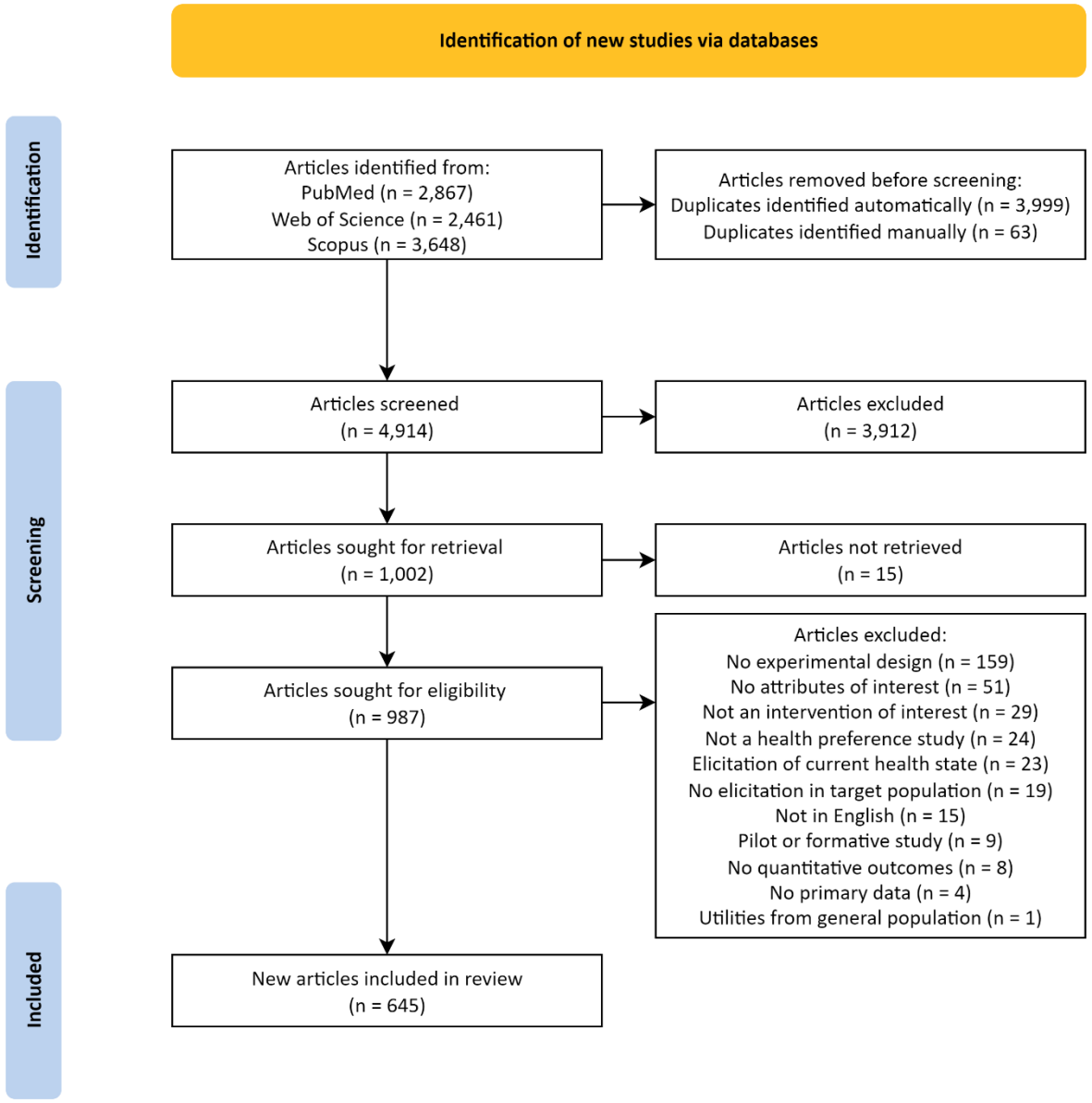
Disease areas where ample data are available for meta-regression, which are comparable in terms of:

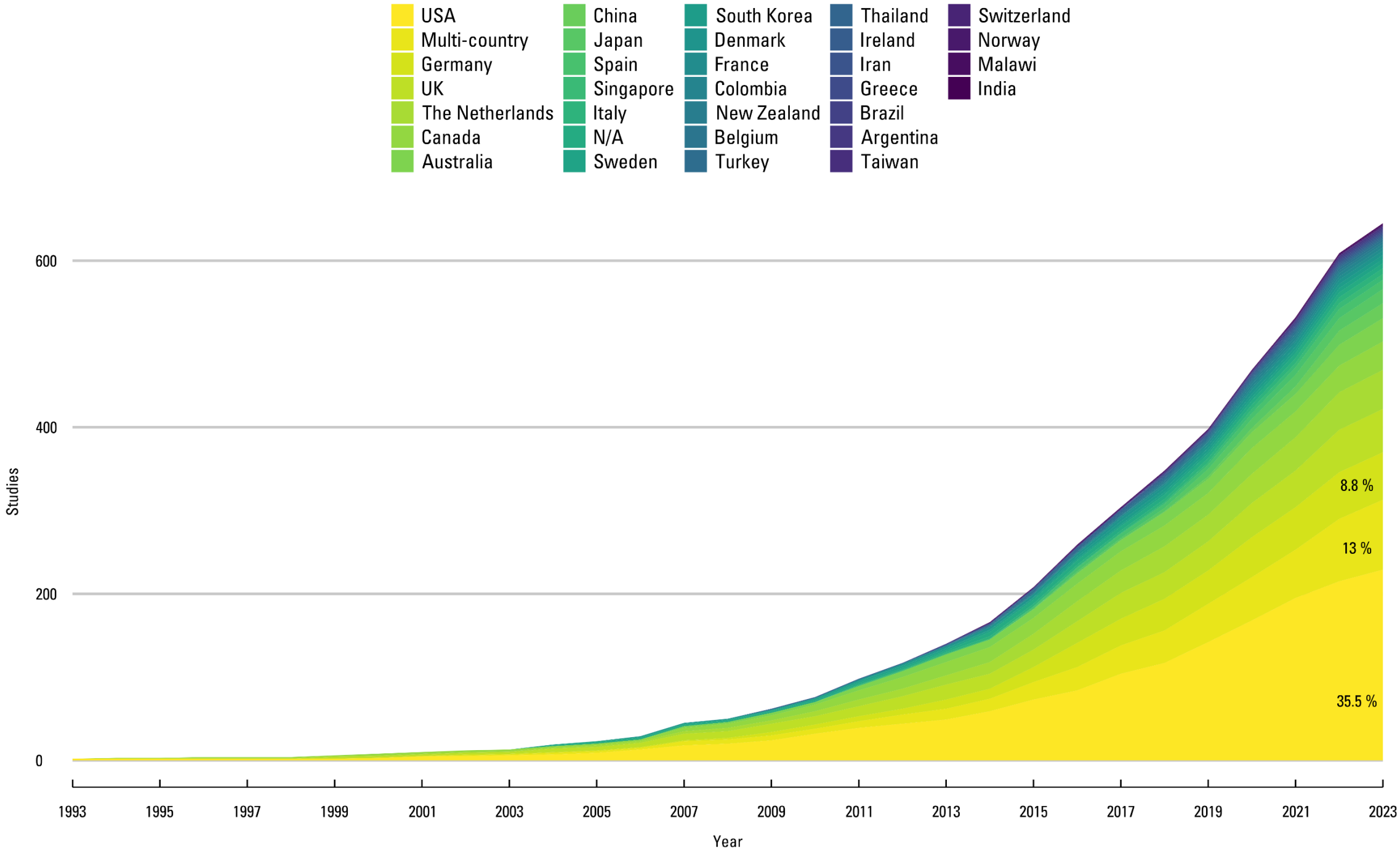
- Study design (preference elicitation methods)
- Studied attributes (characteristics of disease and/or treatments)
- Patient preference information (reported results)

Method

Systematically searched through PubMed, Web of Science and Scopus (14 April, 2023)

- Study scope:
  - Quantitative preference studies
  - Marginal attribute importance
  - Medical treatments (no screening)
  - Must include risk/benefit




USA
Multi-country
Germany
UK
The Netherlands
Canada
Australia
China
Japan
Spain
Singapore
Italy
N/A
Sweden
South Korea
Denmark
France
Colombia
New Zealand
Belgium
Turkey
Thailand
Ireland
Iran
Greece
Brazil
Argentina
Taiwan
Switzerland
Norway
Malawi
India
600
400
200
0
Studies
8.8 %
13 %
35.5 %
1993
1995
1997
1999
2001
2003
2005
2007
2009
2011
2013
2015
2017
2019
2021
2023
Year

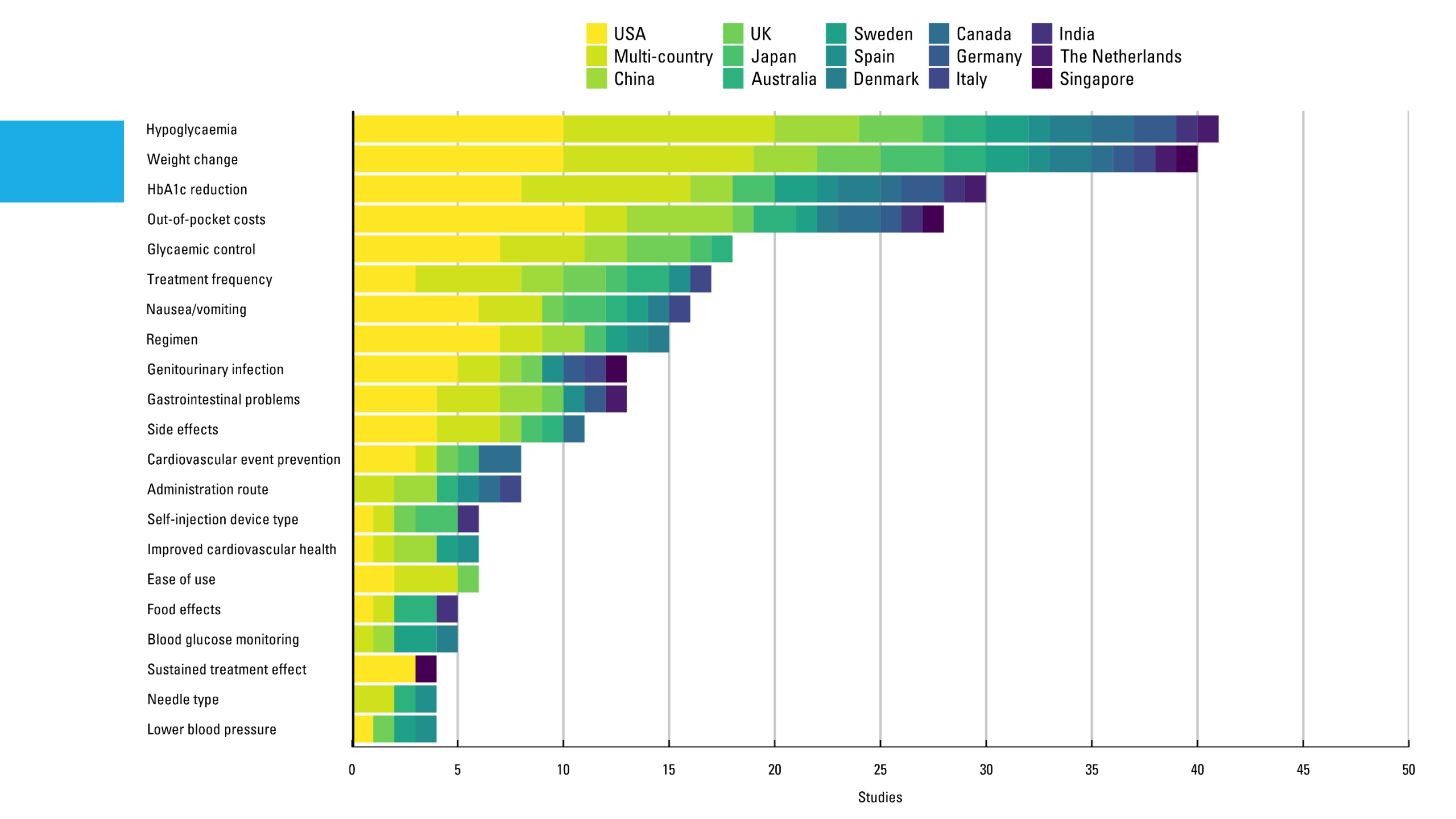
Results

TOP 5 MOST STUDIED INDICATIONS

Table 1. Overview of the number of available patient preference studies in the top five most studied indications. The study counts were stratified by whether discrete choice experiments (DCEs) or non-DCE methods were used.

Indication	DCE			Non-DCE		
	Studies	Total sample	Sample range	Studies	Total sample	Sample range
Type 2 diabetes	43	37,818	58-11,883	7	2,546	114-818
Psoriasis	22	8,897	126-1,608	8	2,522	126-600
Multiple sclerosis	20	7,873	60-1,862	7	1,399	50-350
Breast cancer	15[a]	4,164	78-641	7	1,210	41-310
Prostate cancer	14[b]	3,843	58-1,381	6	894	18-401

[a] Six studies with exclusive focus on metastasised cancer
[b] Three studies with exclusive focus on metastasised cancer


USA
Multi-country
China
UK
Japan
Australia
Sweden
Spain
Denmark
Canada
Germany
Italy
India
The Netherlands
Singapore
Hypoglycaemia
Weight change
HbA1c reduction
Out-of-pocket costs
Glycaemic control
Treatment frequency
Nausea/vomiting
Regimen
Genitourinary infection
Gastrointestinal problems
Side effects
Cardiovascular event prevention
Administration route
Self-injection device type
Improved cardiovascular health
Ease of use
Food effects
Blood glucose monitoring
Sustained treatment effect
Needle type
Lower blood pressure
0
5
10
15
20
25
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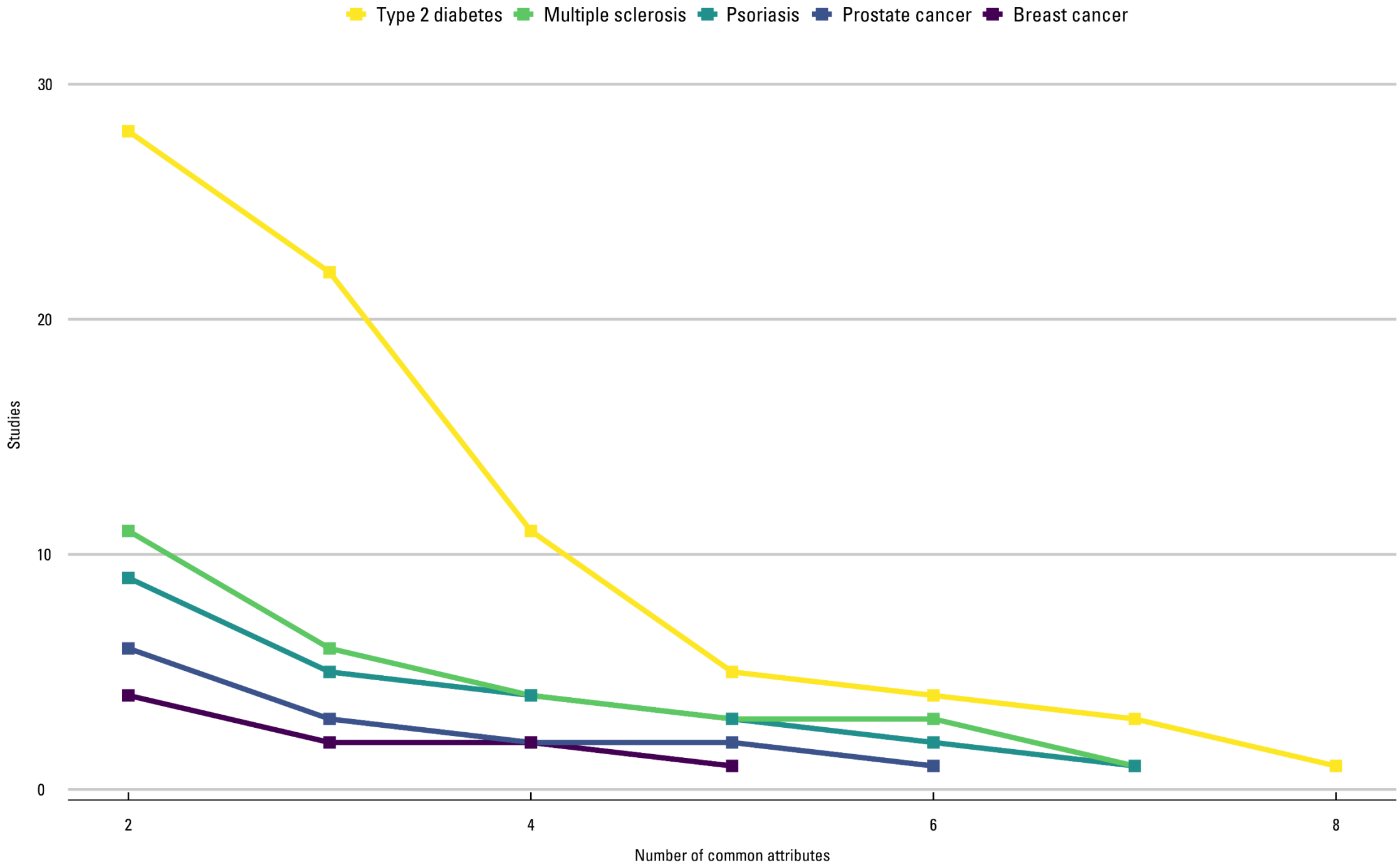
35
40
45
50
Studies


Type 2 diabetes
Multiple sclerosis
Psoriasis
Prostate cancer
Breast cancer
30
20
10
0
Studies
2
4
6
8
Number of common attributes

Results

REPORTED RESULTS IN DCES

Table 2. Reported results in discrete choice experiments within the top five most studied indications. For each result, the relative frequency is provided.

Indication	PWU	OR	RAI	Marginal rate of substitution				Predicted uptake
				MAB	MAR	WTP	Other	
Type 2 diabetes	32/43	6/43	19/43	1/43	4/43	15/43	0/43	3/43
Psoriasis	19/22	2/22	12/22	2/22	4/22	4/22	2/22	1/22
Multiple sclerosis	18/20	3/20	13/20	3/20	7/20	2/20	0/20	1/20
Breast cancer	13/15	0/15	9/15	5/15	1/15	3/15	2/15	1/15
Prostate cancer	14/14	1/14	6/15	6/14	0/14	1/14	1/14	2/14

PWU part-worth utility, *OR* odds ratio, *RAI* relative attribute importance, *MAB* minimum acceptable benefit, *MAR* maximum acceptable risk, *WTP* willingness-to-pay

Conclusions

DCEs in type 2 diabetes mellitus (T2DM) offer the most promising starting point for the development of methods to transfer patient preference information, because:

- They mostly examine similar attributes: glycaemic control, hypoglycaemia risk, weight change, and out-of-pocket costs (consistency in studied attributes)
- They provide the largest number of studies resorting to the same elicitation method (N = 43)
- They report part-worth utilities across almost all studies (consistency in reported results for synthesis, and flexibility for meta-analysts to derive results such as relative importance and marginal rates of substitution)
  - Meta-analyses aiming to support endpoint selection and benefit-risk assessments may both be feasible based on the reported results in literature

Future Perspectives

- **Conduct meta-regression:** Examine how priorities in common aspects of T2DM treatment (glycaemic control, hypoglycaemia risk, weight change and out-of-pocket costs) systematically vary between patient populations in different countries
- **Using transferred preference information:** Guide patient-relevant endpoint selection for future T2DM drugs based on predicted endpoint hierarchy, where the prediction adjusts for patient and country characteristics which influence preferences

ISPOR Europe 2024

19 NOVEMBER – POSTER SESSION 4

The Current Landscape of Patient Preference Studies: Are We Ready for Meta-Analyses and Benefit Transfers?

M. Bui[1], C.G.M. Groothuis-Oudshoorn[1], A.C. Jiménez-Moreno[2], B. Jones[3], C. Berlin[3], J.A. van Til[1]

1 Department of Health Technology and Services Research, Technical Medical Centre, University of Twente, Enschede, The Netherlands

2 Kielo Research UK, York, UK

3 Novartis Pharma AG, Basel, Switzerland

Transferability of Patient Preference Information in Medical Product Decision-Making

BASEL BIOMETRICS SOCIETY 2024

MICHAEL BUI[1]

[1] Department of Health Technology and Services Research, Technical Medical Centre, University of Twente (m.bui@utwente.nl)

KIELO RESEARCH

Regulatory and HTA Perspective on Patient Preference Studies

Basel Biometric Society Webinar

By **Tommi Tervonen**
Chief Scientist

22 October 2024

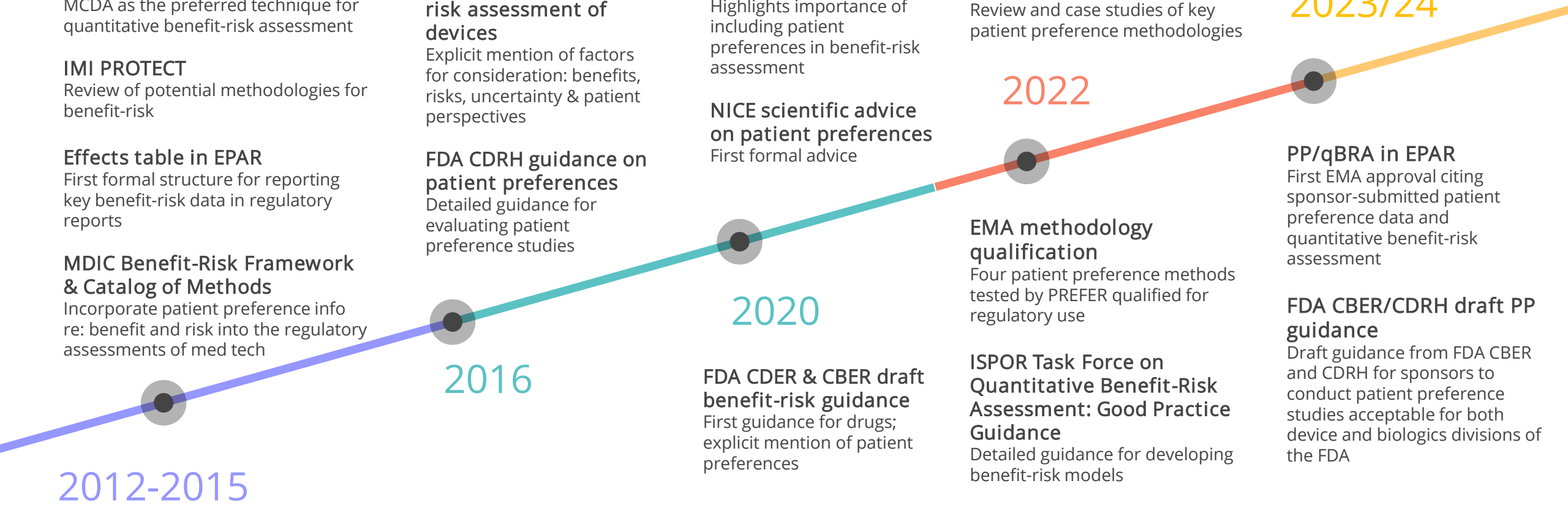
Agenda

1. Where do we come from? Brief history of patient preferences and benefit-risk
2. Two cases of patient preferences for regulatory purposes
3. Two cases of patient preferences for HTA uses
4. Where we are now and the way forward

Abbreviations: HTA, health technology assessment

Brief History of Patient Preferences and Benefit-Risk

Key initiatives and guidance documents



Abbreviations: EMA, European Medicines Agency; MCDA, multi-criteria decision analysis; EPAR, European Public Assessment Report; FDA, Food and Drug Administration; CDRH, Center for Devices and Radiological Health; CDER, Center for Drug Evaluation and Research; CBER, Center for Biologics Evaluation and Research; NICE, National Institute for Health and Care Excellence; qBRA, quantitative benefit-risk assessment

How are Patient Preferences Used in Medical Product Development?

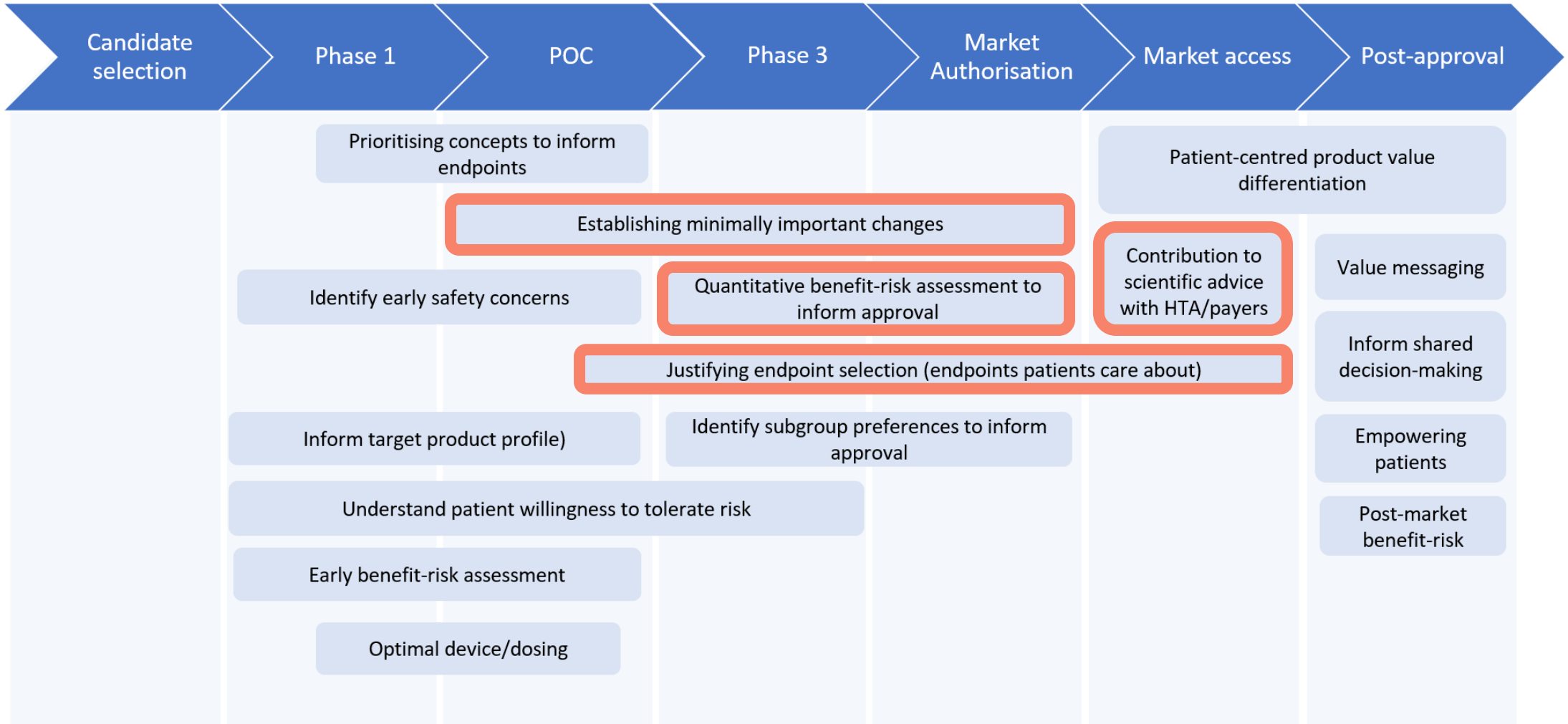


Figure source: Kerrie-Anne Ho, ISPOR EU 2023, Introduction in workshop "Every Patient Matters: Introduction to Multi-Dimensional Thresholding in Health Preference Research"

PP for Regulatory Purposes

Patient Preferences for Regulatory Approval and Dose Selection

Benefit-risk assessment using patient preferences

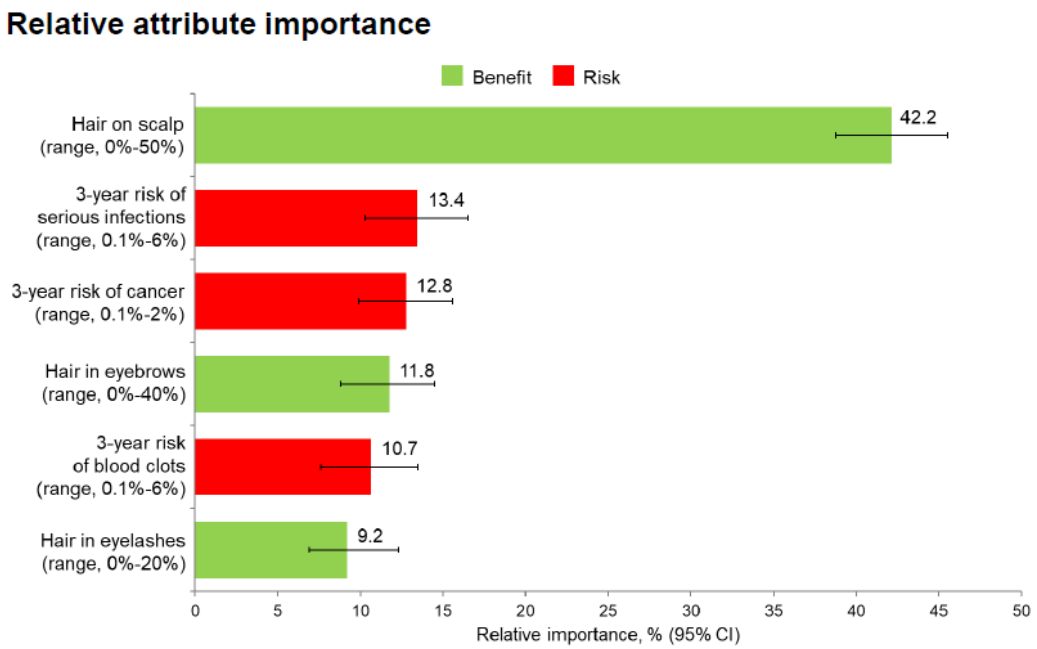
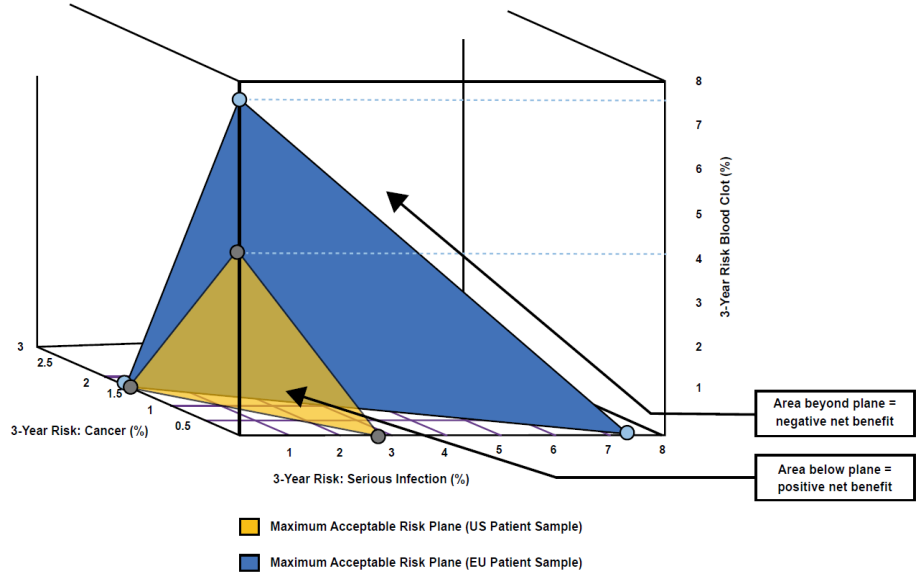


Figure 1. Maximum acceptable combinations of 3 risks in exchange for the increase in efficacy benefits by switching from ritlecitinib 30 mg QD to 50 mg QD for US patients (yellow surface) and EU patients (blue surface)



Problem: Novel JAK inhibitors are being developed for alopecia areata. Although the disease impacts on patients' well-being, regulators had questions about their risk tolerance given seemingly "cosmetic" disease.

Solution: A discrete choice experiment (DCE) instrument was developed based on a targeted literature review, in depth qualitative interviews with 12 patients, and consultation with the US Food and Drug Administration. A separate sub-study was conducted in an adolescent population, and preference data was used to compare benefit-risk profiles of two doses.

Results: Scalp hair growth is the key driver of patient preferences. Patients were willing to tolerate high levels of key JAK risks for the expected treatment benefits. Higher dose was preferred.

Impact: European Medicines Agency (EMA) approved higher dose of ritlecitinib based on the patient preference data and the quantitative benefit-risk assessment.

Sources: Tervonen et al. Benefit-risk preferences for alopecia areata treatments. World Congress for Hair Research 2022, Melbourne. Hauber, Whichello, Mauer, Law, Trapali, Whalen, Wajsbrot, Krucien, Tervonen, Zwillich, Wolk. Using Patient Preference to Inform Ritlecitinib Dose Selection for Alopecia Areata Treatment. ISPOR EU 2022, Vienna

Patient Preferences for PRO Label Claims

Patient Reported Outcome (PRO) endpoint valuation using patient preferences

Table 3. Maximum acceptable increase in annual relapses and maximum acceptable decrease in time to MS progression for a 3.57-point improvement in FSIQ-RMS-S score

		Maximum acceptable increase in annual relapses (95% CI)		Maximum acceptable decrease in time to MS progression in years (95% CI)	
Fatigue level	Corresponding FSIQ-RMS-S score	Physical fatigue	Cognitive fatigue	Physical fatigue	Cognitive fatigue
A little difficulty	25	0.06 (0.02-0.10)	0.09 (0.05-0.13)	0.17 (0.05-0.28)	0.24 (0.13-0.35)
Moderate difficulty	50	0.06 (0.03-0.09)	0.10 (0.07-0.13)	0.15 (0.07-0.23)	0.28 (0.19-0.36)
Quite a bit of difficulty	75	0.21 (0.18-0.25)	0.15 (0.12-0.18)	0.57 (0.48-0.66)	0.40 (0.32-0.49)
Average across all levels	-	0.12 (0.10-0.13)	0.12 (0.10-0.13)	0.32 (0.28-0.36)	0.32 (0.27-0.36)

Problem: Ponesimod demonstrated improvement over teriflunomide in fatigue in the OPTIMUM trial using novel PRO instrument FSIQ-RMS-S. However, clinical relevance and value of the improvement was difficult to establish.

Solution: A discrete choice experiment (DCE) was developed and fielded with multiple sclerosis (MS) patients outside the clinical trial. The DCE contained a mapping exercise to allow measuring importance of between-arm differences in OPTIMUM's clinical and PRO endpoints using patient preference data.

Results: Between-treatment difference in fatigue observed in the OPTIMUM trial is of similar importance as the between-treatment difference in relapses/year, that is deemed clinically meaningful.

Impact: EMA reviewed and provided a positive opinion on the study design and analysis approach. Results were published in a leading clinical journal (Multiple Sclerosis Journal).

Source: Fox, Tervonen, et al. The relevance of fatigue to relapse rate in multiple sclerosis: applying patient preference data to the OPTIMUM trial. Multiple Sclerosis Journal 2023;29(3):427-435.

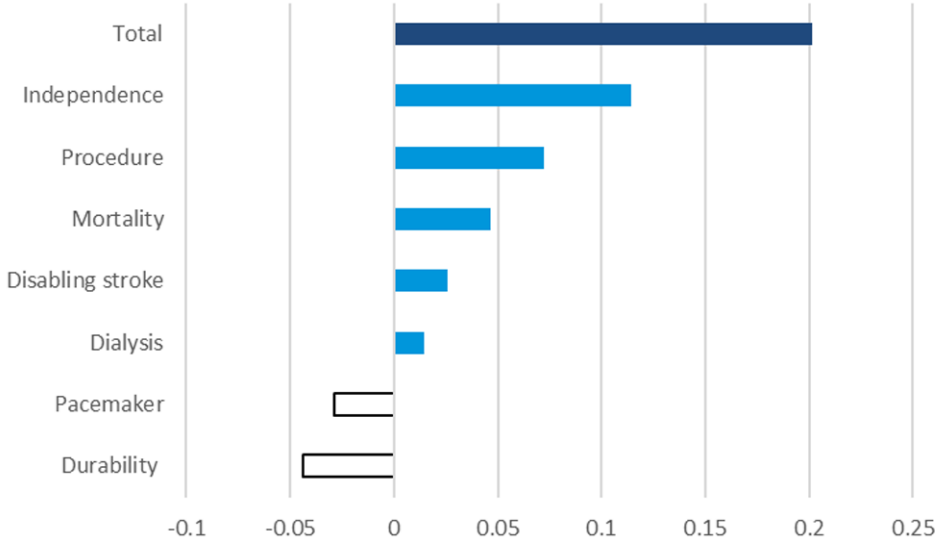
PP for Health Technology Assessment

Bringing the Patient Perspective to Health Technology Assessment

Patient preference data to enable market access

Procedure characteristics	Current situation	Improved situation	Which one of the procedure characteristics would you choose to improve?
Type of procedure	✓ Large incision (25 cm) through skin and muscle ✓ Heart stopped ✓ 12 days in hospital	✓ Small incision (3 cm) through skin but not muscle ✓ Heart is not stopped ✓ 8 days in hospital	○
Number of patients out of 100 who will have a **stroke within 1 year**	16% will have a stroke within 1 year	8% will have a stroke within 1 year	○

Figure:. Incremental value of transcatheter aortic valve replacement vs. surgical aortic valve replacement.



Problem: Transcatheter aortic valve replacement (TAVR) is an alternative to surgical aortic valve replacement (SAVR) in patients with aortic stenosis (AS) requiring open-heart surgery. Cost-effectiveness of TAVR was questionable.

Solution: An online survey was used to elicit attribute trade-offs from patients. Survey data were used to estimate patients' weights for AS treatment attributes, which were incorporated into a quantitative benefit-risk analysis (BRA) to evaluate patients' preferences for TAVR and SAVR.

Results: The patient preference study showed that while clinical outcomes were similar for both procedures, patients with AS who were at low-risk for invasive surgery had a marked preference for TAVR versus SAVR.

Impact: Ontario Health Technology Advisory Committee (OHTAC) applied these preference data to support their rationale to publicly fund TAVR for low-risk patients with AS in Ontario.

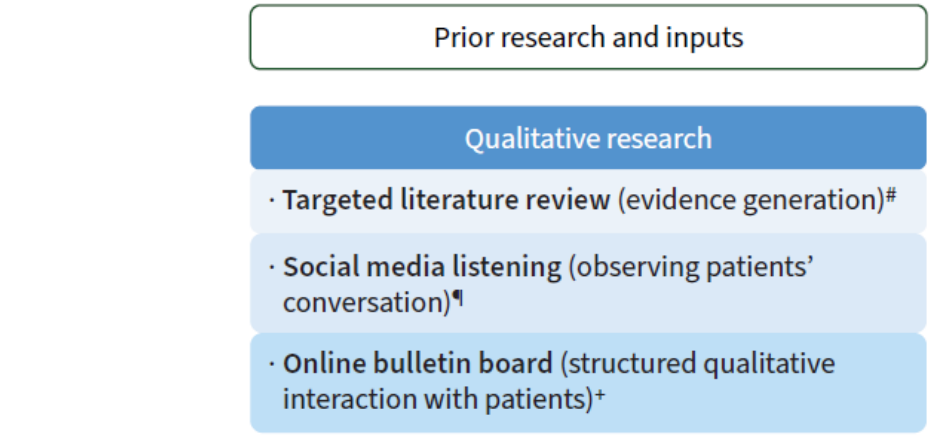
Source: Marsh K, Hawken N, Brookes E et al. Patient-centered benefit-risk analysis of transcatheter aortic valve replacement [version 5; peer review: 3 approved]. F1000Research 2021, 8:394 (https://doi.org/10.12688/f1000research.18796.5)

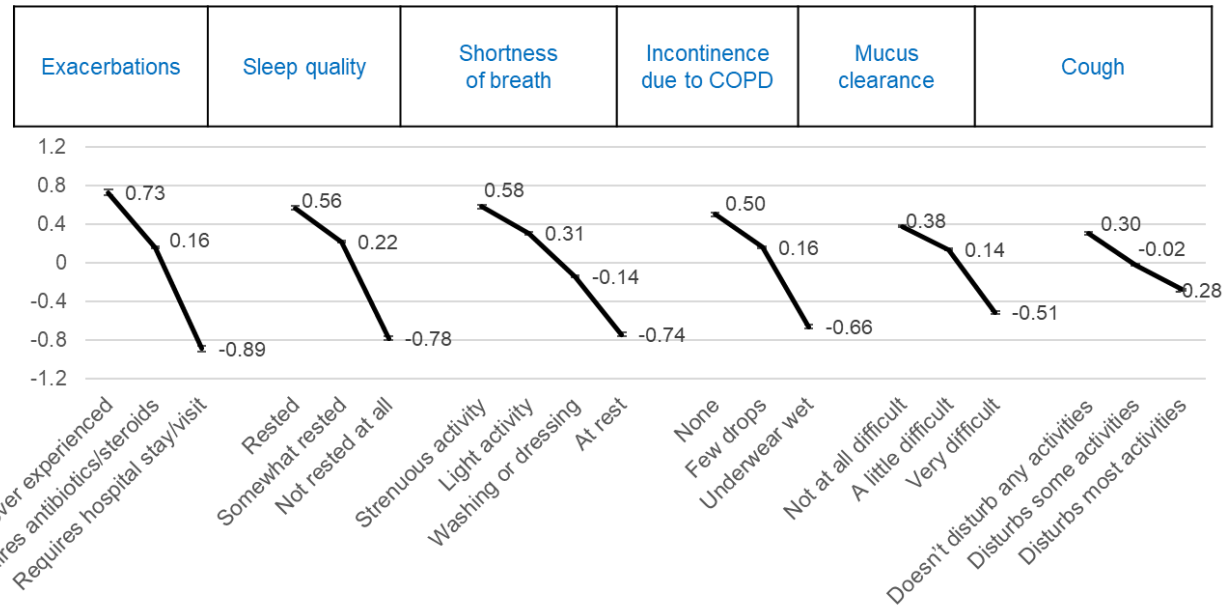
Patient Perspectives in NICE Submission

Use of patient preferences in the European HTA context

- Rate of exacerbations is the key clinical endpoint in COPD trials
- COPD is associated with significant symptom burden beyond exacerbations
- UK NICE provided formal scientific guidance for the patient preference study

"Offering advice and guidance on their patient preference study should help it to generate the data required to help future products meet the needs of COPD patients"





Abbreviations: COPD, chronic obstructive pulmonary disease; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence

Sources: Cook NS, Criner GJ, Burgel PR, et al. People living with moderate-to-severe COPD prefer improvement of daily symptoms over the improvement of exacerbations: a multicountry patient preference study. *ERJ Open Res* 2022; **8**(2). Cook N and Jones B, The importance of different symptoms to people living with Chronic Obstructive Pulmonary Disease. IMI PREFER presentation, 27 Oct 2021.

Where We Are Now and the Way Forward

Where We Are Now

Patient preferences for regulatory and HTA uses

- Conceptual challenges remain on the formal use of patient preferences to inform HTA:

  1. Patient vs. public preferences
  2. Comparability of valuation across health technologies / opportunity cost
  3. “We do not pay for convenience”

- Patient preferences are valid data for regulatory uses
  - Methodological rigour and purpose matters

- We are limited by available preference elicitation methods

Abbreviations: HTA, health technology assessment

Key Methods for Eliciting Patient Preferences

Three main methods for (serious) elicitation of trade-offs (quantitative preferences)

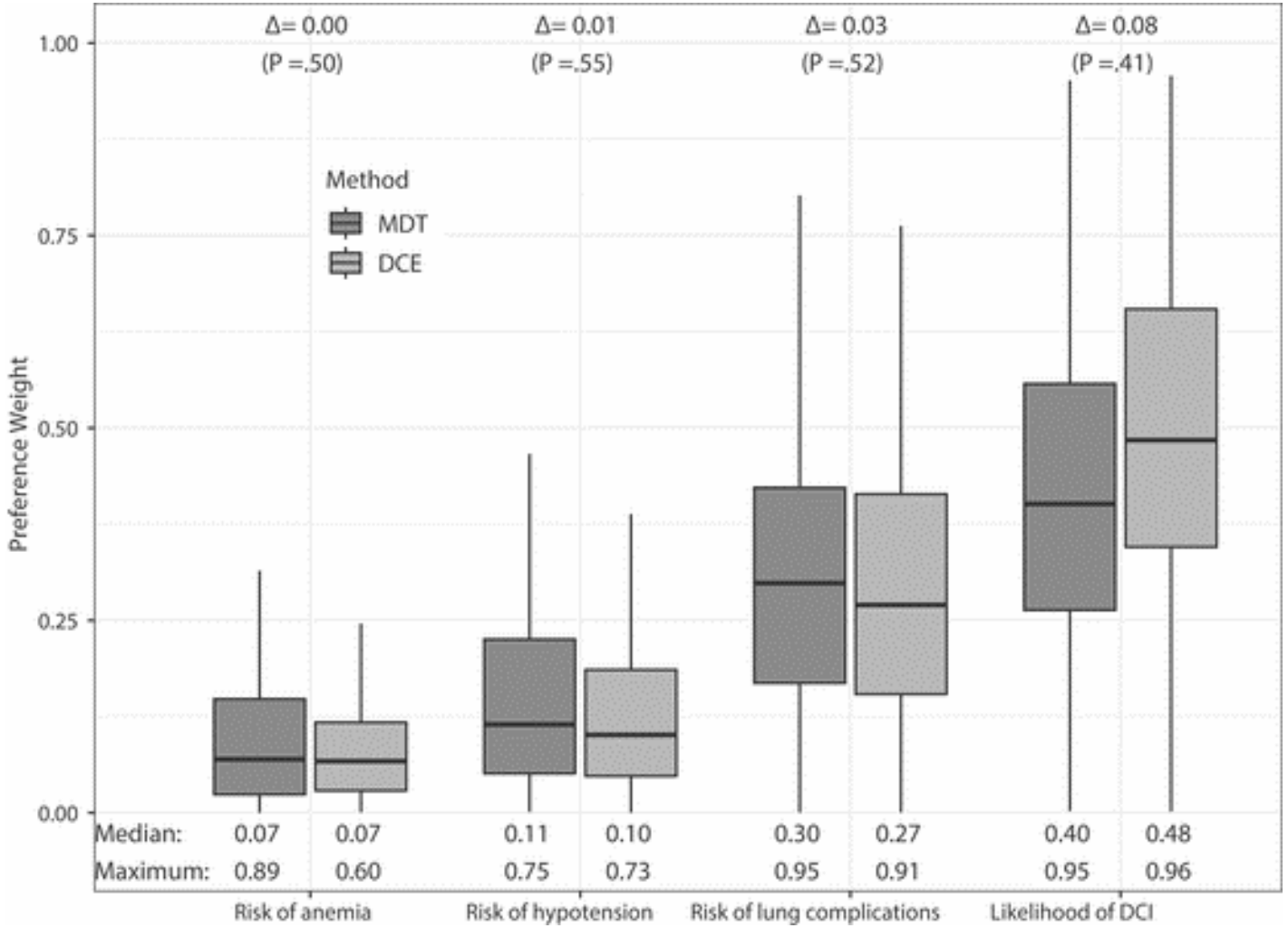
Table 1. Design, implementation and analytical considerations for a DCE (and BWS case 3), TT, and SW.

Consideration	DCE (and BWS case 3)	TT	SW
Taxonomy of Preference Elicitation Method[48]	Discrete choice-based	Indifference	Rating
Design considerations			
Question format and type of preference data*	Choice; ordinal data	Choice; ordinal data	Rating, cardinal data
Number of trade-offs	≥ 2	1†	≥ 1
Number of attribute levels varied in each elicitation task*	All‡	One	Varies§
Can capture interaction effects required for nonadditive models	Yes	No	No
Direct vs indirect elicitation of parameters of interest	Indirect	Direct	Direct
Implementation considerations			
Sample size	Typically > 100, but dependent on number of attributes and levels	Typically < 100; can be as small as required to represent the stakeholders	Typically < 100; can be as small as required to represent the stakeholders
Study duration‖	Typically > 12 months	Typically < DCE	Varies‖
Analytical considerations			
Preference parameters elicited	Full value function (v_i, w_i)	Single trade-off (w_1, w_2)¶	Attribute weights (w_i)£
Allows for status quo alternative	Yes	Yes, the reference alternative can be set as status quo	No

Source: Tervonen, T., J. Veldwijk, K. Payne, X. Ng, B. Levitan, L. G. Lackey, K. Marsh, P. Thokala, F. Pignatti, A. Donnelly and M. Ho (2023). "Quantitative Benefit-Risk Assessment in Medical Product Decision Making: A Good Practices Report of an ISPOR Task Force." Value in Health 26(4): 449-460.

New Methods Need to Demonstrate Convergence vs. DCE

Multi-dimensional thresholding may capture similar preferences as DCE



Heidenreich S, Trapali M, Krucien N, Tervonen T, Phillips-Beyer A. Two Methods, One Story? Comparing Results of a Choice Experiment and Multidimensional Thresholding From a Clinician Preference Study in Aneurysmal Subarachnoid Hemorrhage. Value Health. 2023 Oct 14:S1098-3015(23)06146-6.

Abbreviations: DCE, discrete choice experiment MDT, multi-dimensional thresholding

The Way Forward

What we need to continue impactful patient preference research for regulatory decisions and HTA

1. Further the use of patient preferences in HTA, acknowledging challenges with general population valuation of disease-specific health states

2. Further methodological development to allow capturing patient preferences in rare diseases and in subgroups

3. Expand the use of patient preferences throughout the drug development

4. Bring more biostatisticians to the field of patient preferences

Abbreviations: HTA, health technology assessment

KIELO RESEARCH

Thank you!

Questions?

Patient Benefit-Risk Tradeoff Preferences for NDMM Treatment Options

Basel Biometrics Society
October 22, 2024

Ellen Janssen, PhD
Director, Benefit-Risk/Epidemiology

Johnson&Johnson

Preference study for treatment of early-stage MM

CAR-T as early line treatment

CAR-T is approved as early and late line therapy for RRMM

Need to understand acceptable B-R tradeoffs for CAR-T in earlier line patients with more other treatment options

How do patients value the prospect of a recurrence and treatment free interval considering potential serious upfront AEs

Patient preference study

Study Objective: To est. patients' preferences for key benefits and harms of MM treatments when considering CAR-T as 1st line therapy

NDMM: Newly Diagnosed Multiple Myeloma, **RRMM**: Relapsed Refractory Multiple Myeloma

Decision Context

The study objective was to measure preferences for treatment decisions of newly diagnosed, untreated MM

It was not feasible to recruit patients with newly diagnosed, untreated MM only

- Ask participants to think back to when they were recently diagnosed
- Which treatment options would they recommend for a friend who:
  - is the same gender and about the same age
  - has recently been diagnosed with multiple myeloma
  - cannot have a bone marrow or stem-cell transplant because of their age and/or other health conditions

Recruitment

Source: patients in the Duke Cancer Institute (DCI) Tumor Registry

DCI Tumor Registration:

- Physician-confirmed diagnosis
- Regional referral center for cancer care across the mid-Atlantic
- Includes patients with a variety of treatment experiences including those in remission or with relapsed/refractory disease

Preference Study Inclusion Criteria:

- Diagnosis of multiple myeloma
- 18 years or older
- Able to read and understand English
- Able to provide informed consent

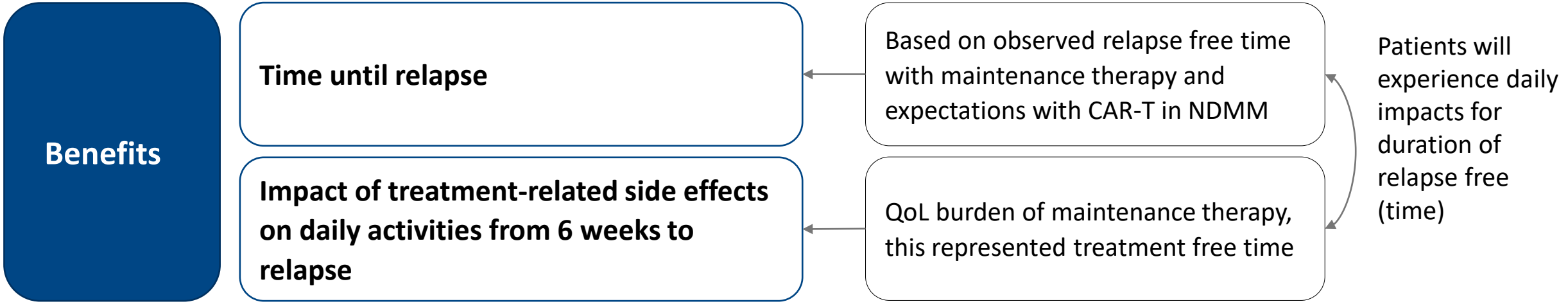
Sample Characteristics (N= 176)

Demographic Characteristic		N (%)
Age (years)	Mean (SD)	65.9 (9.4)
Gender	Female	89 (50.6%)
Marital status	Married/ living as married	137 (77.8%)
Highest educational level completed	4-year college degree +	67.0%
Ethnicity	Not Hispanic, Latino or Spanish origin	169 (96.0%)
Race*	White	131 (74.4%)

Disease and Tx History		N (%)
Years since diagnosed with MM	Mean (SD)	5.6 (3.6)
Bone marrow or stem-cell transplant for MM	Yes	141 (80.1%)
Current MM Tx *	Oral medicines	124 (70.5%)
	Infusion medicines	48 (27.3%)
	Injection	66 (37.5%)
	Radiation therapy	6 (3.4%)
	CAR-T cell therapy	2 (1.1%)
	Other	2 (1.1%)
Experienced an MM relapse	Yes	66 (37.5%)
Have switched MM Tx	Yes	59 (33.5%)
Main reason for switching Tx (n = 59)	Tx stopped working	38 (64.4%)
	Side effect(s)	14 (23.7%)

J&J

Treatment attributes



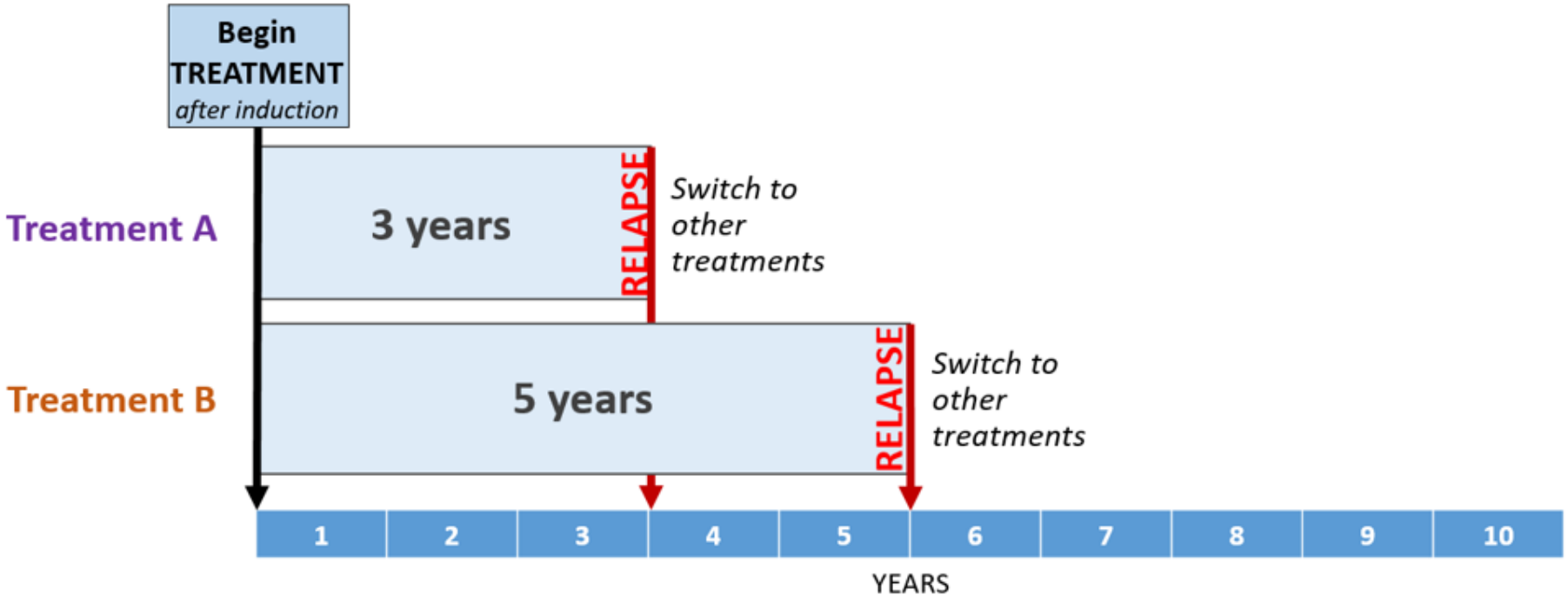
*Risk attributes were chosen to represent those most concerning to patients and that differentiate CAR-T from maintenance therapy

J&J

Representing relapse

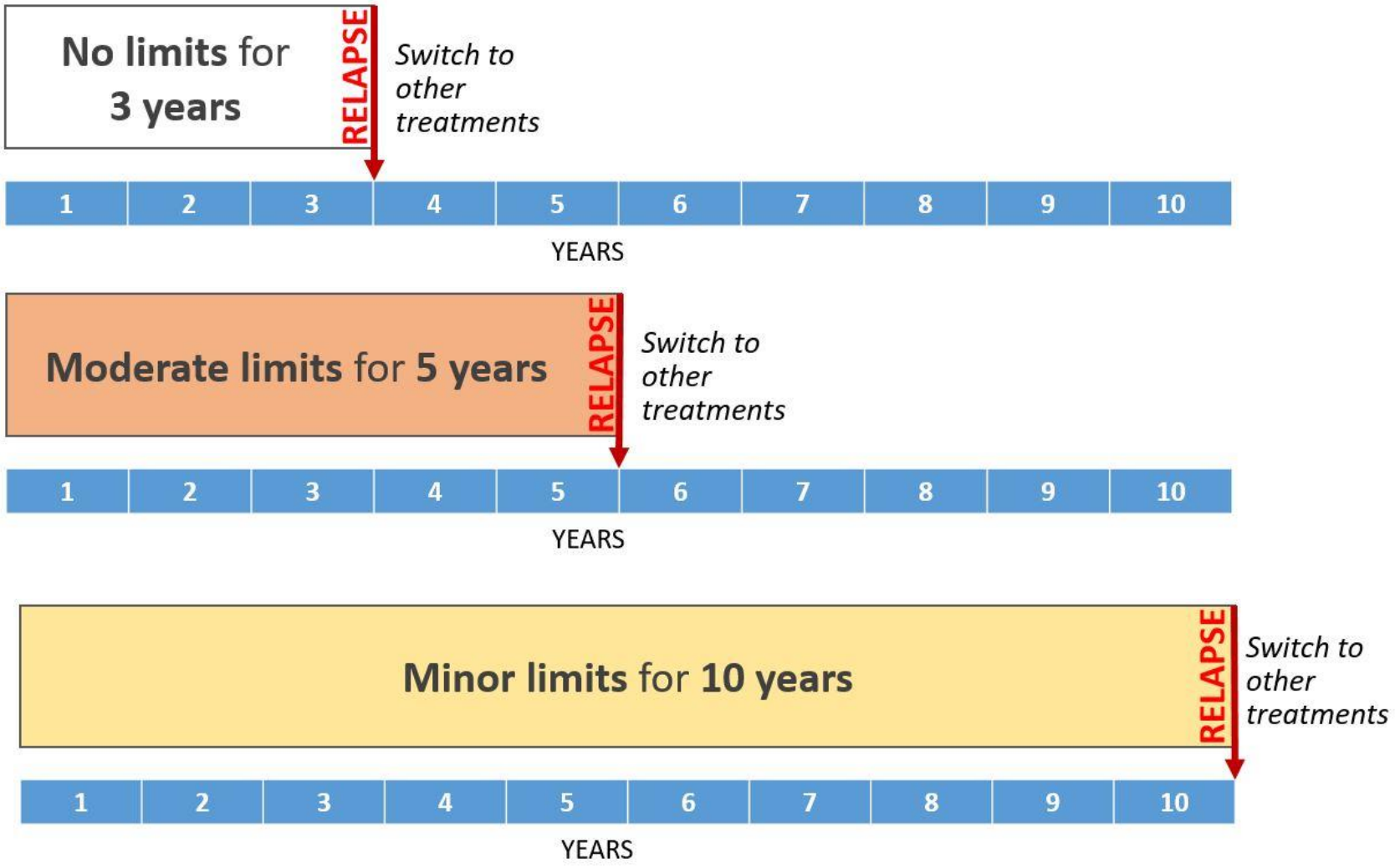
Some treatments worked for a shorter period of time, and others worked for a longer period of time.

In the picture below, **Treatment A** worked for 3 years, and **Treatment B** worked for 5 years before patients had a relapse.

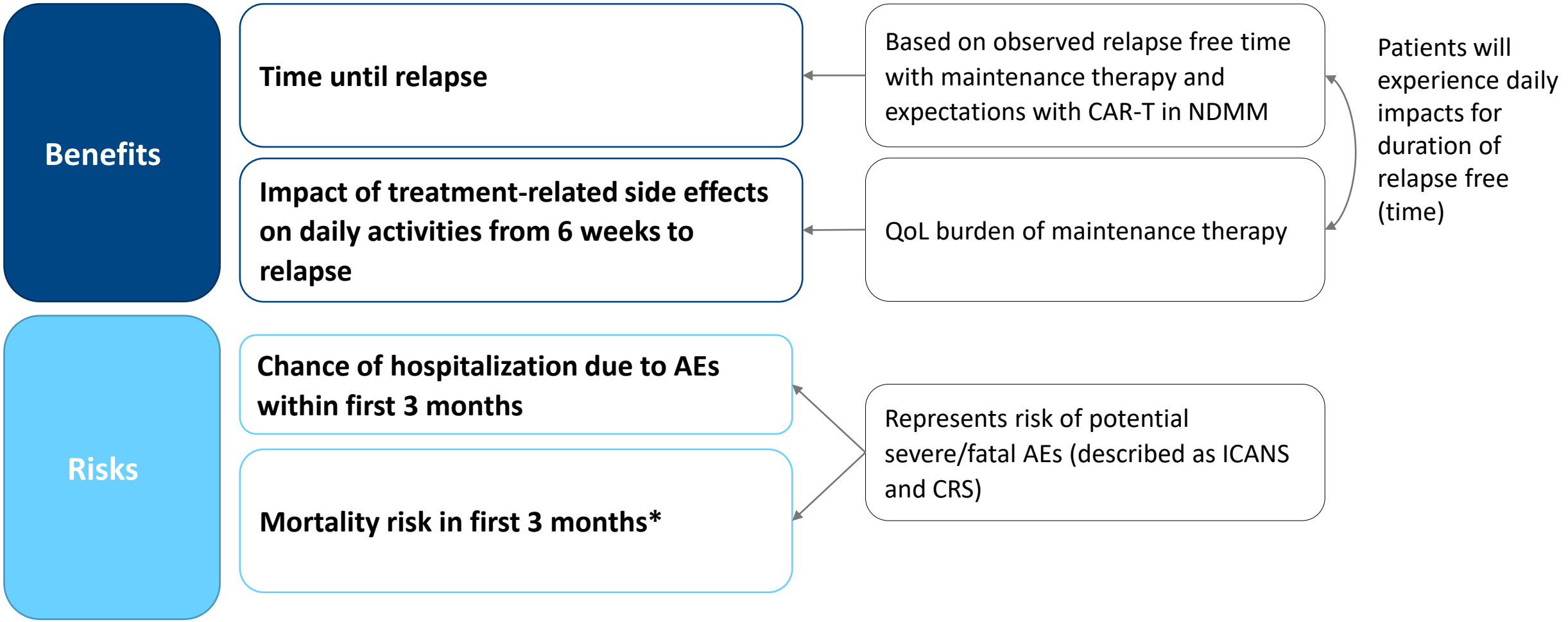


Adding in limitations on daily activities

3 Examples:



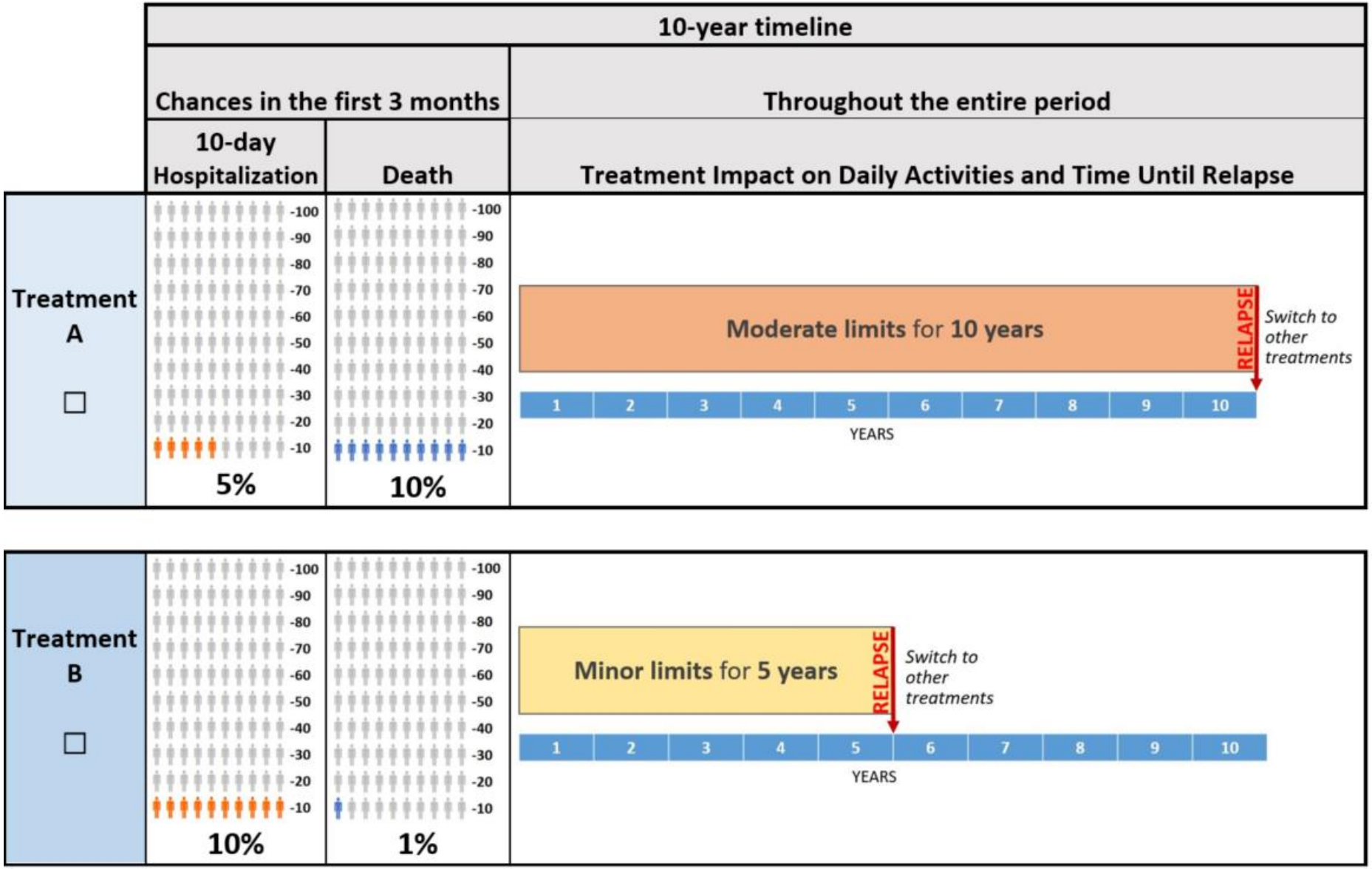
Treatment attributes



*Risk attributes were chosen to represent those most concerning to patients and that differentiate CAR-T from maintenance therapy

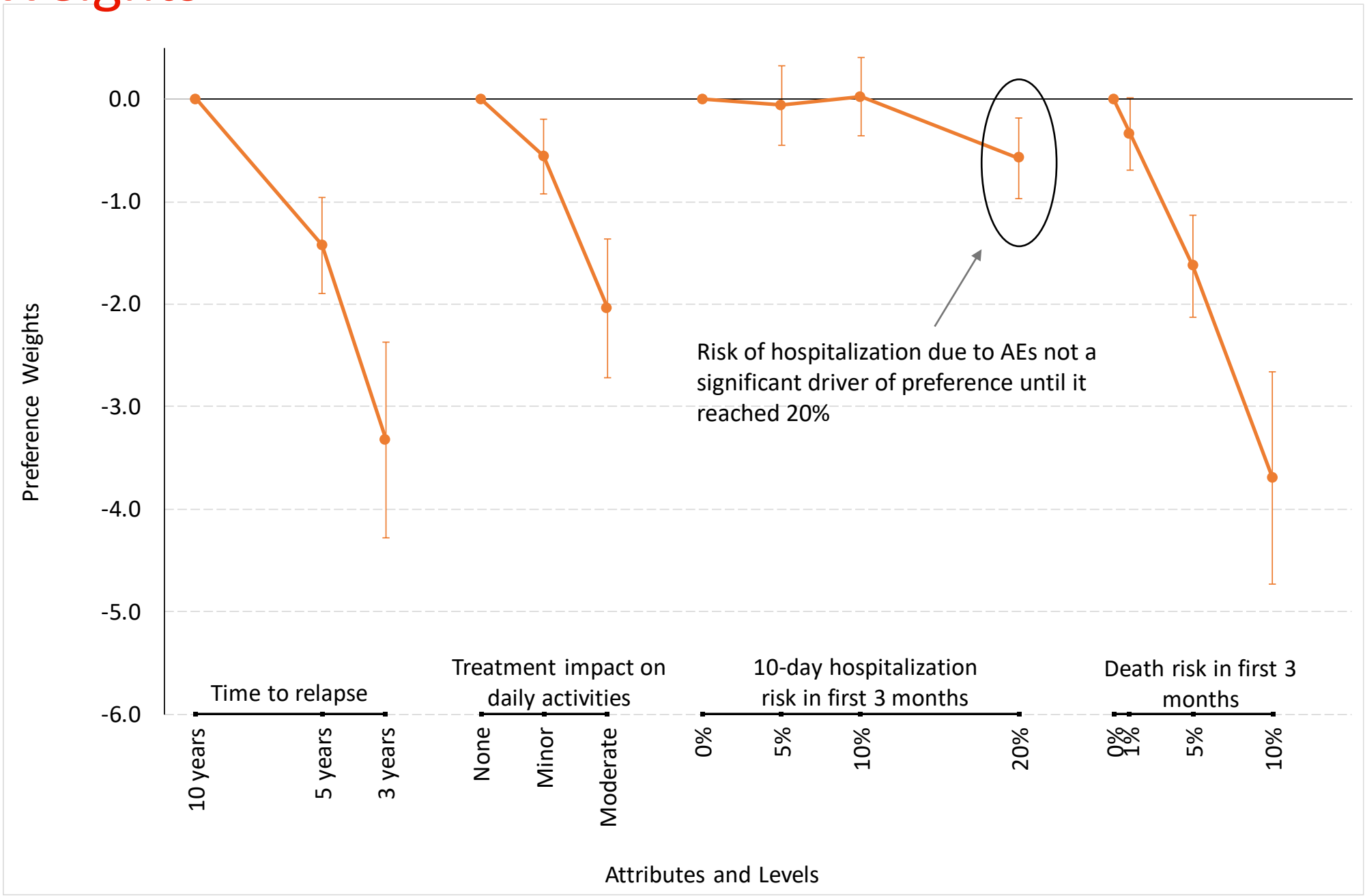
Example DCE Question (1 of 13)

If the treatments below were the only options for your friend, which one do you think your friend should choose?



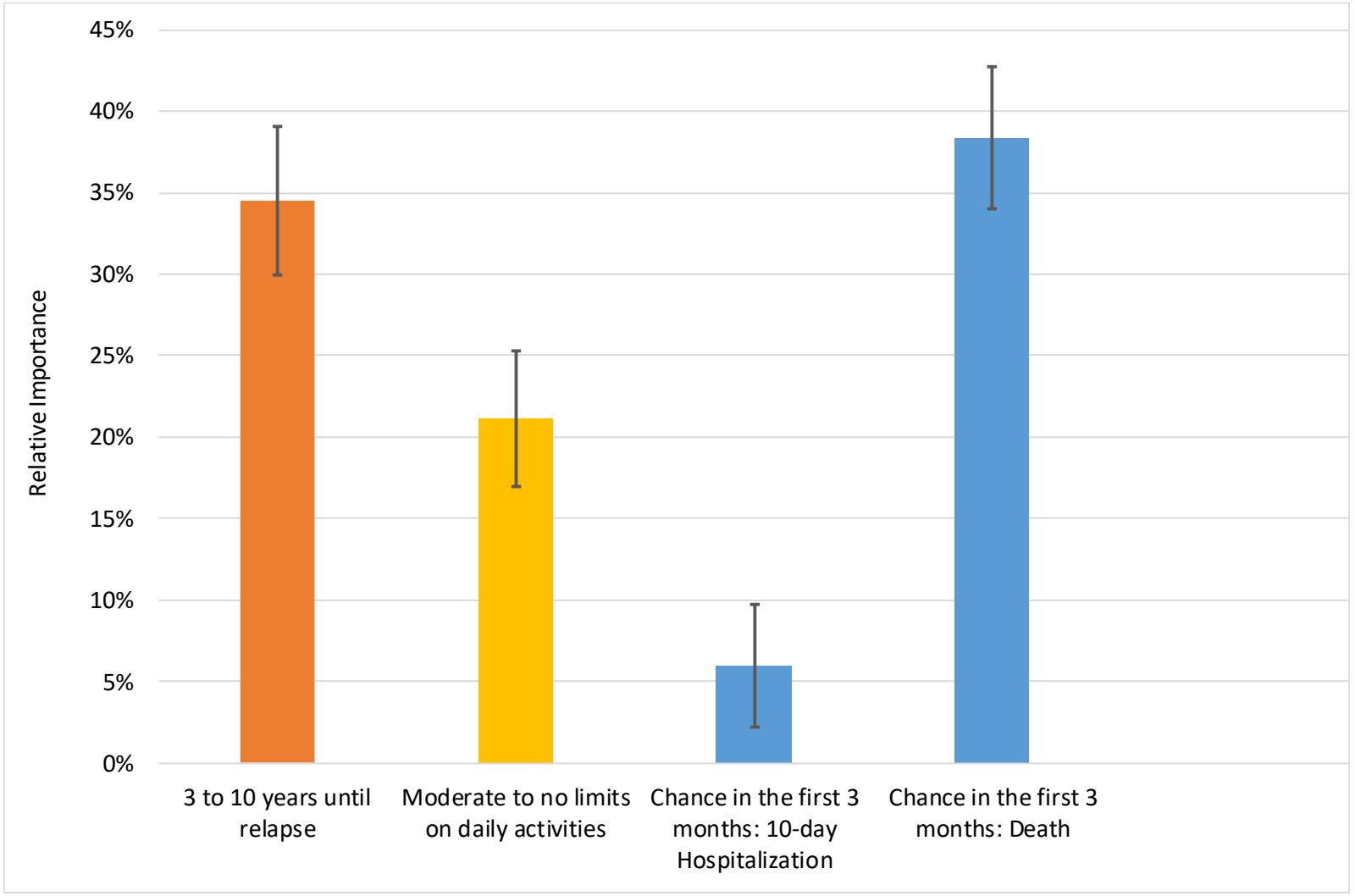
J&J

Preference Weights



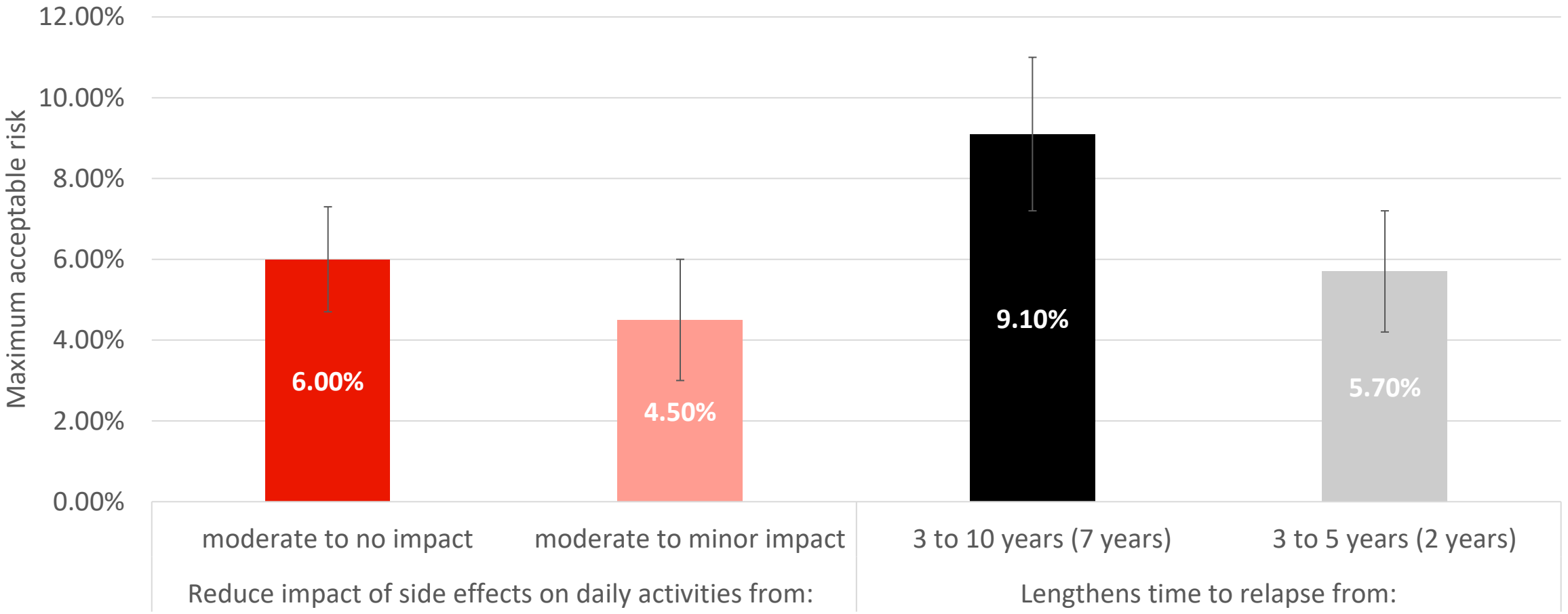
J&J

Relative Importance of attributes



J&J

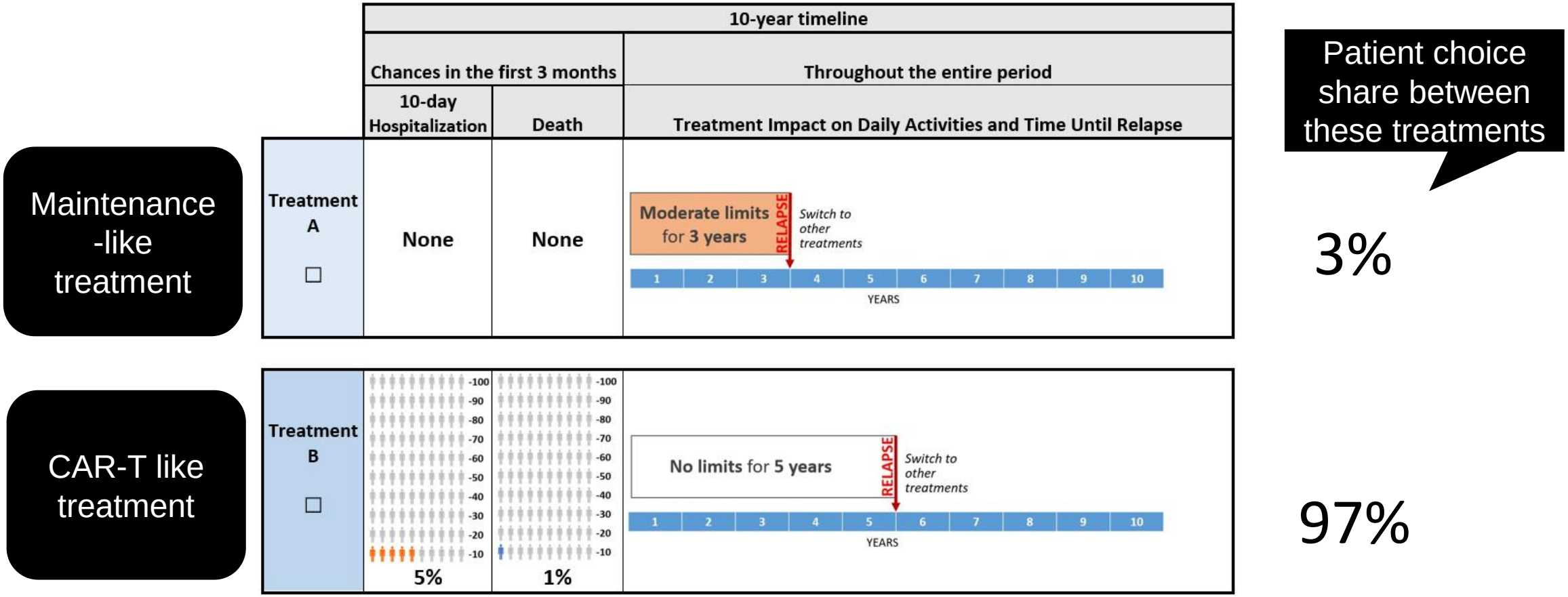
Maximum acceptable risk of 30-day mortality patients are willing to accept for each treatment benefit:



J&J

How would people choose between CAR-T and SoC for 1st line treatment – predicted choice share

Using patient preference survey results, predicted choice share for different treatments can be estimated.



What if the B-R profile of CAR-T or SoC is different?

What if maintenance therapy has lower impact on daily activities?

	Maintenance-like treatment	CAR-T like treatment
	Profile A	**Profile B**
Time Until Relapse	3 years	5 years
Tx Impact on Daily Activities	None	None
10-day Hospitalization due to AEs	0%	5%
Tx-related death	0%	1%
Choice probability	18%	**82%**

What if CAR-T has a longer recurrence free time?

	Maintenance-like treatment	CAR-T like treatment
	Profile A	**Profile B**
Time Until Relapse	3 years	10 years
Tx Impact on Daily Activities	Moderate	None
10-day Hospitalization due to AEs	0%	5%
Tx-related death	0%	1%
Choice probability	1%	**99%**

What if CAR-T has a higher rate of AEs?

	Maintenance-like treatment	CAR-T like treatment
	Profile A	**Profile B**
Time Until Relapse	3 years	5 years
Tx Impact on Daily Activities	Moderate	None
10-day Hospitalization due to AEs	0%	20%
Tx-related death	0%	10%
Choice probability	**58%**	42%

What if CAR-T has a higher rate of AEs and longer recurrence free time?

	Maintenance-like treatment	CAR-T like treatment
	Profile A	**Profile B**
Time Until Relapse	3 years	10 years
Tx Impact on Daily Activities	Moderate	None
10-day Hospitalization due to AEs	0%	20%
Tx-related death	0%	10%
Choice probability	25%	**75%**

Conclusions

- Patients assigned least importance to reversible, short-term side effects that may be associated with CAR-T.
- Specified levels of severe but temporary side effects and treatment mortality were acceptable in exchange for longer relapse free intervals and fewer long-term impacts on daily activities.

Patient Focused Drug Development: The role of Patient Preference Studies BBS Seminar - October 22, 2024

Case Study 2

INNOVUS
Consulting Limited

Andrea Phillips Beyer PhD

Case Study – Best Practices

Conducting a Patient Preference Study – Study Phases

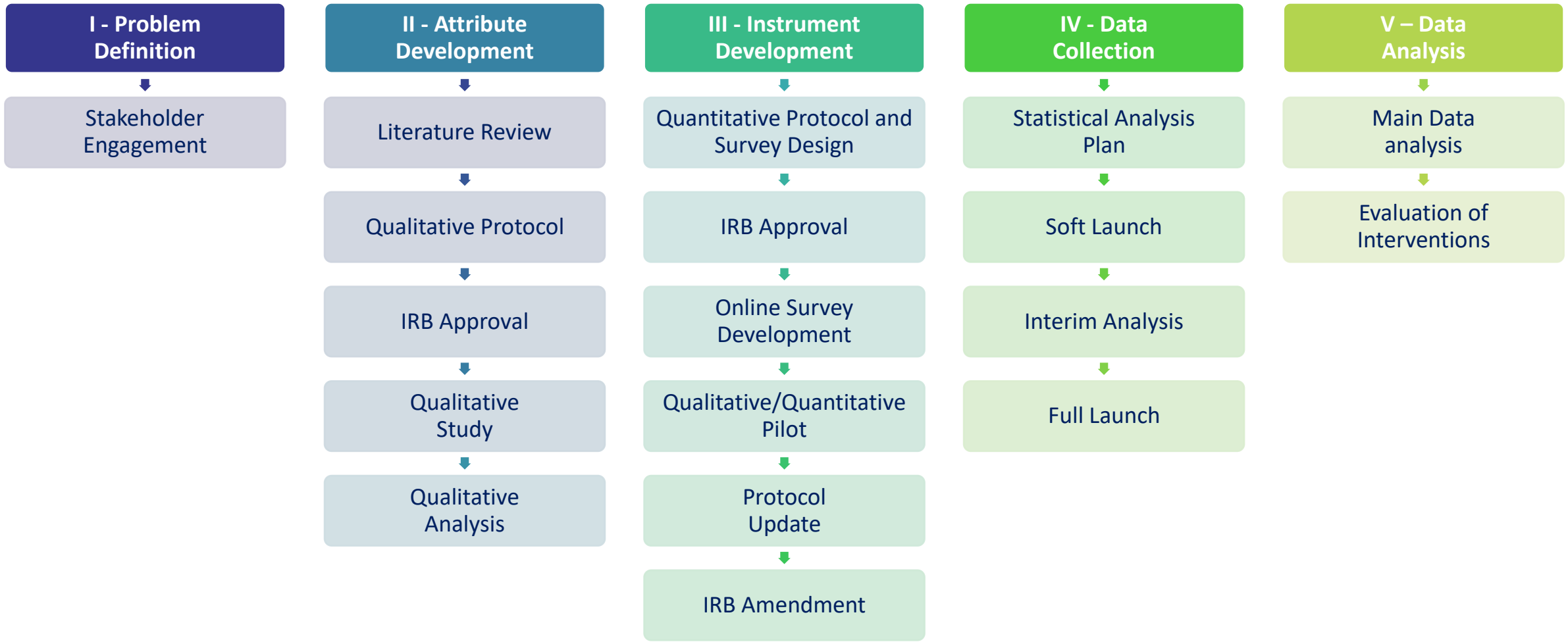
Best-Practice Approach

I - Problem Definition	II - Attribute Development	III - Instrument Development	IV - Data Collection	V – Data Analysis
Objective To describe the decision that the study will inform, the patient group of interest, interventions to be evaluated, and the objectives	**Objective** To identify patient-relevant and decision-relevant treatment attributes and levels that can distinguish between comparators and inform decision making	**Objective** To select and design a patient preference instrument that is fit-for-purpose (i.e. likely valid; generates required outcomes; accepted)	**Objective** To test and demonstrate the validity of the designed instrument before launching the main data collection	**Objective** To estimate the trade-offs the patients are willing to make between attributes and to generate the decision-relevant behavioral outputs

Conducting a Patient Preference Study – Study Phases

Best-Practice Approach

Overall duration
12 – 18 months



Methods Overview

Overview of Different Stated Preference Methods

Method		Description
Direct elicitation methods (Participants rank or rate treatments or treatment attributes)	Direct elicitation	"Direct preference" methods are used to evaluate patient preferences for actual interventions. Patients are presented the intervention choices they face in the real world. Patients do not have to have experienced the interventions to provide their preferences.
	Direct elicitation within a cross-over trial	"Direct preference" methods are used in clinical studies to directly elicit patients' preferences for treatments they have experienced in the study.
	Swing Weighting	Swing weighting requires participants to rate changes in attributes ('swings'). Participants are shown worst and best levels on attributes, which define the swings. After ranking the swings in the order they would choose to make the improvements, participants then rate the swings to reflect their relevant importance.
Indirect elicitation methods (Preferences and trade-offs are inferred from hypothetical choices)	Discrete Choice Experiment (DCE)	Participants complete a number of choice tasks in which they select between two or more hypothetical interventions. The performance of the interventions are varied between choices. Analysis of the choices can then determine the impact of variations in performance on different attributes on the likelihood that participants will choose an intervention.
	Best-Worst Scaling – Case 3	Participants choose between interventions and repeat this task multiple times as the performance of interventions is varied across all attributes.
	Best-Worst Scaling – Case 2	Participants are given a list of attribute levels and asked to indicate which they consider the best and worst. Rather than choosing between profiles (as in DCE or BWS type 3, participants are asked to choose the most and least acceptable features within a profile.
	Best-Worst Scaling – Case 1	Participants are given a list of attributes and asked to indicate which they consider the best and worst.
	Thresholding	Participants complete a number of choice tasks in which they select between two or more hypothetical intervention. Thresholding differs from DCEs in that only the performance of one intervention on one attribute is varied between choice tasks. Responses can then be used to estimate the level of that attribute at which participants would be indifferent between interventions A and B.
	MACBETH	MACBETH is a non-numerical elicitation approach. During the elicitation process, participants will be asked to distinguish the value between paired attribute levels/ attributes over a series of tasks on six semantic categories ranging from Very Weakly Preferable to Extremely preferable. These qualitative judgments about differences in preference between pairs of attribute levels/ attributes are then used to build numerical scores for each attribute levels/attributes.

Selecting The Appropriate Patient Preference Method (1)

Method	Pros	Cons
Direct elicitation	• Simple to design, implement and analyze • Only requires a small amount of participants' time • Does not require a separate study – can be added to any questionnaire • Well suited for complementing other methods	• Requires precise estimates of performance of treatment alternatives • Unable to model how choices vary with performance • Only provides a single outcome • Not robust if preferences are not well established or instable
Direct elicitation within cross-over trial	• Possible to achieve a preference-based label claim • Simple to design • Does not require a separate study – can be in existing cross-over RCT	• Expensive to set up if it cannot be administered in an existing study • Only provides a single outcome • Not robust if preferences are not well established or instable
Swing Weighting	• Can be implemented in very small sample • Results in individual level preferences	• Cognitively demanding • Should be implemented in workshop setting
Discrete Choice Experiment (DCE)	• Robust and widely accepted • Focus on trade-offs between all attributes • Strong theoretical foundations • Methods to measure heterogeneity	• Typically requires a sample of > 150 • Limited number of attributes (<10) • Sophisticated analysis required • Can be challenging if relative importance of attributes is very different

Selecting The Appropriate Patient Preference Method (2)



Method	Pros	Cons
Best-Worst Scaling – Case 3	• Relaxes sample size requirements of DCE • Focus on trade-offs between all attributes • Individual level modelling may be possible	• Weaker theoretical foundations than DCE • Limited number of attributes (<10) • Sophisticated analysis required
Best-Worst Scaling – Case 2	• Descriptive statistics can be used • Relatively small sample size requirements • Individual level modelling often possible	• Not well known outside health economics • Little focus on trade-offs • Very weak theoretical foundations
Best-Worst Scaling – Case 1	• Can be implemented in very small sample • Easy to design • Possible if attributes cannot be defined	• Cannot distinguish between attributes • Not suitable for eliciting trade-offs
Thresholding	• Simple design with 2 attributes • Can be adapted to a multi-dimension thresholding if >2 attributes • Results in individual level preferences	• Not suitable for trade-offs where attributes levels are categorical/ qualitative in nature • Requires performance on attributes to be known • Sophisticated analysis required in multi-dimension thresholding
MACBETH	• Can be implemented in very small sample • Results in individual level preferences	• Few applications within health economics • Little focus on trade-offs

Case Study 2
PAtient preference stUdy in inSomnia (PAUSe I)

Daridorexant Phase 3 Pivotal Studies – Study Objectives

- The **overall aim** of the study was to interpret the daridorexant phase III trials from patients' perspective.
- The **primary objectives** of this study were:
  - To identify the attributes and levels of insomnia treatments that are relevant to and tradeable by subjects
  - To develop, test, and refine a DCE aiming to elicit subjects' preferences for the identified treatment attributes
  - To quantify the trade-offs that subjects were willing to make between attributes by integrating the developed DCE into the ID-078A301 and ID-078A302 trials, based on preference data collected at visit 4
  - To compare daridorexant 50mg and daridorexant 25mg to placebo in a quantitative benefit-risk assessment (BRA) that combines both the preference data (i.e., from visit 4) and the phase III clinical performance data
- The **secondary objectives** of this study were to:
  - To test if average preferences differ between the following pre-specified subgroups: trial participants (ID-078A301; ID-078A302); age groups (18-44; 45-64; 65+); sex (male; female); ISI score (15-21; 22-28); MMSE score (25-27; 28-30); and BMI (<30; 31+)
  - To test if average preferences changed between visit 4 and visit 8

S Heidenreich, M Ross, G Chua, D Sebok Kinter, A Phillips Beyer. Preferences of patients for benefits and risks of insomnia medications using data elicited during two phase III clinical trials. Sleep 2022; 45(11): 1-12.

Design

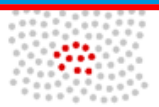
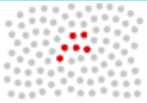
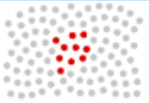
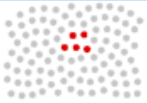
Attributes and Levels

Attribute	Levels
Time it takes to fall asleep	30 minutes to fall asleep 45 minutes to fall asleep 1 hour to fall asleep
Total time asleep	5 hours 6 hours 7 hours
Daytime functioning	Fully functioning Restricted functioning Difficulty functioning
Likelihood of daytime dizziness/grogginess	0% 10% 20%
Likelihood of abnormal thoughts and behavioural changes	0% 6% 12%
Likelihood of falls in the night	0% 5% 10%
Treatment withdrawal	No withdrawal Moderate withdrawal Severe withdrawal

- **Concept elicitation with qualitative research was conducted in two phases:**
  1. **Digital ethnography**
  2. **One to one interview**
- **The aim of the qualitative study was to understand patients' everyday experience with insomnia, factors that influence the way they manage their symptoms, the trade-offs they are willing to make, and general aspects of insomnia that are important to them.**
- **Participant treatment decisions are influenced by their ability to function the next day at home, work and socially.**
- **Participants desire more personalized approaches that will work for them in the long-term.**
- **Final attributes and levels were selected based on the qualitative data, Phase II data, and endpoints included in the Phase III trial.**

Design

Attribute Levels

	Treatment A	Treatment B
Likelihood of dizziness/Grogginess	 10 out of 100 patients (10%)	 20 out of 100 patients (20%)
Likelihood of abnormal thoughts and behavioural changes	 12 out of 100 patients (12%)	 6 out of 100 patients (6%)
Likelihood of falls in the night	 10 out of 100 patients (10%)	 5 out of 100 patients (5%)
Treatment withdrawal	 Moderate withdrawal	 No withdrawal
Time to fall asleep	 45 minutes to fall asleep	 1 hour to fall asleep
Total time asleep	 7 hours asleep	 5 Hours asleep
Daytime functioning	 Fully functioning	 Restricted functioning
Choice:		

Levels
Levels are the performance of the alternatives in the choice task on the different attributes.

Choice Question
A DCE experimental design with 24 choice tasks split into two blocks was generated. Patients indicate which alternative they prefer over 12 choice tasks.

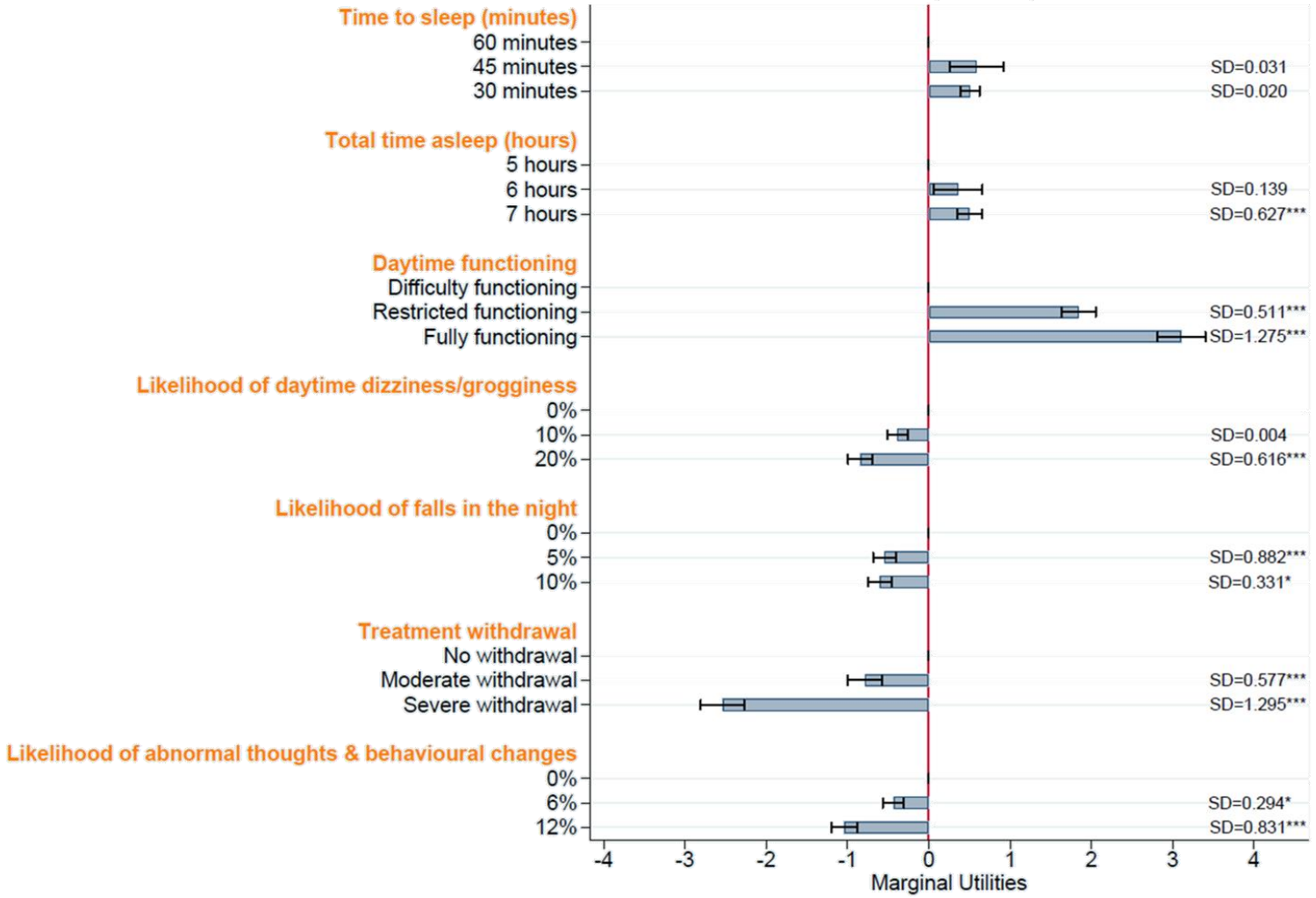
Implementation

Pilot Testing and Data Collection

- **Qualitative pilot:**
  - Twenty-four participants (Germany: n = 12; US: n = 11) completed the survey with an interviewer who probes on their understanding and interpretation.
  - This led to minor adjustment of wordings and attribute definitions.
- **Quantitative pilot:**
  - The quantitative pilot was conducted as a standalone study in the US and UK with 201 participants.
  - This led to minor adjustment such as widening of attribute levels to ensure patients are making trade-offs and presentation of risks before benefits in the DCE.
  - The pilot also explored the optimal presentation order of the attributes in the DCE.
- **Main study**
  - A total of 602 participants completed the DCE in Visit 4 sample, with 300 subjects from the ID-078A301 trial and 302 from and the ID-078A302 trial.

Analysis

Preference Estimates

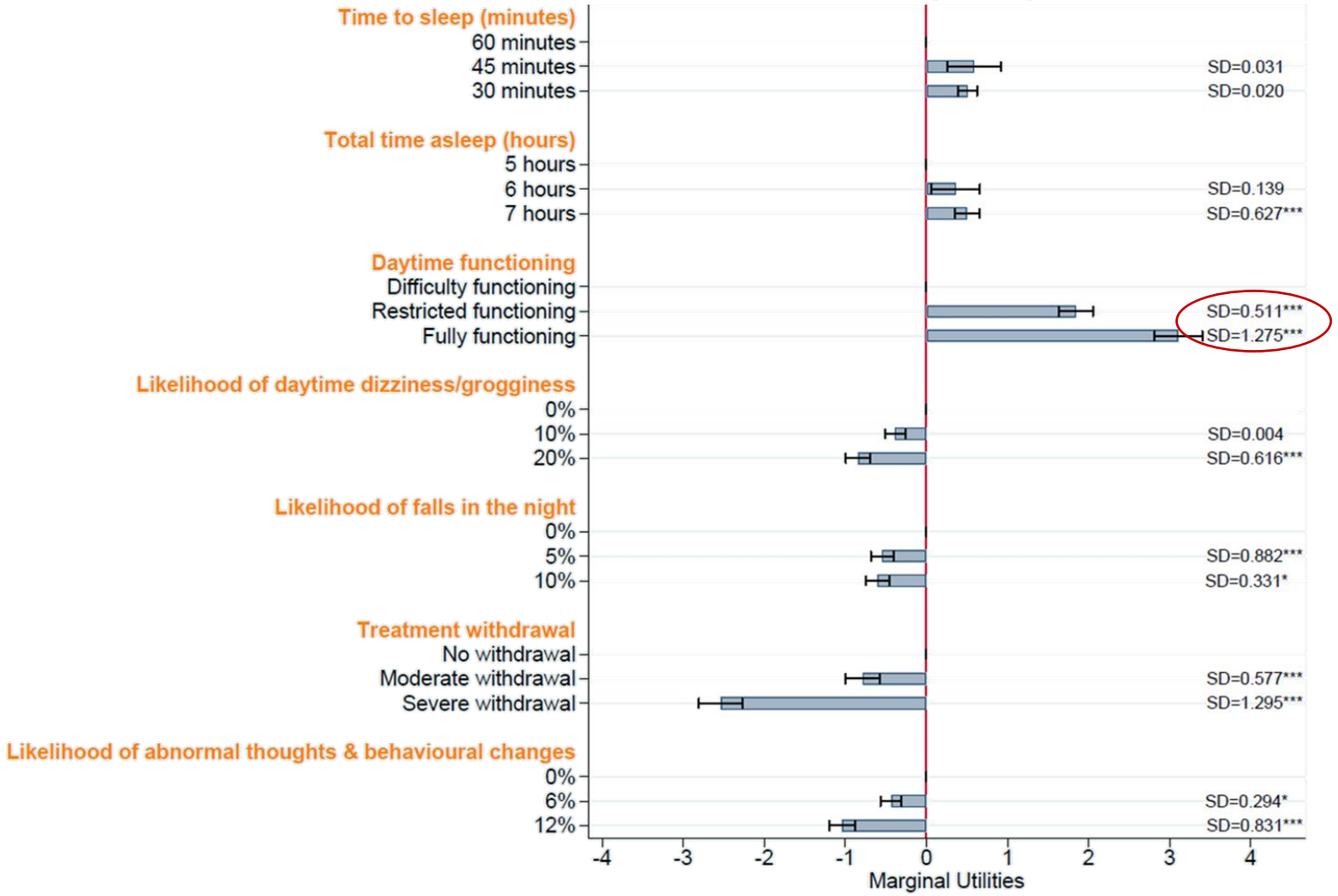


Econometric analysis estimates '**marginal utility**' which measures the effect of changes in attributes on preferences. The marginal utilities estimated from different models cannot be compared directly. For meaningful interpretation, marginal utilities can be used to compute other behavioral outputs such as **maximum acceptable risk** or **predicted choice probabilities**.

Positive coefficient: Change in the attribute increases the probability that a patient will choose a treatment.
Negative coefficient: Change in the attribute decreases the probability that a patient will choose a treatment.
Larger coefficients suggest the change in the attribute has a larger impact on treatment choice.
Significance: All seven attributes ($p<0.05$) influence patients' treatment decisions.

Analysis

Preference Estimates



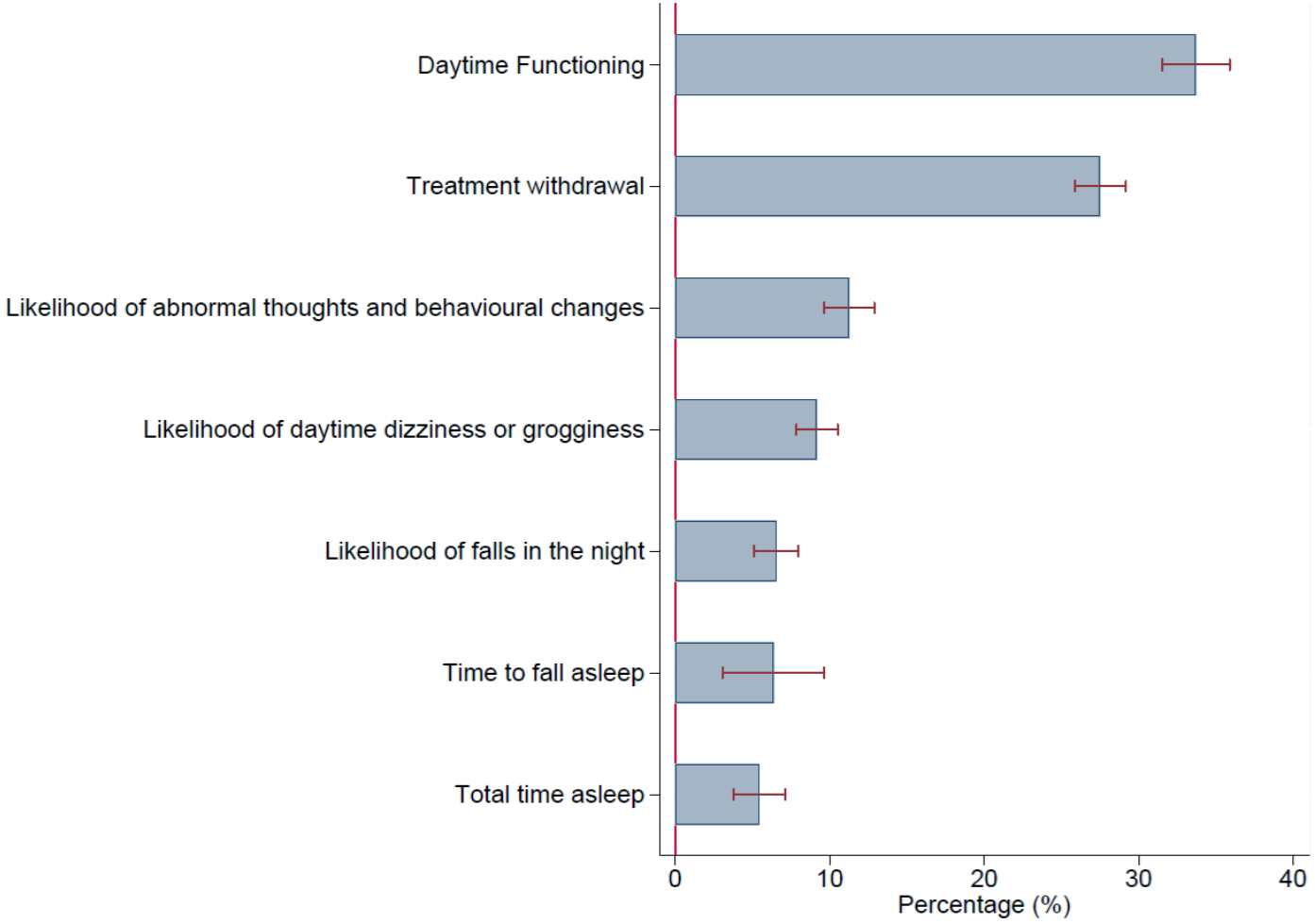
A multinomial logit (MNL) model is the most basic choice model and assumes that preferences are homogenous. More advanced models can account for preference heterogeneity and assume that preferences are either continuously distributed (e.g., mixed logit) or patients can be sorted into preference groups (e.g., latent class logit).

In this study, a mixed logit (MXL) model was estimated. A significant standard deviation (SD) denotes the presence of preference heterogeneity.

Analysis

Relative Attribute Importance

- Marginal utility were also expressed in terms of relative attribute importance (RAI).



RAI scores measure the proportion of changes in treatment utility than can be attributed to changes in a particular attribute.

Daytime functioning (33.7%) and treatment withdrawal (27.5%) were the most important drivers of treatment preferences, followed by the likelihood of abnormal thoughts and behavioral changes (11.3%).

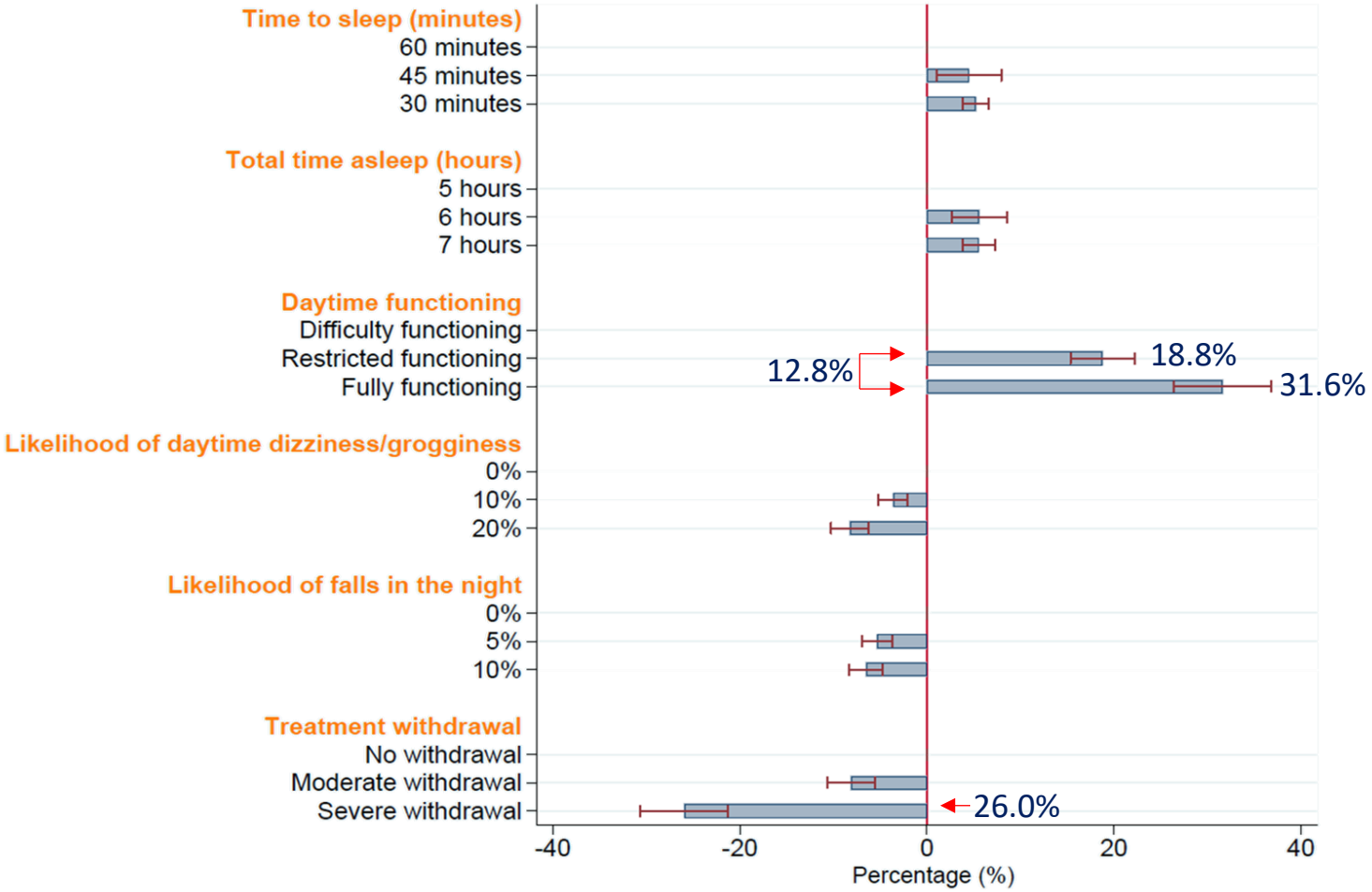
Improvements in daytime functioning were six times more important than improvements in total time asleep and five times more important than improvements in sleep onset.

All treatment risks together (54.4%) were of similar importance to patients as all benefits together (45.5%).

Analysis

Maximum Acceptable Risk (MAR)

MAR of Abnormal Thoughts and Behavioral Changes



MAR= Maximum acceptable risk

Maximum acceptable risk (MAR) is a measure of trade-offs and expresses how much additional risk of an attribute participants were willing to accept for changes in other attributes. The MAR allows the comparison of attributes using a common unit (i.e. % risk).

Patients are willing to accept 31.6% additional risk in abnormal thoughts and behavioral changes to improve daytime functioning from difficulty to fully functioning ($p < 0.001$).

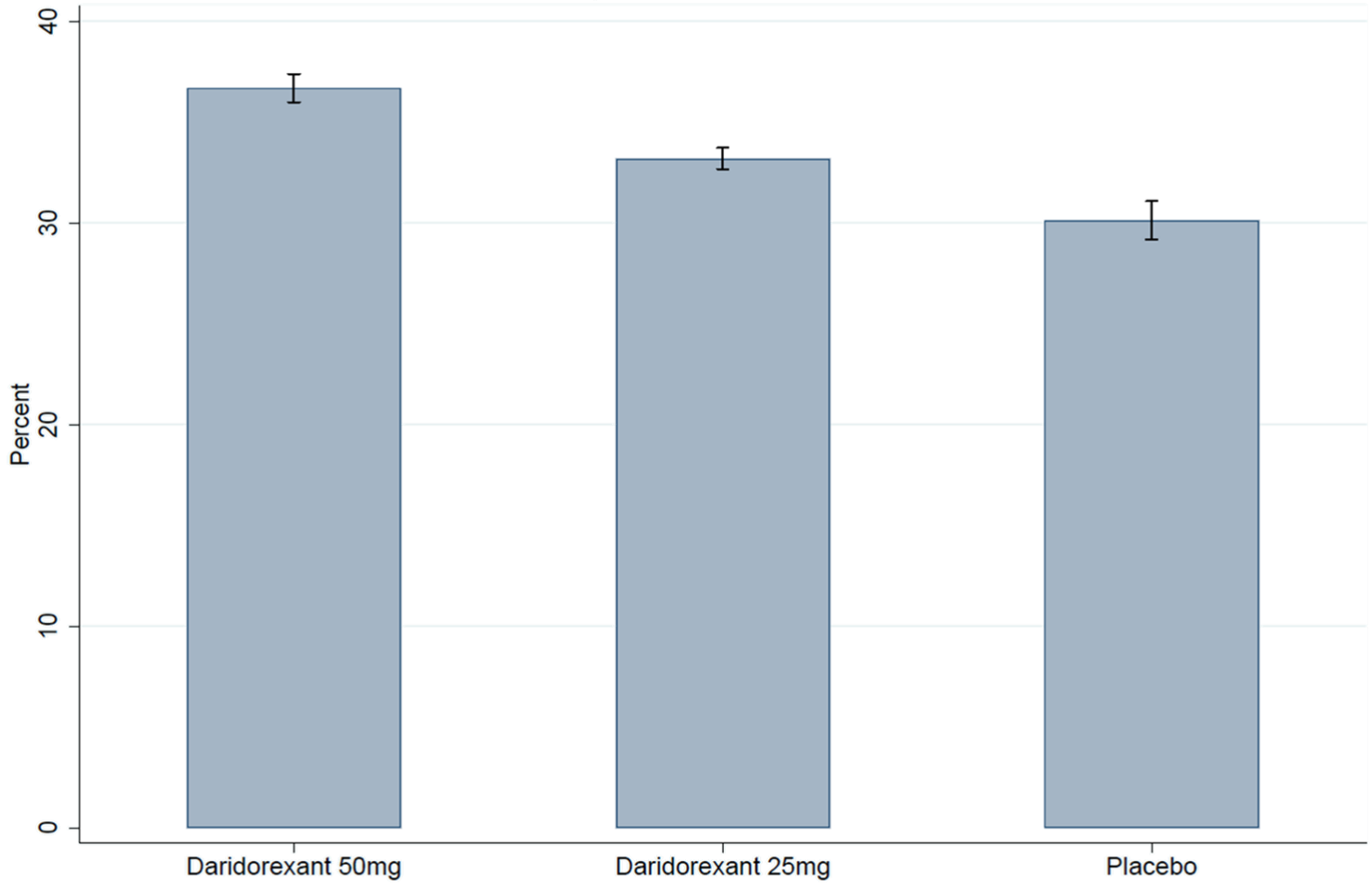
Patients are willing to accept 12.8% additional risk in abnormal thoughts and behavioral changes to improve daytime functioning from restricted to fully functioning ($p < 0.001$).

Severe withdrawal effects can be compensated by improvements from difficultly functioning to fully functioning.

Analysis

Predicted Choice Probabilities

Predicted Choice Probabilities of Daridorexant vs. Placebo

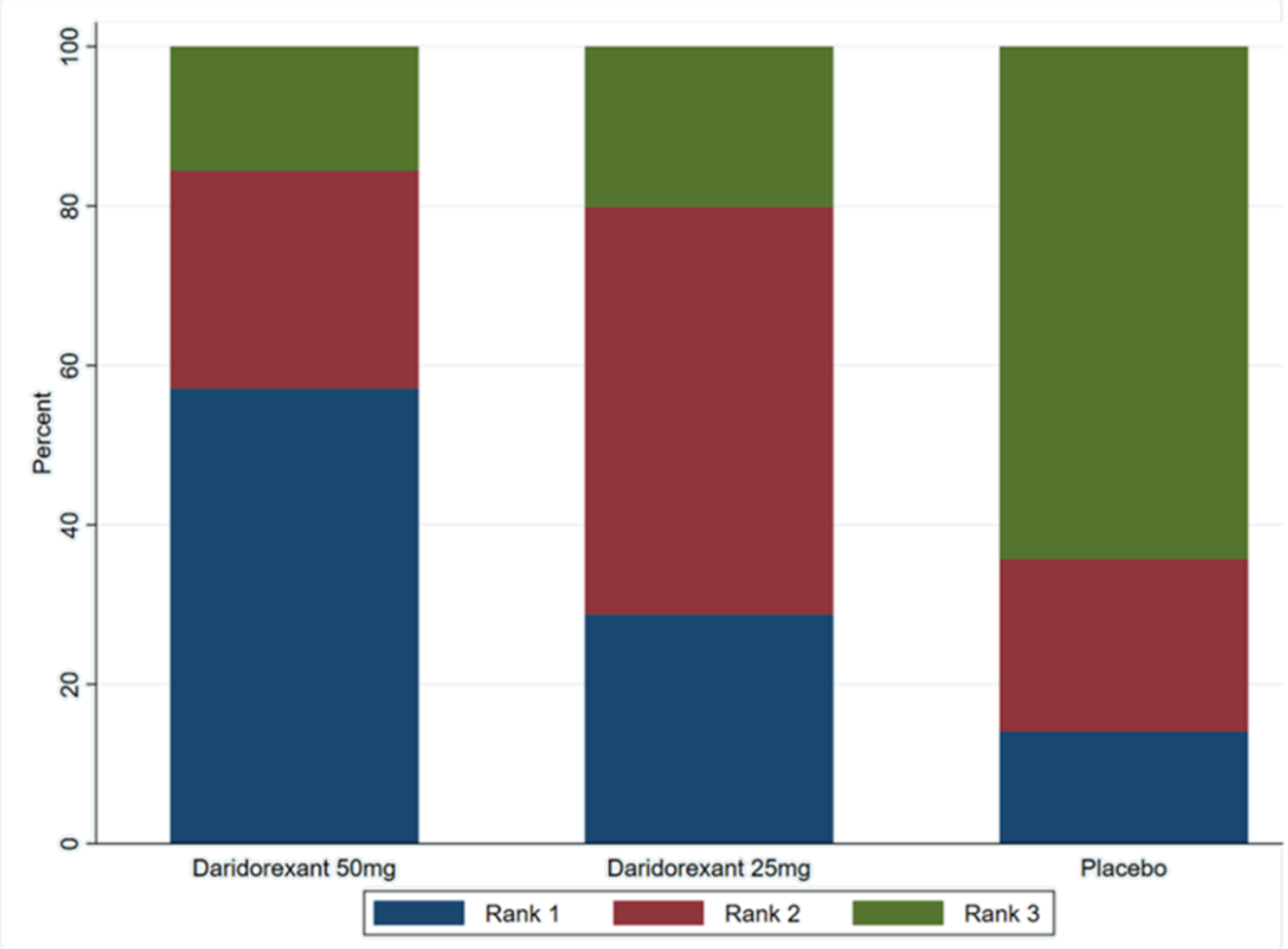


Predicted choice probabilities (PCP) captures the probability of an alternative being preferred over comparators. It is important to be careful when judging the absolute difference, which is a function of the error variance in the model and the assumed functional form of utility. Focusing on significance and rank order is a preferrable approach.

Daridorexant 50 mg (PCP 36.7%) and daridorexant 25 mg (PCP 33.2%) are both significantly preferred (p-value <0.001) over placebo (PCP 30.1%).

Analysis

Interpreting Study Outputs



The impact of uncertainty in both preference and clinical data on the overall value of an alternative can be accounted for in sensitivity analysis. Rank probabilities are the likelihood of a preference rank, given uncertainty in preference and trial data.

Daridorexant 50 mg had a 57.1% chance of having the highest predicted preference rank (Rank 1).

Daridorexant 25 mg had a 51.0% chance of having the second highest preference rank (Rank 2).

Placebo had a 64.3% chance of having the third highest preference rank (Rank 3).

The probability of placebo being preferred over both daridorexant 50 mg and daridorexant 25 mg was 14.1%.

Conclusion and Key messages

- Patient preference studies are an important tool to support the understanding of the trade-offs that patients are willing to make between the benefits and risks of a treatment
- Multiple approaches are possible for the collection of preference data. The decision of what model is appropriate should be based on the objectives of the study
- Patient preference studies should be conducted early in the lifecycle to support the

Product Design
Explore treatment need
Refine TPP
Dose/frequency setting
Device development

Trial Design
Endpoint selection
Endpoint justification
Inform sample size
Support recruitment

Approval
Benefit-risk assessment
Interpret trial data

Reimbursement
Demonstrate value
Demonstrate efficiency

Uptake
Interaction with PAGs
Interaction with prescribers
Decision aid tools

Back-up slides

How Can Patient Preference Data Be Used? – Illustrative Example:

REGULATORY STRATEGY

BACKGROUND

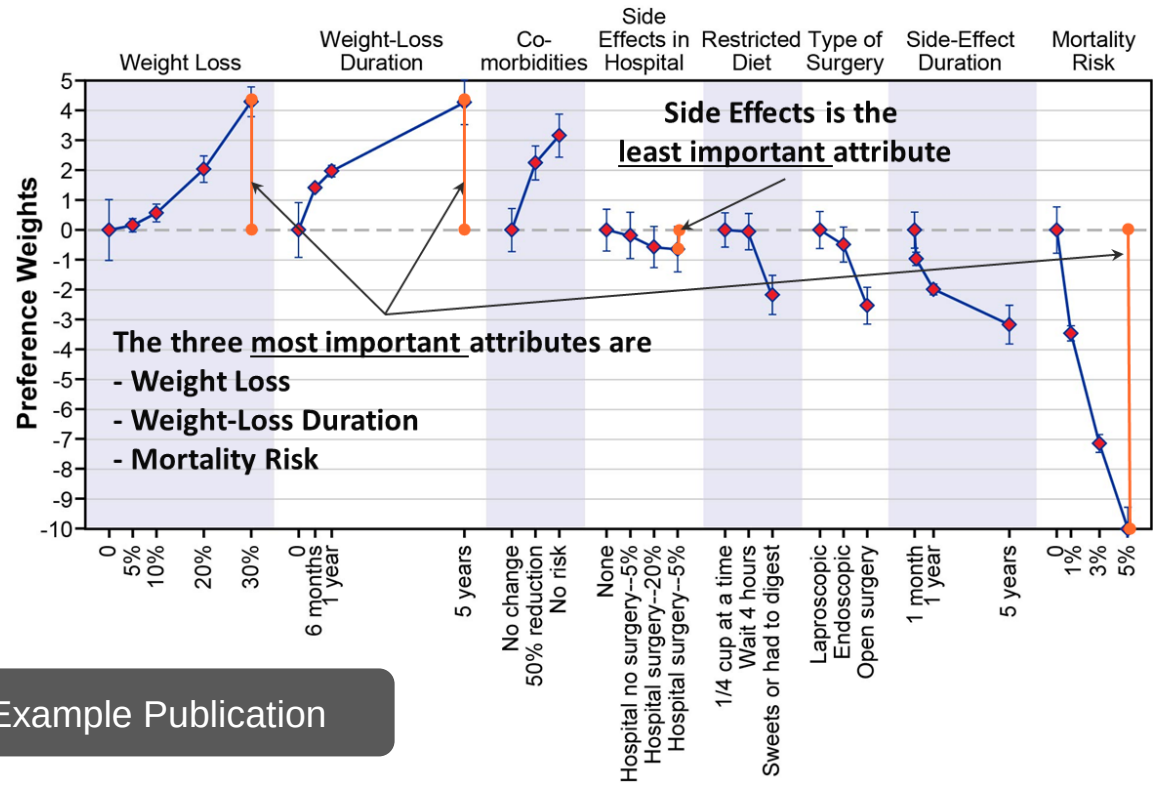
- The FDA's Center for Devices and Radiological Health (CDRH) conducted a pilot preference study.
- No weight loss device had been approved in decades due to not meeting key endpoints.
- Specifically, CDRH was concerned with patients' willingness to accept mortality risks.

APPROACH

- A preference instrument was developed using qualitative research and pilot tested.
- Preferences of N=540 adults in the US with BMI ≥ 30kg/m^2 were elicited and maximum acceptable risk measures obtained.
- The analysis specifically explored how preferences differed between individuals.

IMPACT

- The heterogeneity of patient preferences allowed market approval by showing at least some patients accepted the risks for the given benefit despite endpoints not being met.
- CDRH is using the study to define minimum clinical effectiveness to evaluate new weight-loss devices.



Example Publication

How Can Patient Preference Data Be Used? – Illustrative Example:

HTA STRATEGY

Background

- Under AMNOG, a cost-benefit dossier may be submitted to G-BA in Germany.
- IQWiG economic evaluations require an aggregated benefit function.
- IQWiG trialed a pilot using an efficiency frontier (EF) methodology to assess cost-effectiveness of health technologies.

Approach

- Preferences for Hepatitis C treatments were elicited.
- Treatment outcomes were weighted with partial utilities.
- An EF was derived, and uncertainty analysis was conducted.

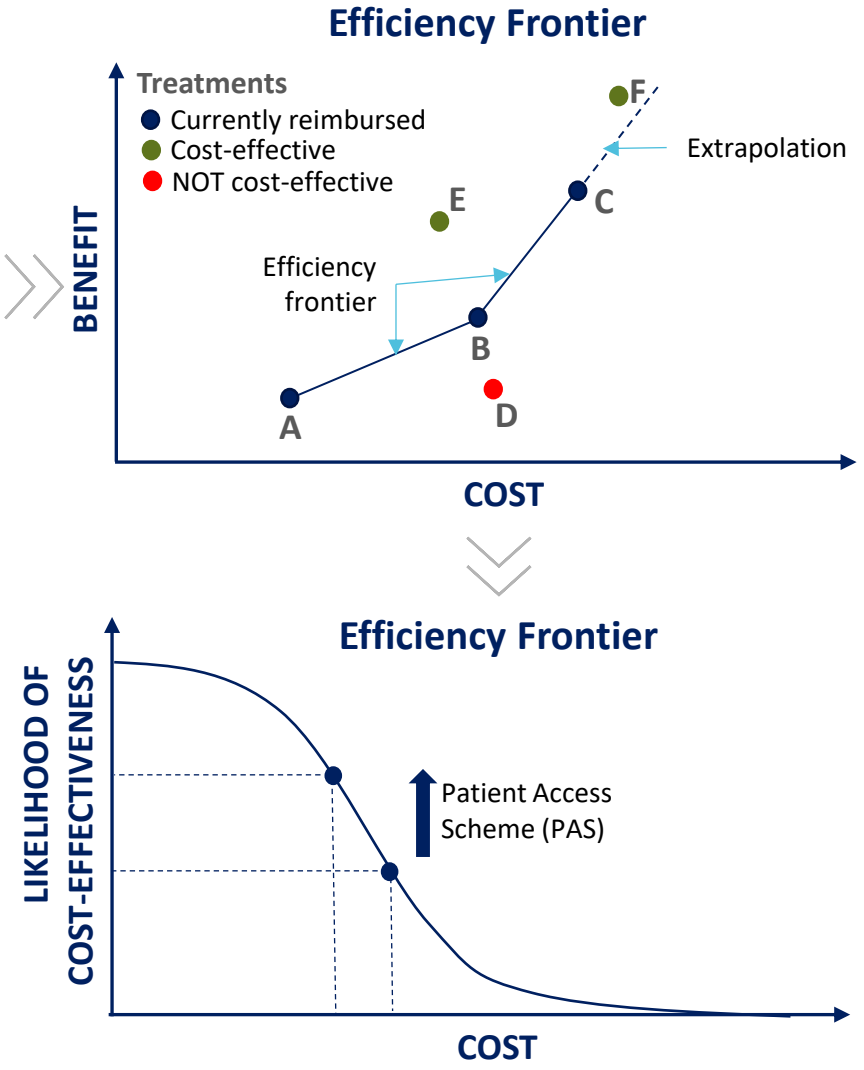
Impact

- For the first time, a study demonstrated how preference data can support a cost-benefit dossier submitted to G-BA in line with IQWIG's method guidance.

PREFERENCES

TRIAL DATA

Example Publication



AMNOG - Arzneimittelmarkt-Neuordnungsgesetz (English translation: "Pharmaceuticals Market Reorganisation Act" in Germany); G-BA - Gemeinsamer Bundesausschuss (English translation: "The Federal Joint Committee" in Germany); IQWiG – Institute for Quality and Efficiency in Health Care

How Can Patient Preference Data Be Used? – Illustrative Example:

COMMERCIAL STRATEGY

BACKGROUND

- In early rheumatoid arthritis, the choice between triple therapy versus methotrexate monotherapy can be driven by individuals benefit-risk preferences.

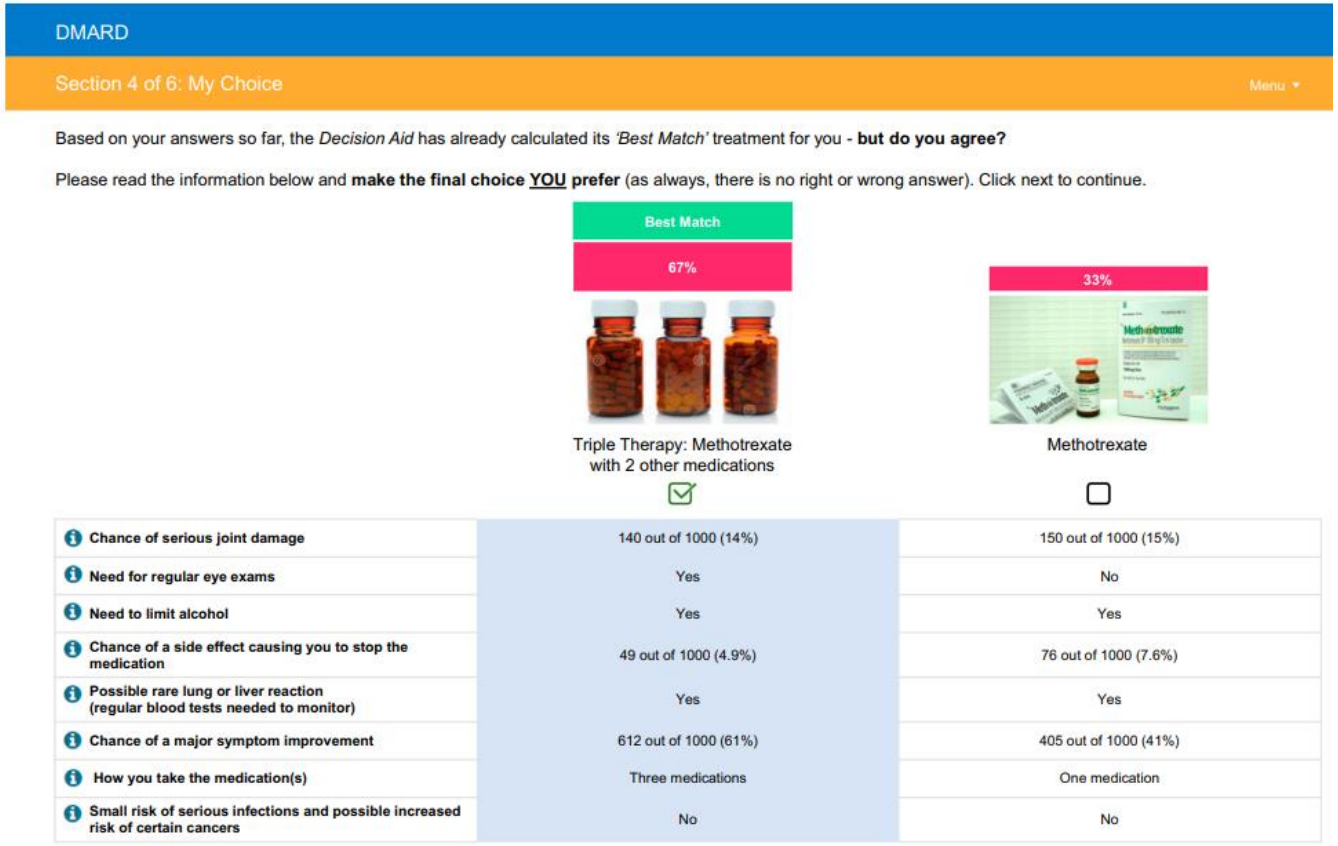
APPROACH

- A pilot study with N=39 patients was used as a proof-of-concept study to develop a decision aid.
- Preferences were elicited and the treatment most aligning with their preferences highlighted.

IMPACT

- Demonstrates how preference data can be used to help, in a shared-decision context, identify the treatment that provides most values to patients
- Shows how preferences can help to widen the clinical paths and nudge people into optimal decisions

Example publication



 AE = adverse event