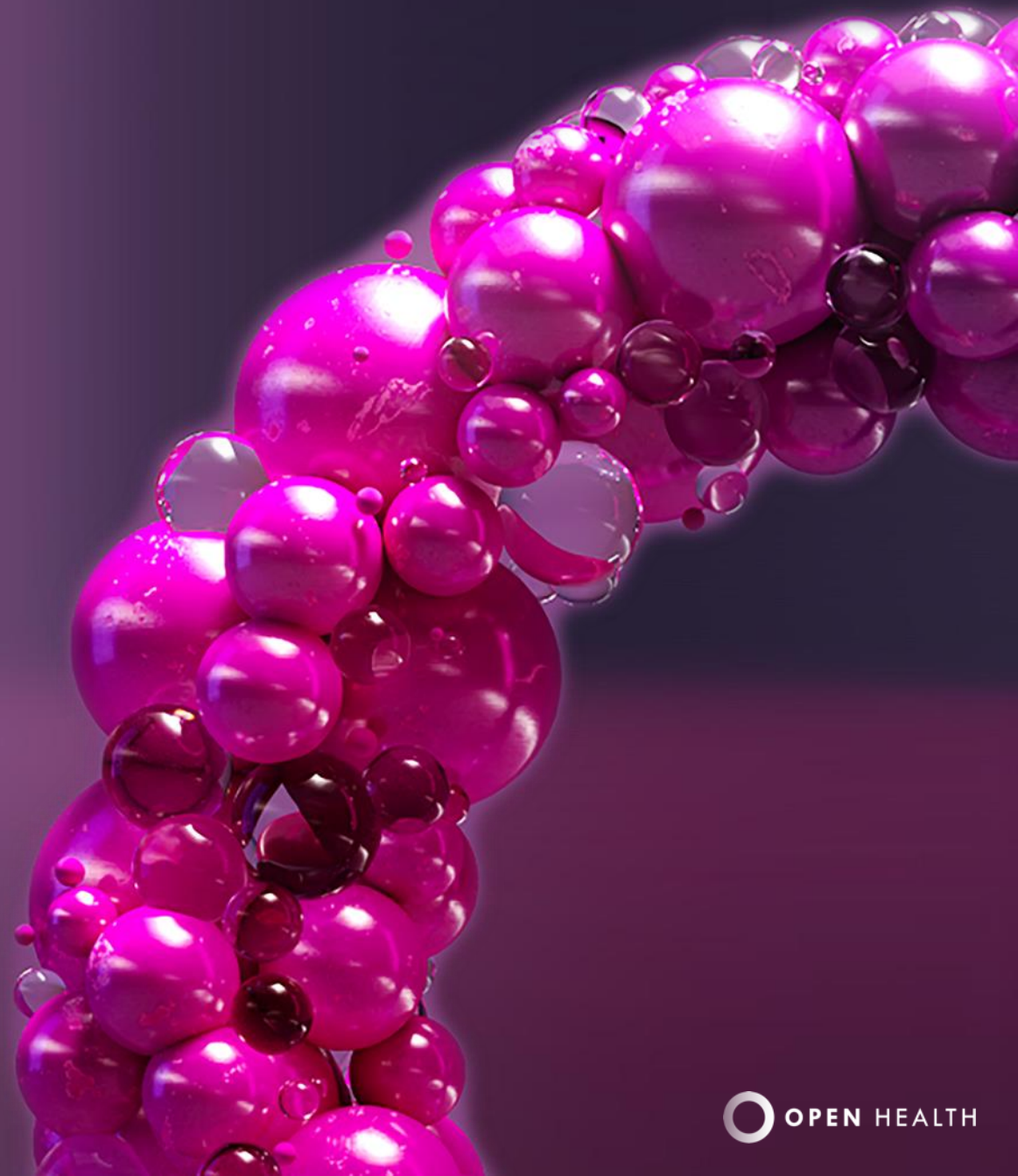
Preference Research in Action: Applications in Pharma

Behavioural Modelling Course 2025
Porto Cristo, Mallorca, Spain | May 7th – May 9th



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Modelling is all good and fun, then you hit reality

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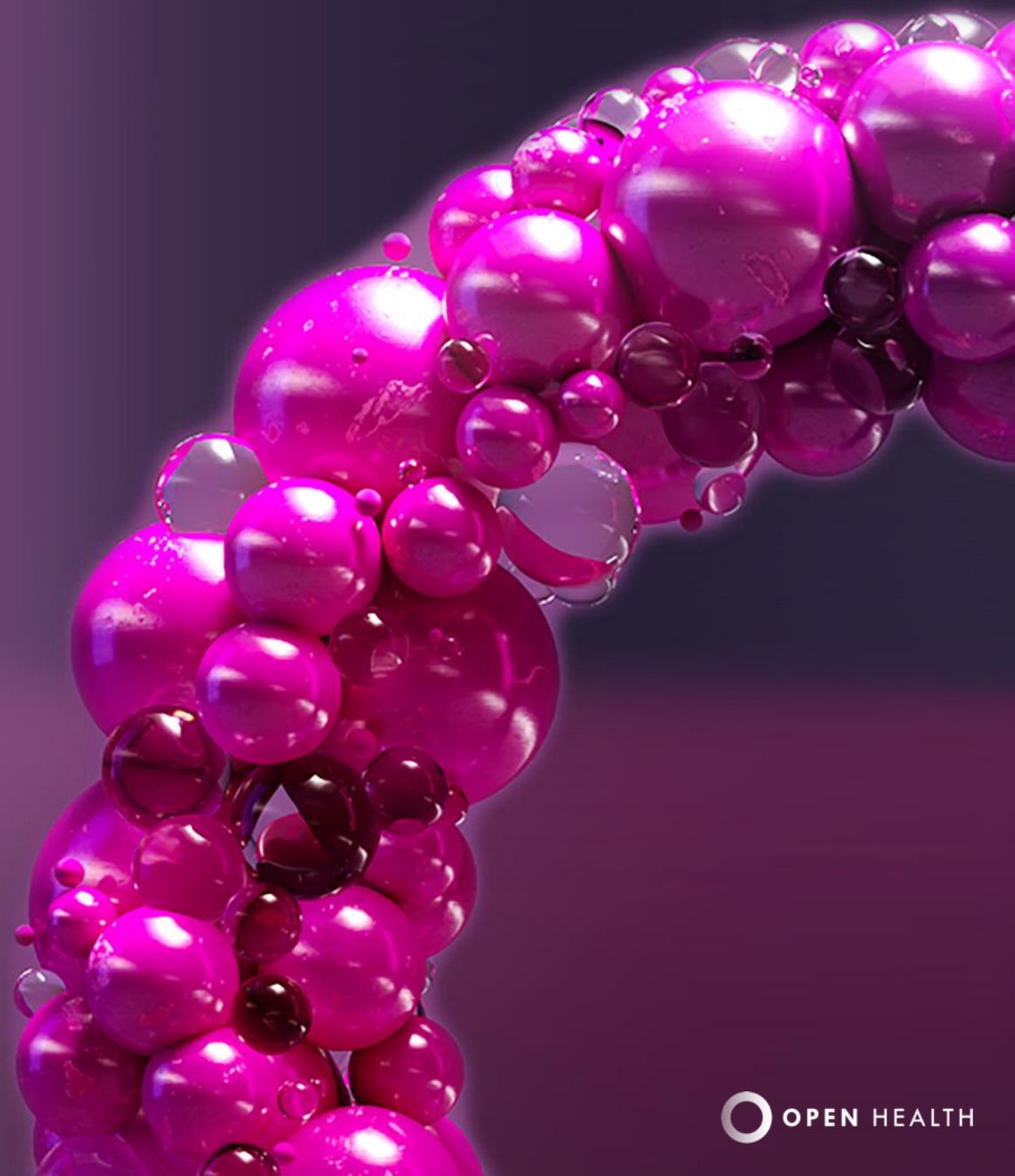

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Content

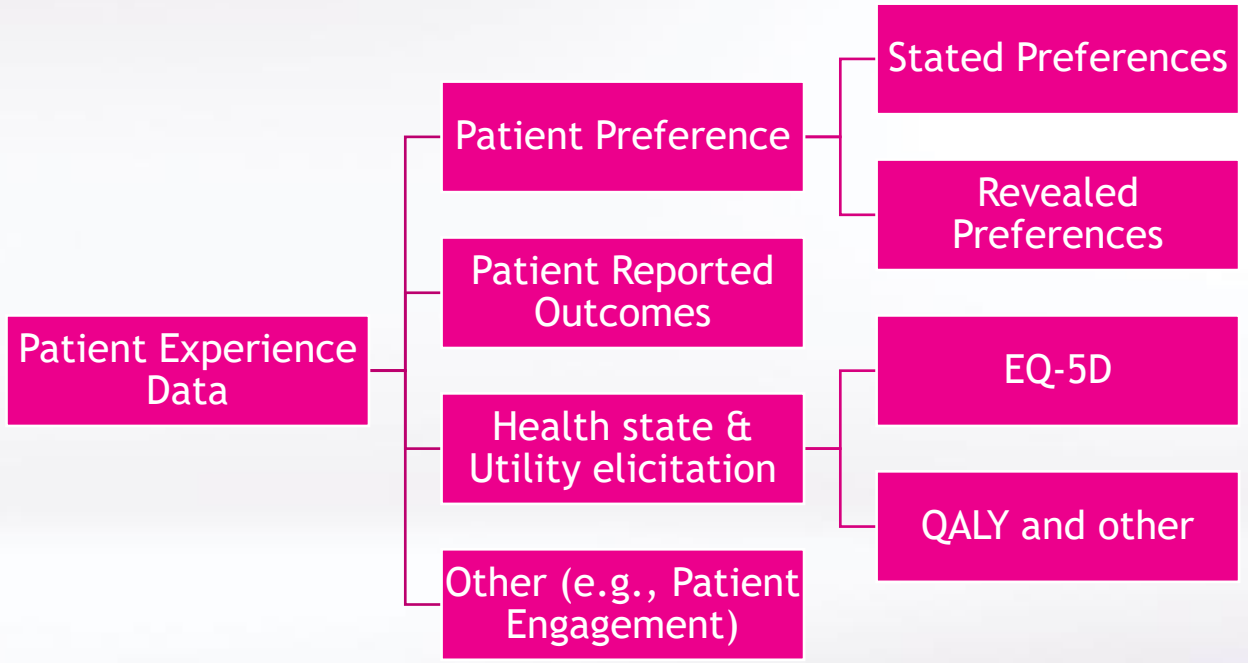
1. Preference Research in Pharma
2. The concept of preference sensitive decisions
3. The use of Preference Research in Regulatory and HTA Decisions
4. Example of Typical Project Output in pharma
5. The focus on Marginal Rates of Substitution (MAR, MAB, WTP) in Pharma
6. Preference Research in clinical settings

1

Preference Research in Pharma

Patient Experience Data

- Patient preference data can help painting the picture of patient experience
- There are multiple methodologies that can be used to collect and analyse patient preference data
  - Patient perspectives/preferences are incorporated
  - Other types of patient centric data are also included (e.g., patient testimony at meetings)
- Not all methods can be used in every decision making
  - Regulatory bodies are more focussed on tradeoffs
  - HTA bodies are more focussed on comparison across new and existing drugs, particularly focussed on value (Cost-Effectiveness modelling)



Adapted from Medical Device Innovation Consortium (MDIC). Patient centered benefit-risk project report. Available at: https://mdic.org/wp-content/uploads/2018/05/MDIC_PCBR_Framework_Web.pdf. Accessed 16 Oct 2023

Many Stated Preference Methodologies

- Many preference methods are accepted and used
- IMI-PREFER taxonomy (Soekhai et al., 2019) of widely used preference methodologies:

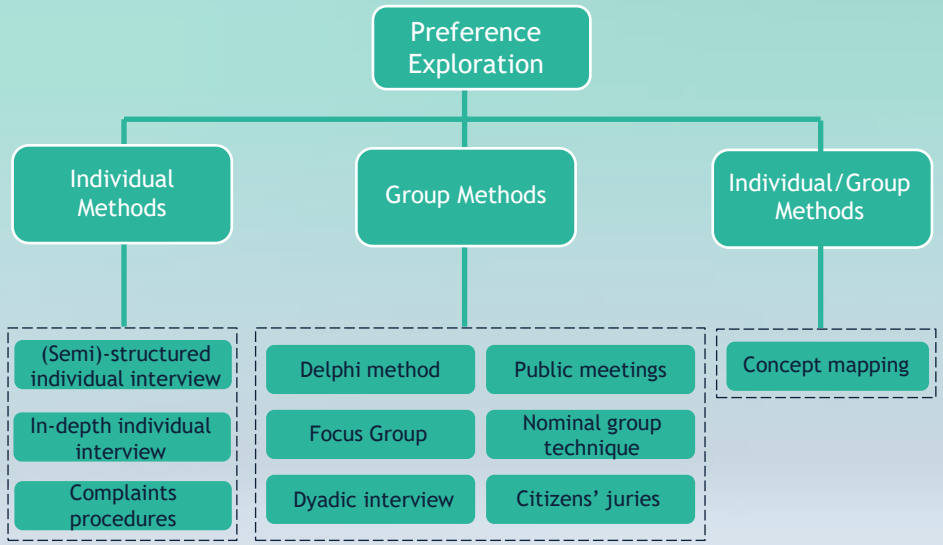


Figure 1
Grouping of preference exploration (qualitative) methods into three groups: Individual, group and individual/group methods.

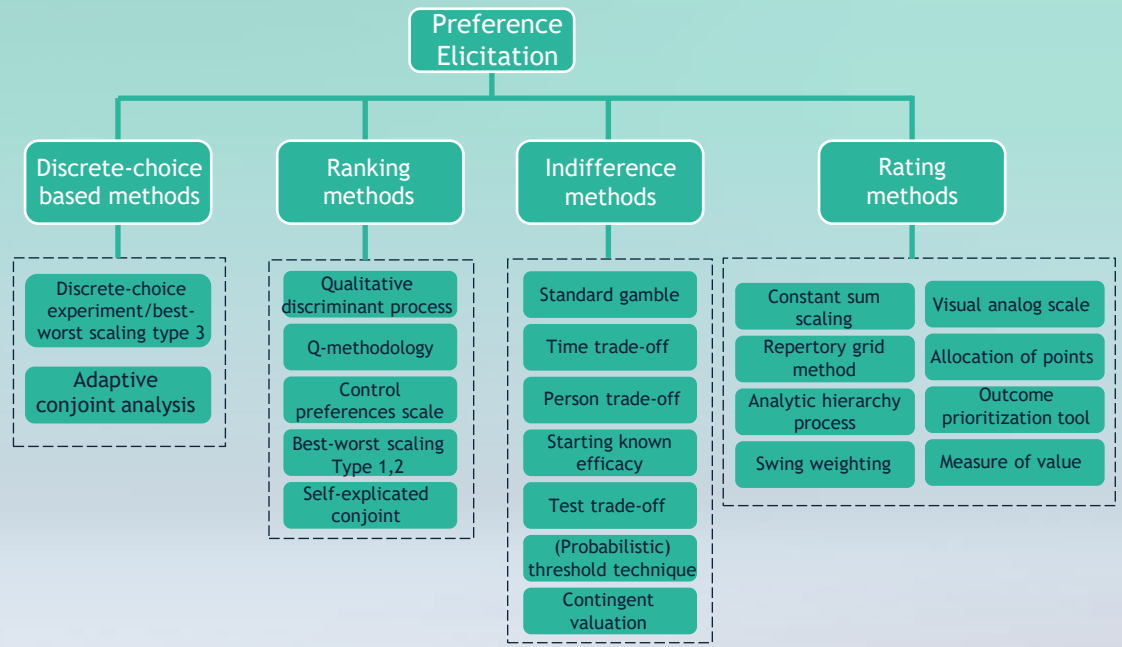


Figure 2
Grouping of preference elicitation (quantitative) methods into four groups: Discrete choice based, ranking, indifference and rating methods.

Source: Soekhai V, Whichello C, Levitan B, Veldwijk J, Pinto CA, Donkers B, Huys I, van Overbeeke E, Juhaeri J, de Bekker-Grob EW. Methods for exploring and eliciting patient preferences in the medical product lifecycle: a literature review. Drug Discov Today. 2019;24(7):1324-31. doi: 10.1016/j.drudis.2019.05.001.

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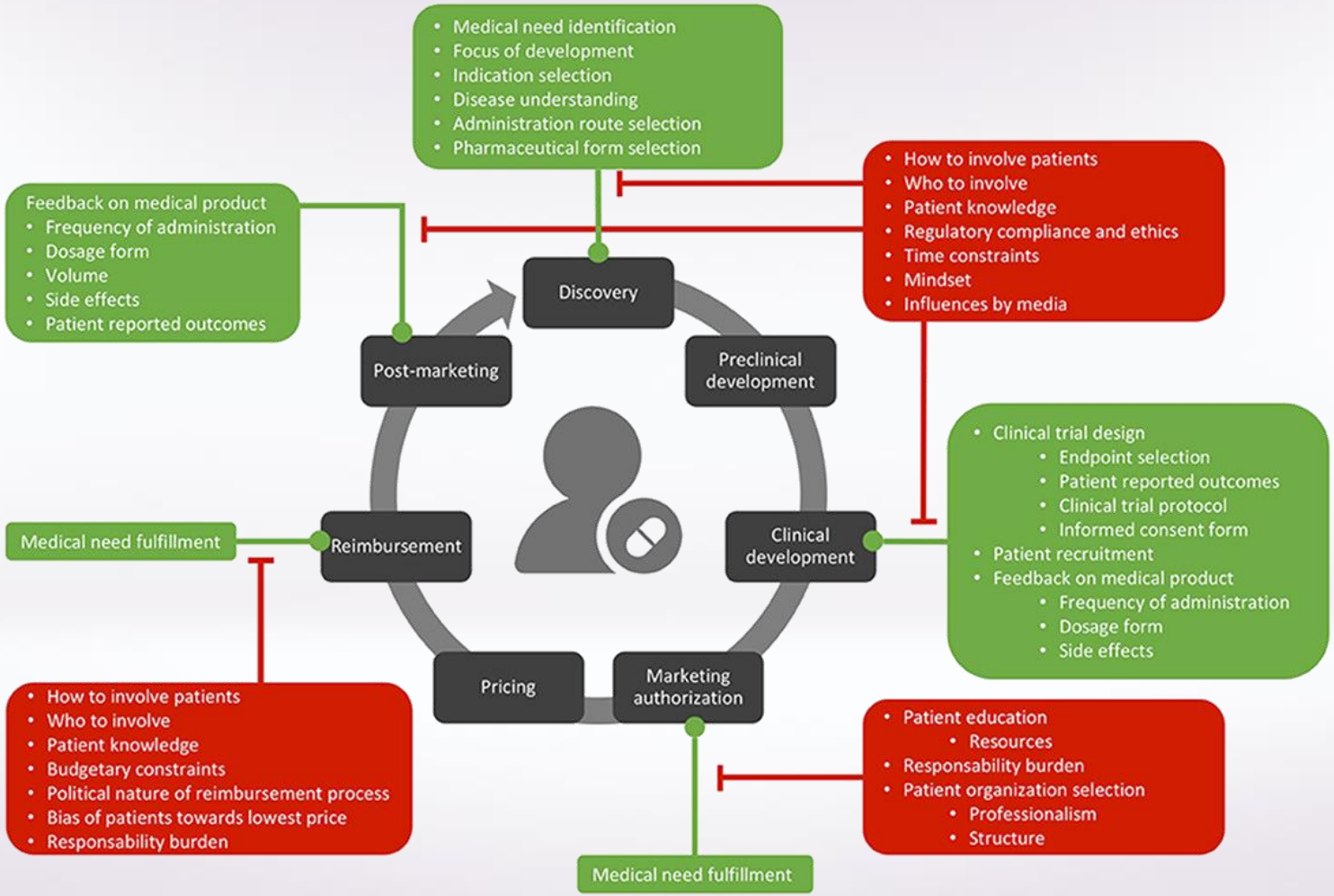
Patient Data in the Lifecycle of Medicines



- Source: Janssens R, van Overbeeke E, Verswijvel L, Meeusen L, Coenegrachts C, Pauwels K, Dooms M, Stevens H, Simoens S, Huys I. Patient Involvement in the Lifecycle of Medicines According to Belgian Stakeholders: The Gap Between Theory and Practice. Front Med (Lausanne). 2018 Oct 11;5:285. doi: 10.3389/fmed.2018.00285. PMID: 30364285; PMCID: PMC6193089.

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Applications of patient preferences in the Lifecycle of Medicines

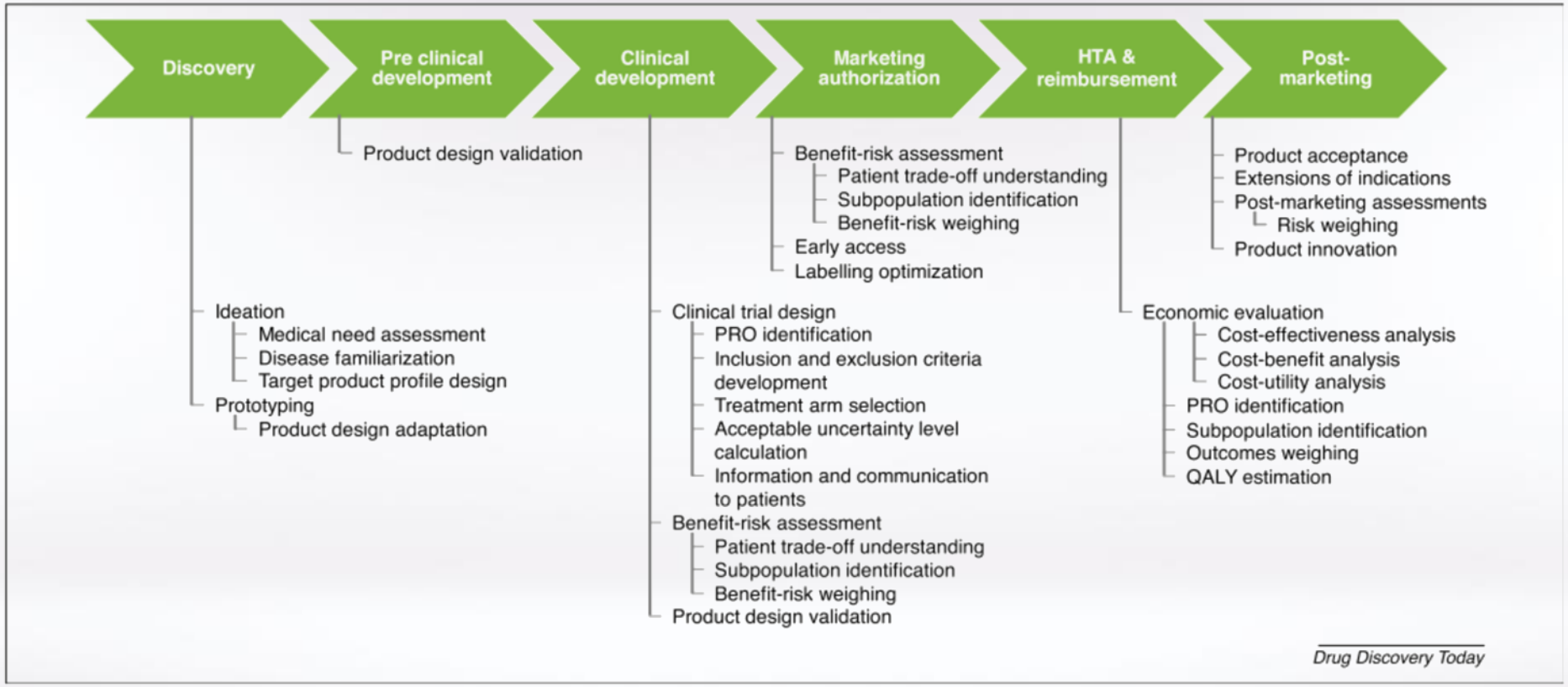

FIGURE 1

Applications of patient preferences along the medical product lifecycle (MPLC). Applications of patient preferences were mapped along the phases of the MPLC. Applications were identified for all phases of the MPLC. Stages of the MPLC and their organization were identified as they emerged from the literature. Abbreviations: HTA, Health Technology Assessment; PRO, patient-relevant outcomes; QALY, quality-adjusted life year.

- Source: Van Overbeeke E, Whichello C, Janssens R, Veldwijk J, Cleemput I, Simoens S, et al. Factors and situations influencing the value of patient preference studies along the medical product lifecycle: a literature review. Drug Discov Today. 2019;24(1):57-68.

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Factors And Situations Influencing The Value Of Patient Preference Studies for Pharma (and others)

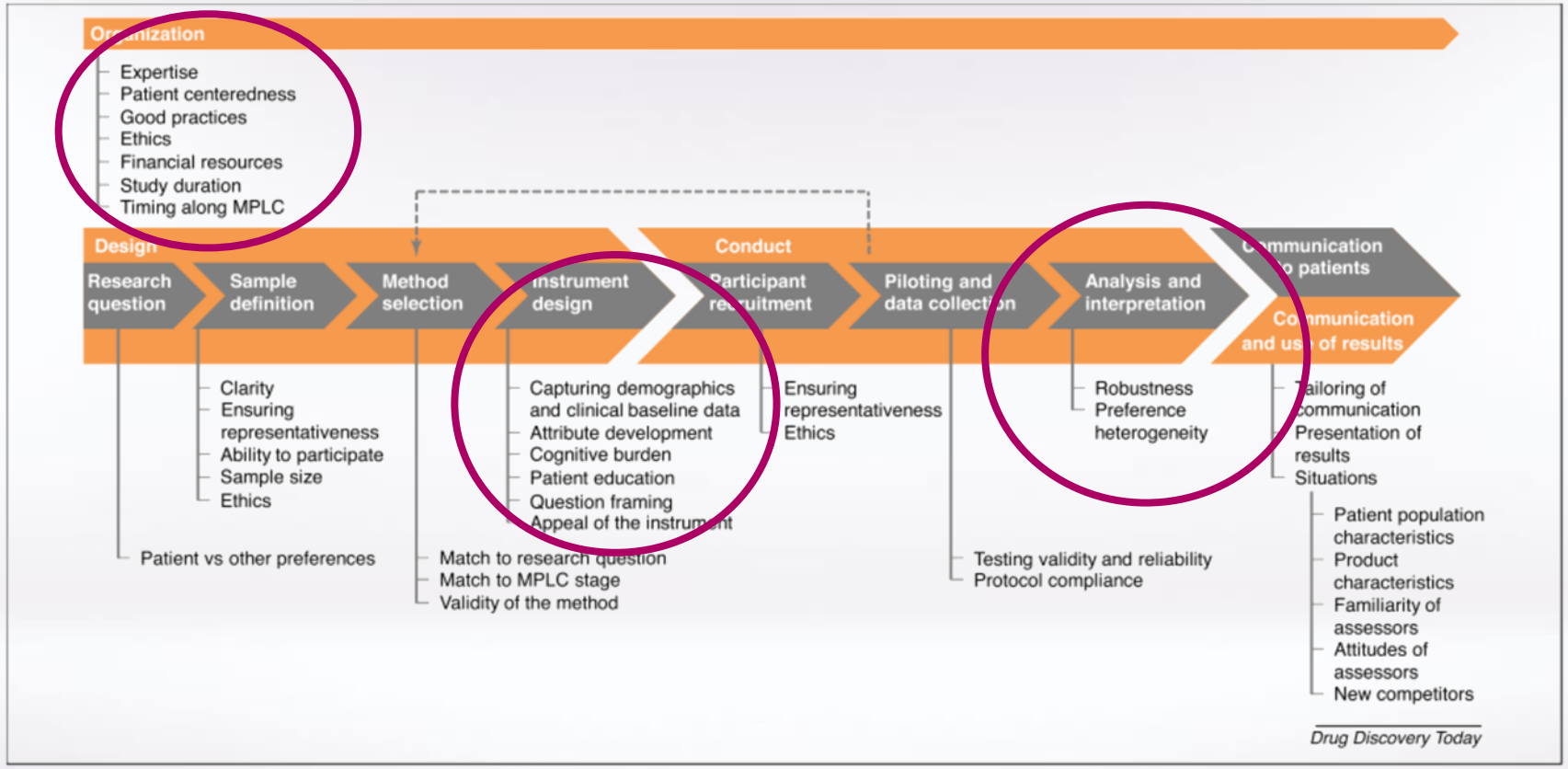

FIGURE 2

Factors and situations influencing the value of patient preference studies. Factors and situations were mapped along the organization, design, conduct, and communication and use of results of patient preference studies. Stages and steps of patient preference studies and their organization were identified as they emerged from the literature. Abbreviations: MPLC, medical product lifecycle.

- Source: Van Overbeeke E, Whichello C, Janssens R, Veldwijk J, Cleemput I, Simoens S, et al. Factors and situations influencing the value of patient preference studies along the medical product lifecycle: a literature review. Drug Discov Today. 2019;24(1):57-68.

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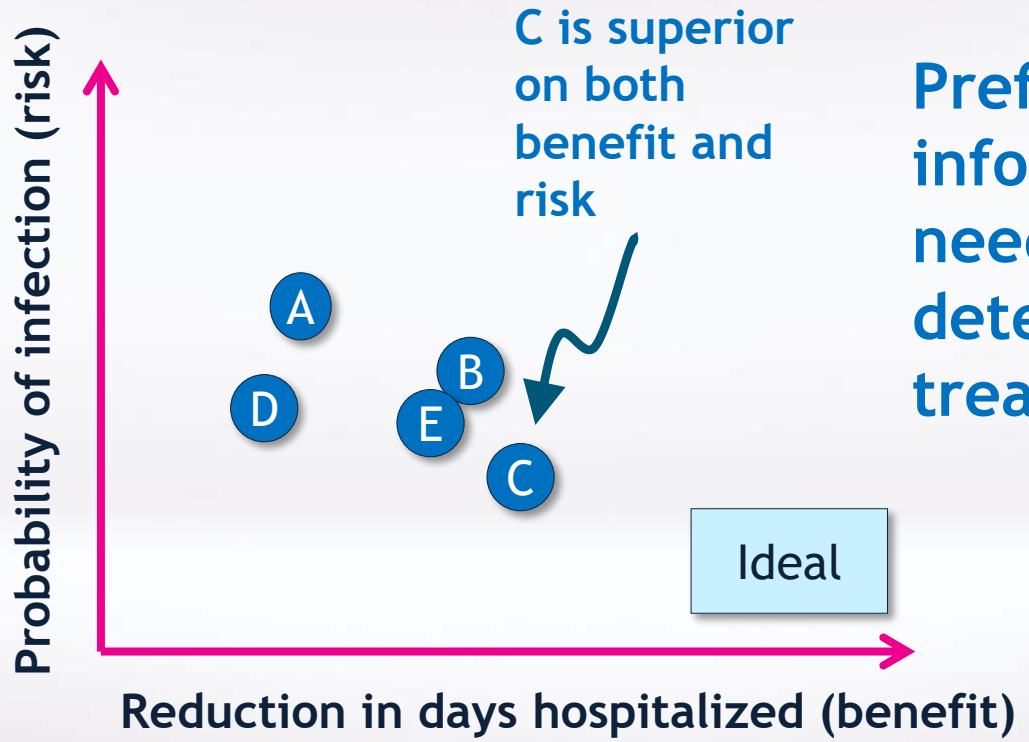
Example Research Questions We Can Answer with Preference Research

1. What are the drivers of treatment choice in specific conditions?
2. What are the priorities for patients, physicians, or other stakeholders?
3. What is the relative importance to patients, physicians, or other stakeholder of the outcomes and features associated with different treatments?
4. What tradeoffs would patients and physicians be willing to make between efficacy (e.g., reduction in serious depression episodes) and tolerability (e.g., weight gain)?
5. How heterogeneous are these results across different types of respondents? (e.g., do patients with different sociodemographics have different preferences?)
6. Can we identify segments based on preferences?
7. What is the probability that a patient, physician, or other stakeholder would choose a treatment profile compared to another one with different levels of the attributes included in the study?

2

The concept of preference sensitive decisions

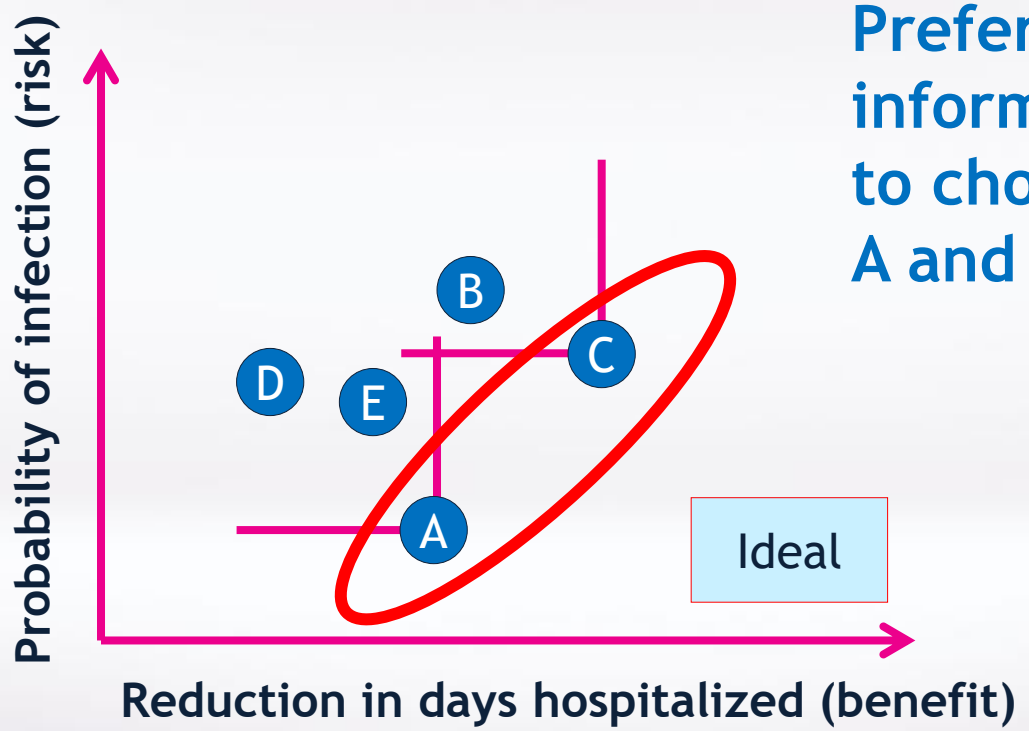
Which Treatment is Best?



Preference information is not needed to determine the best treatment

- Source: MDIC Patient Centered Benefit-Risk Framework Report Public Release, May 13,2015 http://mdic.org/pcbr-framework-report-release/

Now Which Treatment is Best?

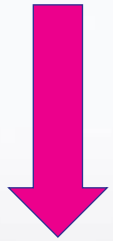


Preference information is needed to choose between A and C

- Source: MDIC Patient Centered Benefit-Risk Framework Report Public Release, May 13,2015 http://mdic.org/pcbr-framework-report-release/

Preference Sensitive Decisions

- Preference sensitive decisions
  - Those decisions in which there are multiple options (diagnostic or treatment) and the decision as to which option to pursue depends upon the preferences of the decision maker.



    - No option is clearly superior over a plausible range of preferences (or the evidence supporting one option over others is considerably uncertain)

- Source: Medical Device Innovation Consortium (2015) http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web1.pdf
- Elwyn G, Frosch D, Rollnick S. Dual equipoise shared decision making: definitions for decision and behaviour support interventions. Implement Sci. 2009;4:75.

3

The use of Preference Research in Regulatory and HTA Decisions

Patient Preference Studies (PPS) are important evidence in drug development

The FDA has launched a project dedicated to Patient-focused Drug Development (PFDD)

"PFDD is a systematic approach to help ensure patients' experiences, perspectives, needs and priorities are captured and meaningfully incorporated into drug development and evaluation."

FDA is developing a series of four methodological patient-focused drug development (PFDD) guidance documents to address, in a stepwise manner, how stakeholders can collect and submit patient experience data and other relevant information from patients and caregivers for medical product development and regulatory decision making. This series of guidance documents is intended to facilitate the advancement and use of systematic approaches to collect and use robust and meaningful patient and caregiver input that can better inform medical product development and regulatory decision making.

These guidances are part of FDA's PFDD efforts in accordance with the 21st Century Cures Act and The Food and Drug Administration Reauthorization Act of 2017 Title I.

This webpage contains information and documents related to FDA's development of the methodological PFDD guidances, including public workshops, draft guidances, and hypothetical scenarios, which are all intended to serve as a basis for dialogue. For an outline of FDA's planned timeframe for development of the guidance, please refer to the Plan for Issuance of Patient-Focused Drug Development Guidance.

- **Guidance 1: Collecting Comprehensive and Representative Input**
- **Guidance 2: Methods to Identify What is Important to Patients**
- **Guidance 3: Selecting, Developing or Modifying Fit-for-Purpose Clinical Outcomes Assessments**
- **Guidance 4: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making**

- https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development

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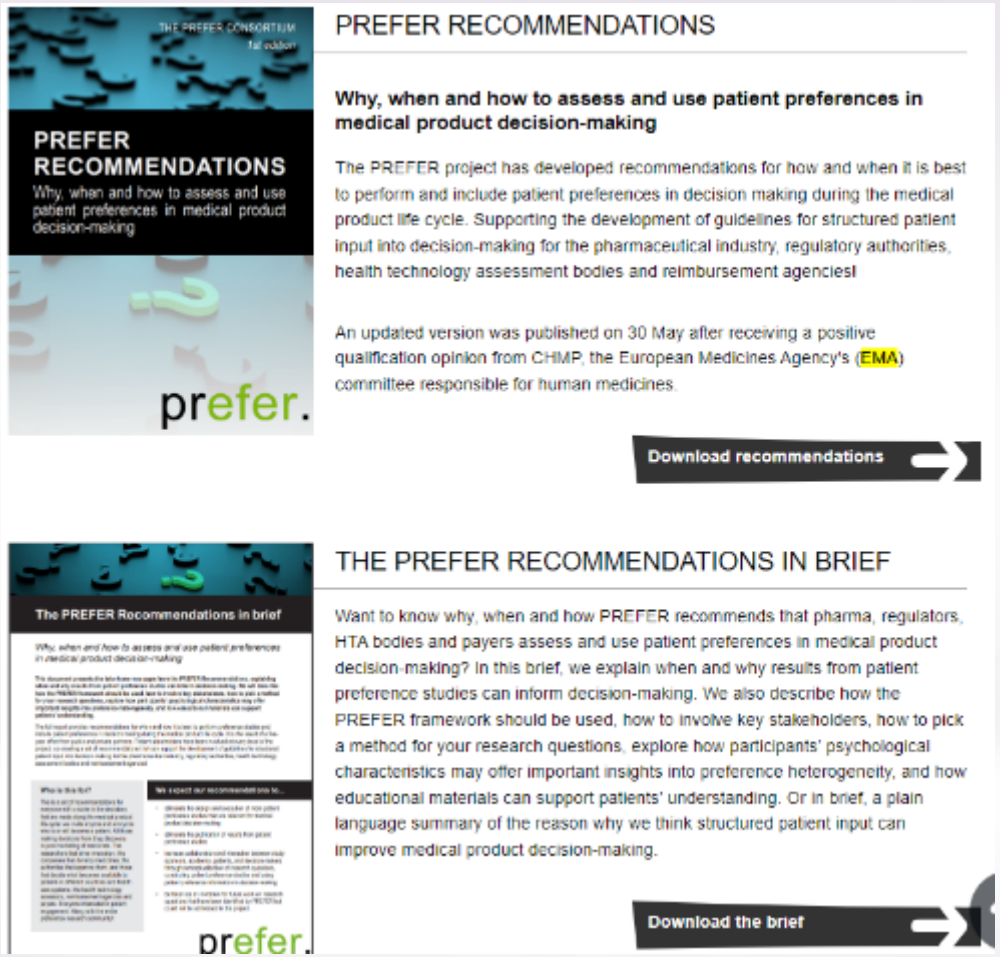
EMA have given a positive qualification opinion on the IMI-PREFER recommendations



- https://www.ema.europa.eu/en/documents/scientific-guideline/ich-reflection-paper-proposed-ich-guideline-work-advance-patient-focused-drug-development-pfdd_en.pdf
- https://www.imi-prefer.eu/

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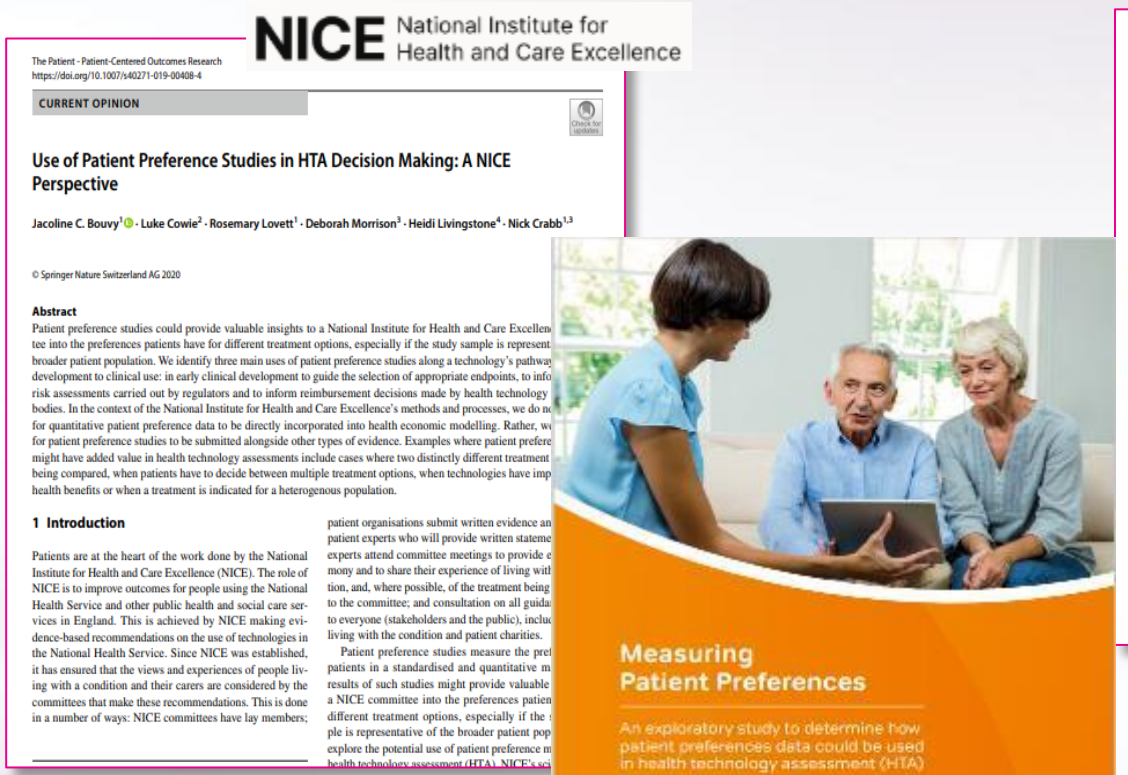
HTA bodies, including NICE, have also shown an increasing interest in Patient Preference Studies to inform their decision-making



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Preference Studies in Regulatory Decisions are longer as Involve More Stakeholders

- Need to use Patient centered background research to identify research questions, relevant attributes, and potential subgroups (patient centered research must engage patients)
  - Attributes must be important to patients but should also be tied to clinical study endpoints
- Need to involve FDA in the design of the research (inception, key decisions in protocol and survey design)
  - Attribute should reflect what is important for FDA's decisions
  - Attributes are described in a way that is acceptable to FDA
  - Check question format (i.e., inclusion of Opt-out) with FDA
- Obtain transcripts of qualitative research
- Pretest and inclusion of comprehension questions to demonstrate that:
  - survey instrument is understandable to patients and reliably elicits PPI
  - attribute levels are understood by patients and encompass what is relevant and realistic for patients and clinically
  - Inclusion of scope test, validity tests such as dominated pairs, monotonicity, repeated questions might be needed
- Confirmed diagnosis and top rated sampling strategy might be required (not rely on commercial panels only)
- Follow good research practice (e.g., ISPOR).

Why Patient Preference Elicitation in Regulatory Decision?

Approval:

- VBLOC Maestro® Rechargeable System: FAILED one primary endpoint, but it was APPROVED!
  - FDA-sponsored preference survey showed a group of patients would accept the risks
- Patient preferences mentioned by EMA in ritlecitinib approval for alopecia areata (AA)
  - "Given the high value patients with severe AA placed on scalp hair regrowth in the patient preference studies in adults and adolescents, the net B/R for ritlecitinib 50 mg, compared to no treatment, is considered positive from the patient's perspective."

https://www.ema.europa.eu/en/documents/assessment-report/litfulo-epar-public-assessment-report_en.pdf

Inclusion in Label:

- Subcutaneous vs. Intravenous Rituximab
  - Simple design
  - Open-label cross-over design
  - Compared IV vs. SC (both experienced)

https://www.gene.com/download/pdf/rituxan_hycela_prescribing.pdf

Post Approval, Market Access

- Scientific Publications

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Not all methods can be used in every decision making

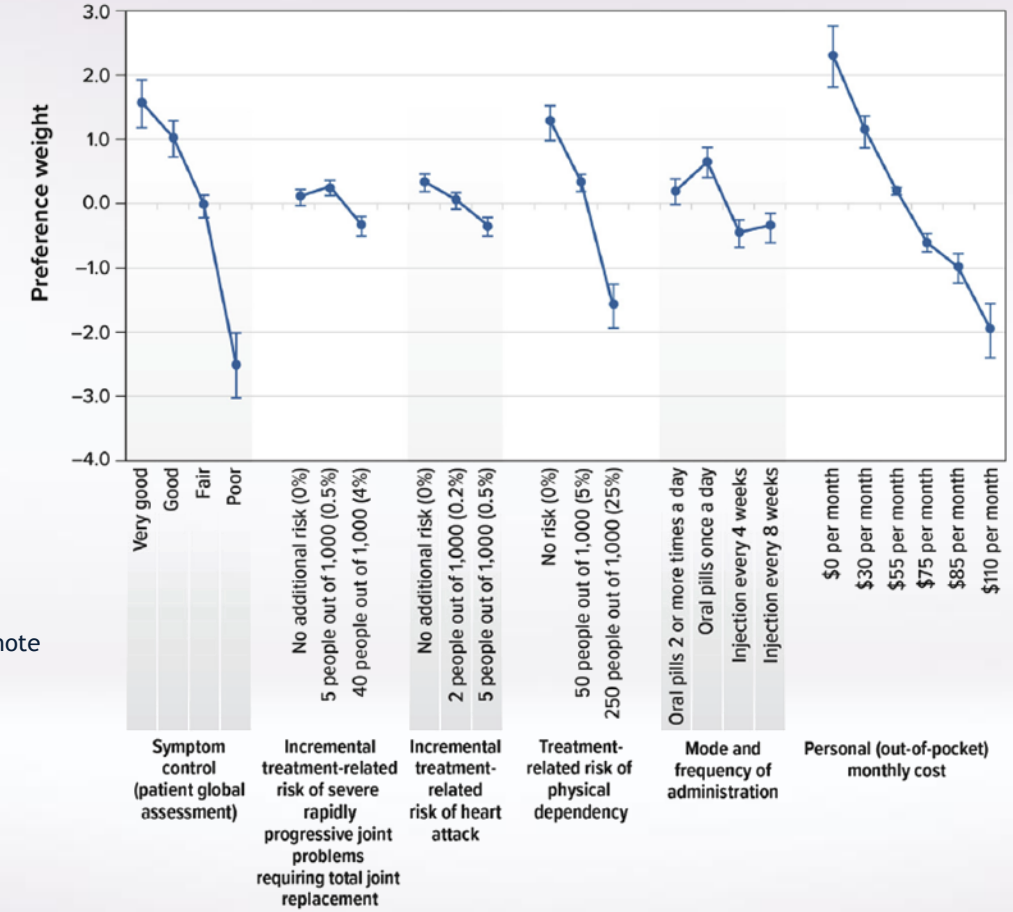
- Regulatory bodies are more focussed on tradeoffs
  - Preference research (i.e., using DCE) is welcome and acceptable as evidence to support decision making
  - Maximum Acceptable Risk and Minimum Acceptable Benefit are key to inform decisions

- HTA bodies are more focussed on comparison across new and existing drugs, particularly focussed on value
  - Cost-Effectiveness modelling is more important; Quality of life, evaluated at general population level (QALY), utility measures from standard gamble and time-trade off studies.

4

Example of Typical Project Output in pharma

Example Results Generated from DCE



The vertical bars surrounding each mean preference weight denote the 95% confidence interval (computed by delta method).

Turk D, Boeri M, Abraham L, Atkinson J, Bushmakin AG, Cappelleri JC, et al. Patient preferences for osteoarthritis pain and chronic low back pain treatments in the United States: a discrete-choice experiment. Osteoarthritis Cartilage. 2020;28(9):1202-13.

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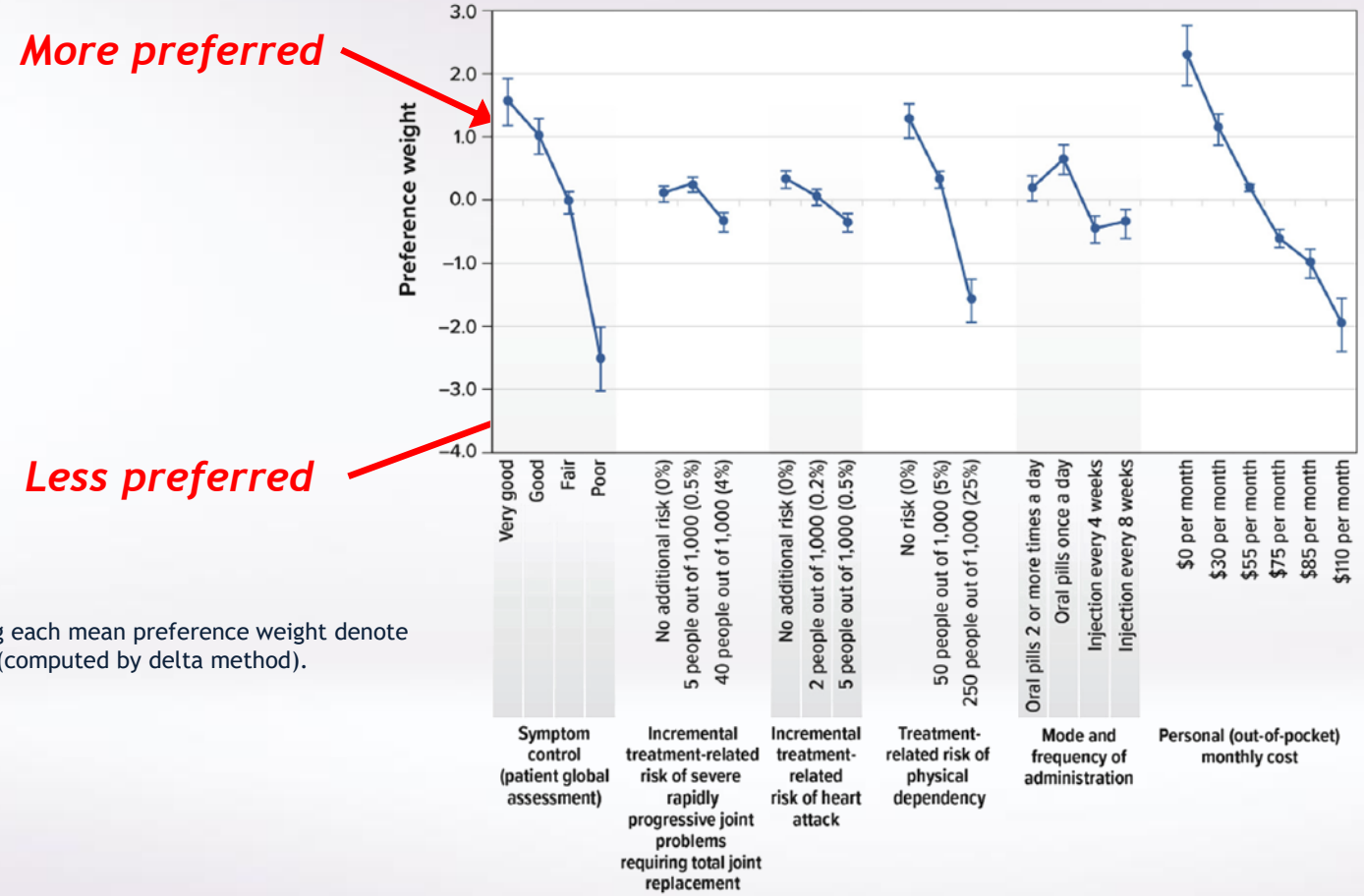

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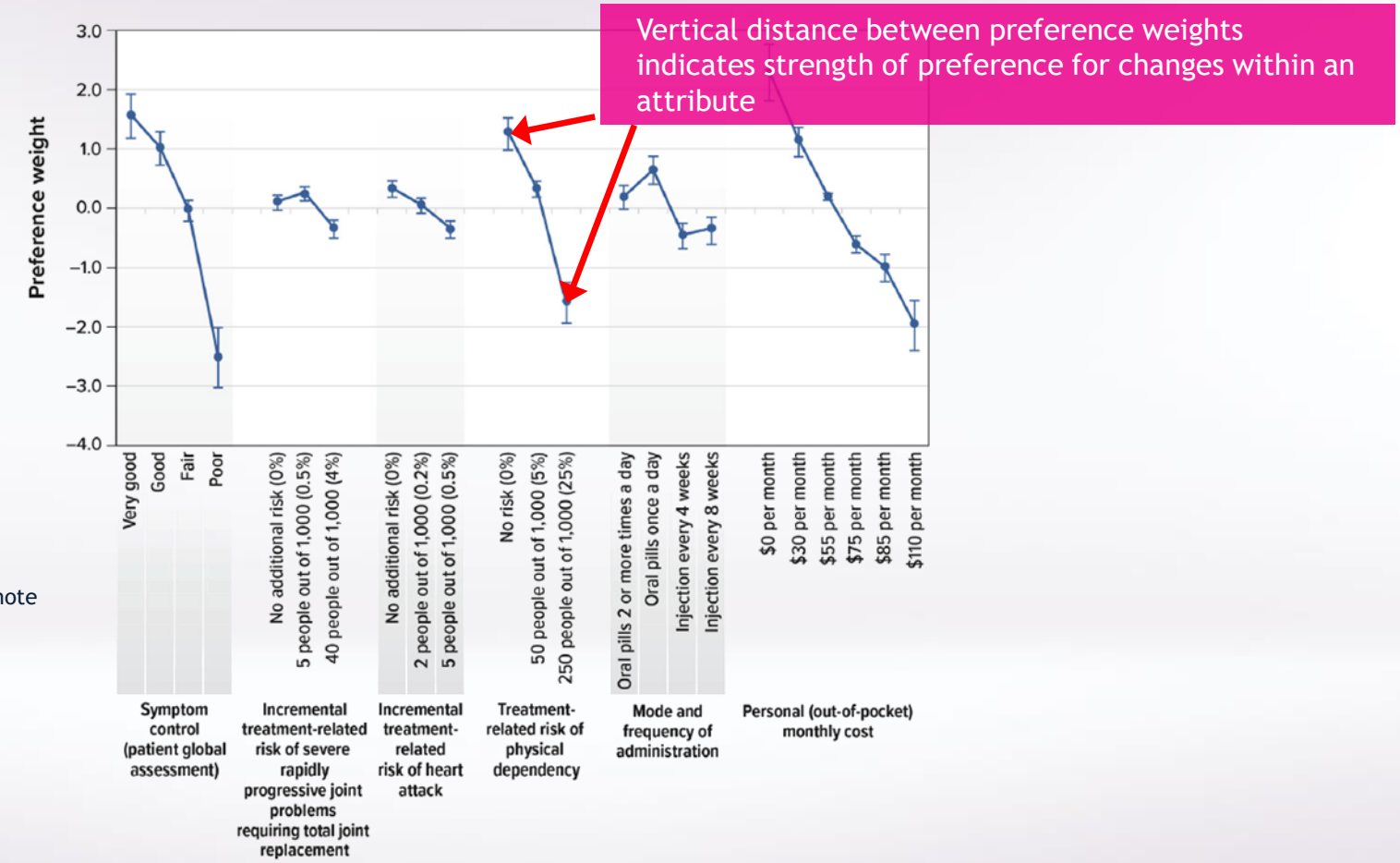

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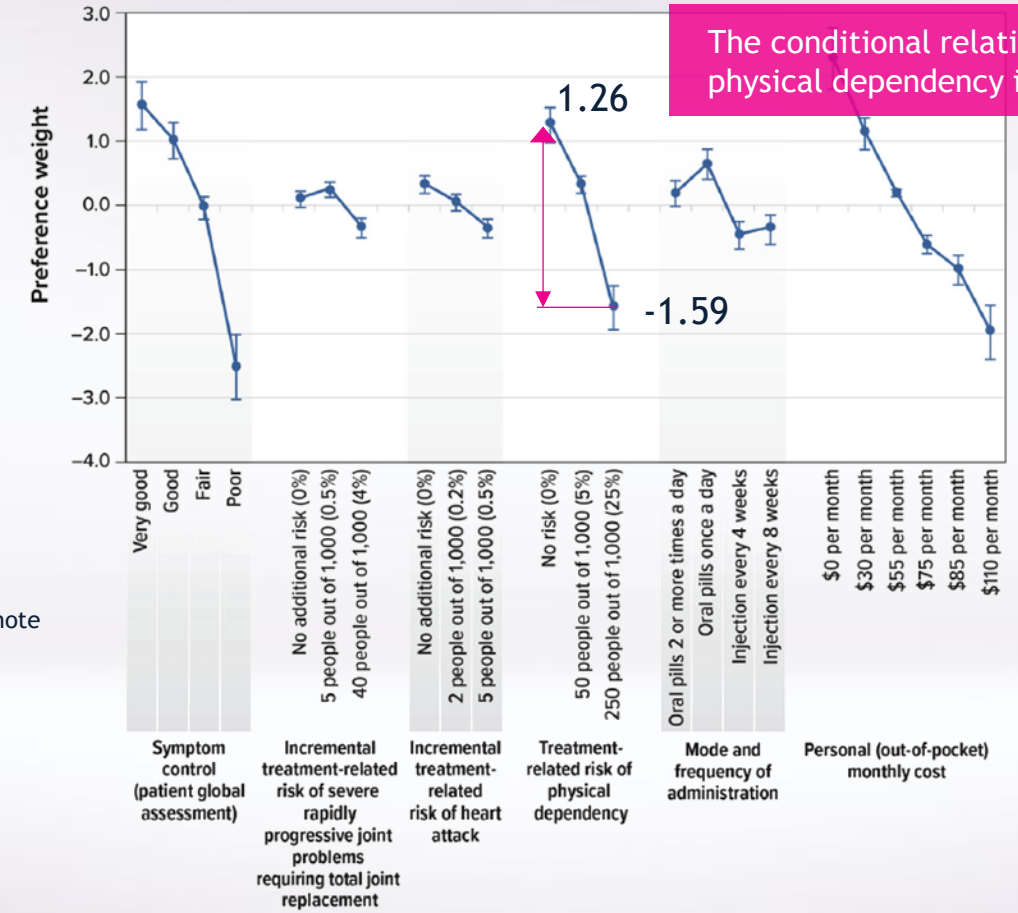

The conditional relative importance of treatment related risk of physical dependency is 2.85 (2.85 = 1.26 − [−1.59]).

The vertical bars surrounding each mean preference weight denote the 95% confidence interval (computed by delta method).

Turk D, Boeri M, Abraham L, Atkinson J, Bushmakin AG, Cappelleri JC, et al. Patient preferences for osteoarthritis pain and chronic low back pain treatments in the United States: a discrete-choice experiment. Osteoarthritis Cartilage. 2020;28(9):1202-13.

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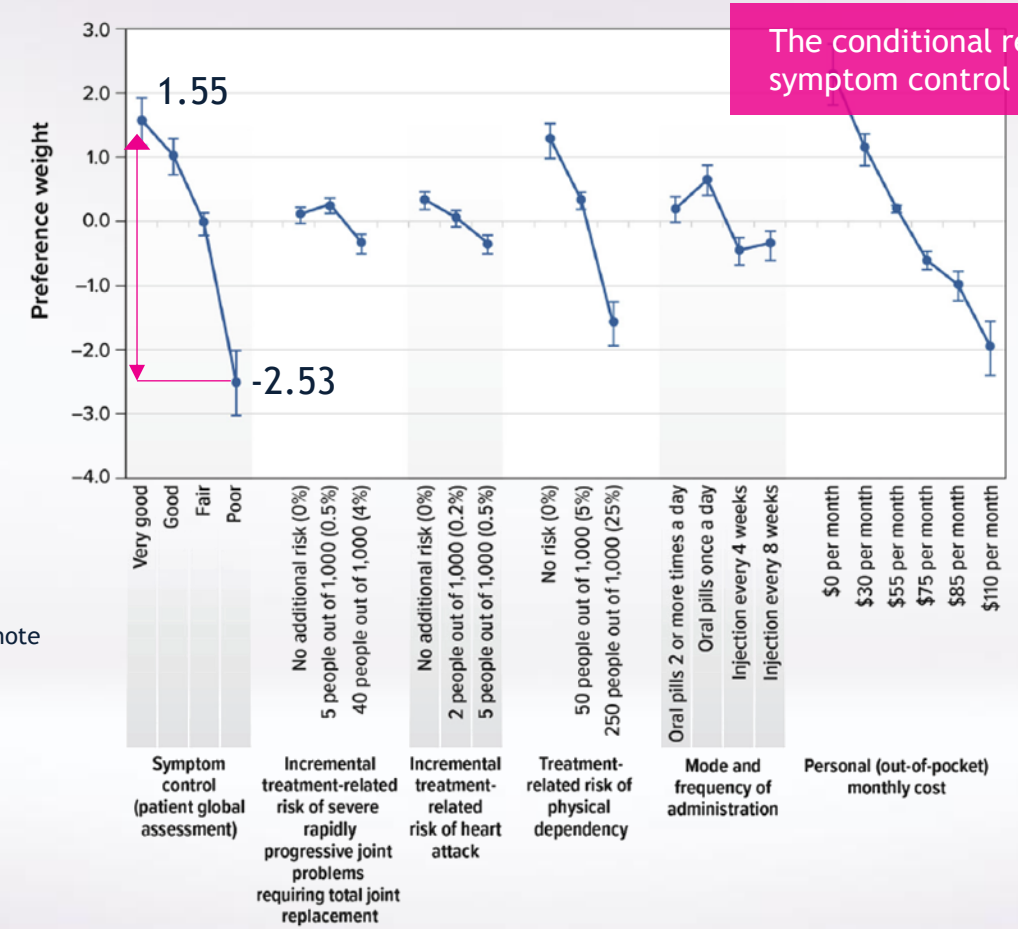

The conditional relative importance of going from poor pain and symptom control to very good is 4.08 (4.08 = 1.55 − [−2.53]).

The vertical bars surrounding each mean preference weight denote the 95% confidence interval (computed by delta method).

Turk D, Boeri M, Abraham L, Atkinson J, Bushmakin AG, Cappelleri JC, et al. Patient preferences for osteoarthritis pain and chronic low back pain treatments in the United States: a discrete-choice experiment. Osteoarthritis Cartilage. 2020;28(9):1202-13.

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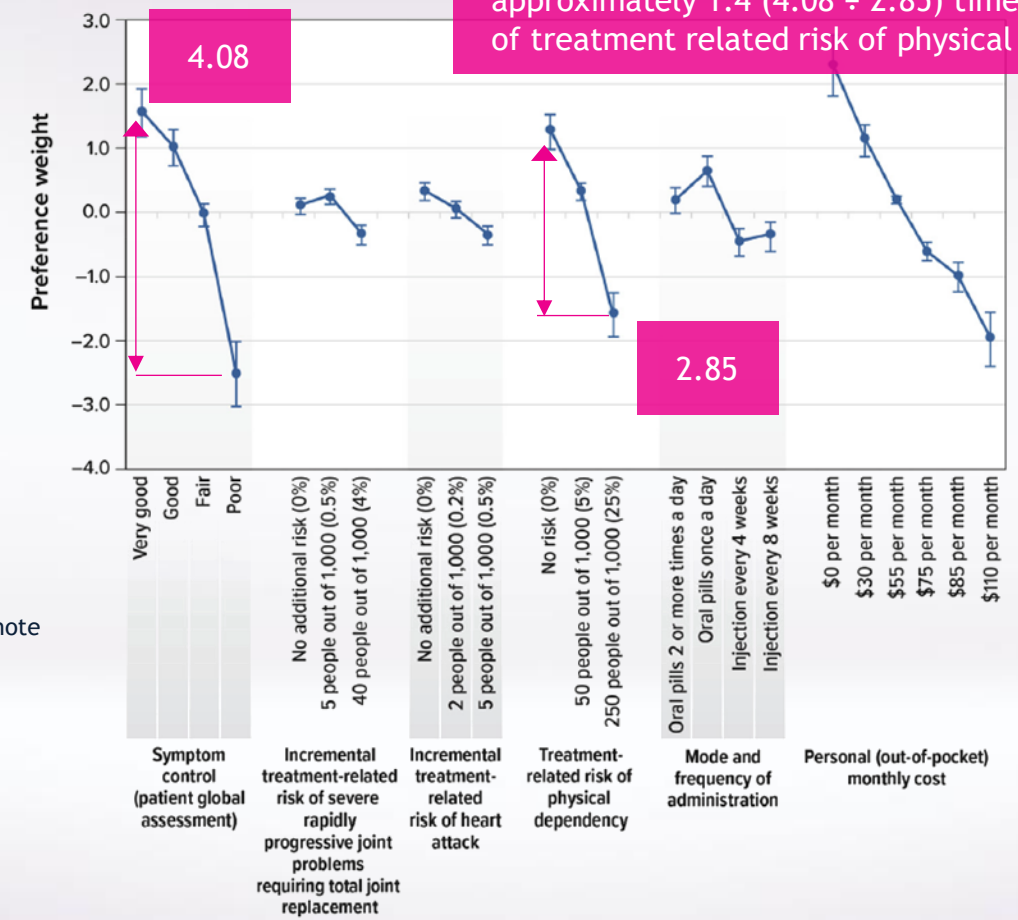
Example Results Generated from DCE

The relative importance of pain and symptom control is approximately 1.4 (4.08 ÷ 2.85) times the relative importance of treatment related risk of physical dependency



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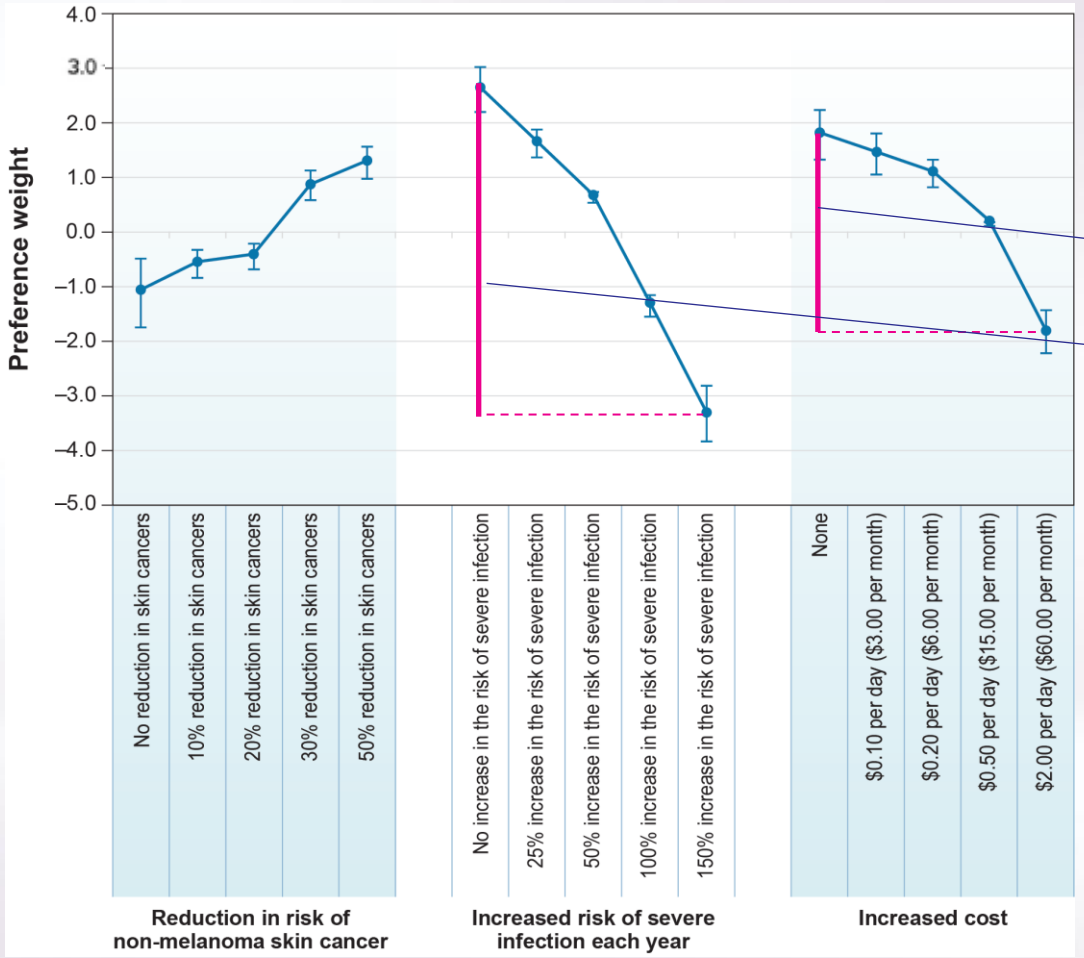
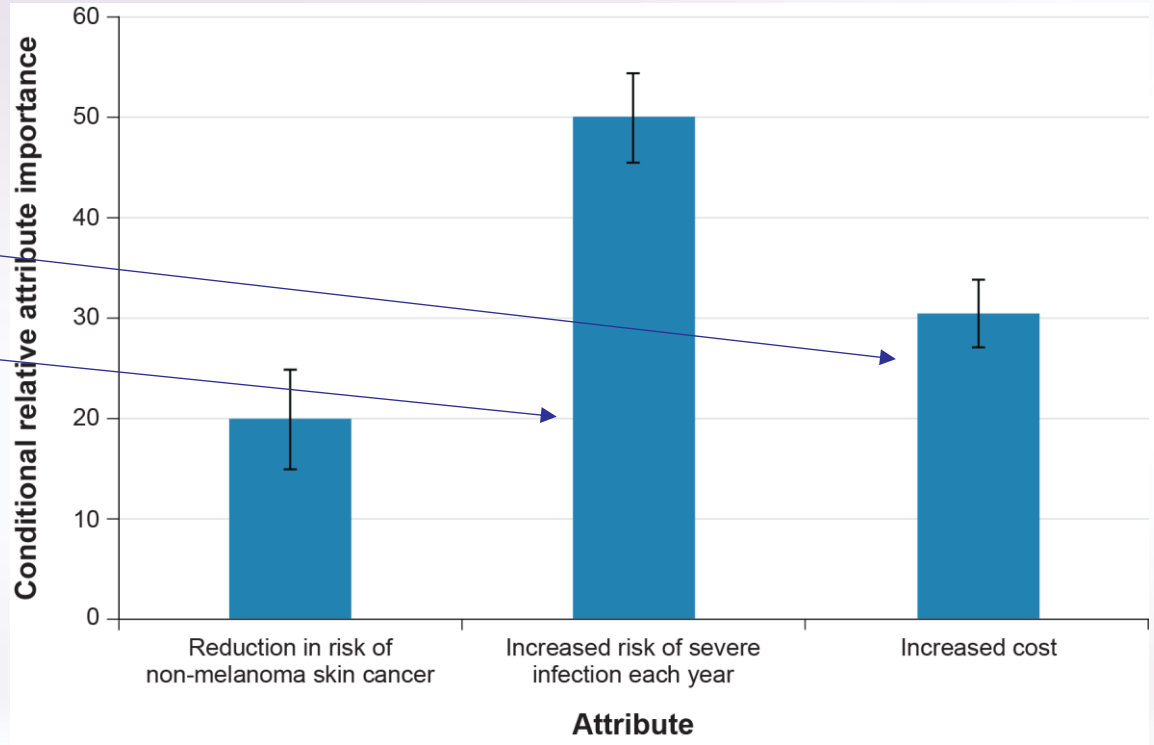
Conditional Attribute Relative Importance





No reduction in skin cancer represents the opt-out alternative specific constant

Within our data and experiment:

- Risk of severe infection 2 ½ times as important as efficacy and 2/3 more important than cost
- Cost 1/3 more important than efficacy
- Efficacy is the least important attribute

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5

The focus on Marginal Rates of Substitution (MAR, MAB, WTP) in Pharma

What is a MAR/MAB?

- **Maximum acceptable risk (MAR):** The maximum level of risk that people are willing to accept in exchange for a given increase in benefit

- **Minimum required/acceptable benefit (MAB):** The minimum level of benefit that people are willing to accept in exchange for a given increase in risk

These measures can support target product profile development, endpoint selection, benefit-risk assessment, and regulatory approval

Utility Function --- Getting to MAR/MAB

$$U_{in} = g(\alpha, Risk_i) + h(\beta, X_i) + \varepsilon_{in}$$

Marginal effect of Risk (or others)

Marginal effect of other attributes

The MAR (which is a Marginal Rate of Substitution), can be expressed as the change in Risk (ΔRisk) that decreases the respondents' utility by the same amount a given improvement (ΔX^*) increases it. Therefore:

$$h(\beta, \Delta X^*) = -g(\alpha, \Delta Risk)$$

MAR depends on the specific project (attributes and levels) and analysis needs (what's the baseline considered for MAR)

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Model output (using continuous or categorical assumptions)

		Assuming continuous (linear)		Assuming categorical (effect coded)	
Attribute	Levels	Coefficient	SD normal dist.	Coefficient	SD normal dist.
Efficacy	9 months	0.356**	0.239**	-3.334**	Not applicable
	12 months			-0.489**	0.341**
	18 months			1.148**	0.295**
	24 months			2.676**	1.934**
Risk	1%	-0.455**	0.401**	1.343**	1.456**
	3%			1.054**	0.554**
	6%			-0.264**	0.376**
	10%			-2.133**	Not applicable
Mode	Injection at hospital	-0.343**	0.407**	-0.327**	0.443**
	IV at hospital	-0.590**	0.766**	-0.622**	0.742**
	Oral tablets at home	0.933**	Not applicable	0.950**	Not applicable

* Statistically significant at the 95% confidence level. ** Statistically significant at the 99% confidence level.
IV = intravenous infusion; SD = standard deviation.

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Computing MAR in practice

- If we assume continuous for risk and efficacy

$$MAR = -\frac{\beta_k * change}{\beta_{risk}}.$$

- If we assume categorical for risk and efficacy

$$MAR = -\frac{(\beta_{k,l=2} - \beta_{k,l=1})}{(\beta_{risk,l=3\%} - \beta_{risk,l=1\%})/(3\% - 1\%)}.$$

What if the MAR is higher than 2% (difference between first and second level or risk in our example)? We need to consider the change in slope in the utility function

Computing MAR in practice

- If MAR is higher than the difference between the first (baseline) and the second level, the total MAR has to take into account the change in slope of disutility of increased risk

$$MAR = -\frac{(\beta_{k,l=2} - \beta_{k,l=1}) + (\beta_{k=risk,l=3\%} - \beta_{k=risk,l=1\%})}{(\beta_{k=risk,l=6\%} - \beta_{k=risk,l=3\%})/(6\% - 3\%)} + 2\%,$$

Utility given by the efficacy

Disutility covered by 2% (first difference) increase in risk

Next Risk disutility

What if the MAR is higher than 5% (difference between first and third level or risk in our example)? Next …

Computing MAR in our example

$$MAR = -\frac{(\beta_{k,l=1} - \beta_{k,l=2}) + (\beta_{k=risk,l=3\%} - \beta_{k=risk,l=1\%}) + (\beta_{k=risk,l=6\%} - \beta_{k=risk,l=3\%})}{(\beta_{k=risk,l=10\%} - \beta_{k=risk,l=6\%})/(10\% - 6\%)} + 5\%.$$

- What if the MAR is even higher than 9%
- We could estimate a specific value for the MAR only by making the strong assumption that the disutility of each incremental increase in risk remains constant beyond 10%.
- Rather than making this assumption in such case, we can only state that the MAR is greater than 9%

Examples of Calculated Marginal Rates of Substitution

MAR: results

Benefit	From	To	Assuming continuous linear (95% CI)	Assuming categorical effect coded (95% CI)
Efficacy	MAR for 1 month between 9 and 12		0.78 (0.67-0.89)	3.50 (2.86-4.14)
	9 months	12 months	2.34 (2.02-2.67)	7.65 (6.51-8.79)
	9 months	18 months	7.03 (6.05-8.01)	Greater than 9%
	9 months	24 months	11.72 (10.08-13.35)	Greater than 9%
	MAR for 1 month between 12 and 18		0.78 (0.67-0.89)	1.89 (0.11-3.66)
	12 months	18 months	4.69 (4.03-5.34)	5.07 (4.36-4.77)
	12 months	24 months	9.37 (80.6-10.68)	8.64 (7.35-9.32)
	MAR for 1 month between 18 and 24		0.78 (0.67-0.89)	1.76 (0.07-3.45)
	18 months	24 months	4.69 (4.03-5.34)	4.82 (3.91-5.73)
Mode	Injection at hospital	IV at hospital	0.54 (0.08-1.00)	2.01 (1.19-2.84)
	Injection at hospital	Oral tablets at home	2.81 (2.24-3.37)	4.25 (3.49-5.01)
	IV at hospital	Oral tablets at home	3.35 (2.69-4.00)	4.92 (4.04-5.80)

CI = confidence interval; IV = intravenous infusion; MAR = maximum acceptable risk.

MAR: results

Benefit	From	To	Assuming continuous linear (95% CI)	Assuming categorical effect coded (95% CI)
Efficacy	MAR for 1 month between 9 and 12		0.78 (0.67-0.89)	3.50 (2.86-4.14)
	9 months	12 months	2.34 (2.02-2.67)	7.65 (6.51-8.79)
	9 months	18 months	7.03 (6.05-8.01)	Greater than 9%
	9 months	24 months	11.72 (10.08-13.35)	Greater than 9%
	MAR for 1 month between 12 and 18		0.78 (0.67-0.89)	1.89 (0.11-3.66)
	12 months	18 months	4.69 (4.03-5.34)	5.07 (4.36-4.77)
	12 months	24 months	9.37 (80.6-10.68)	8.64 (7.35-9.32)
	MAR for 1 month between 18 and 24		0.78 (0.67-0.89)	1.76 (0.07-3.45)
	18 months	24 months	4.69 (4.03-5.34)	4.82 (3.91-5.73)
Mode	Injection at hospital	IV at hospital	0.54 (0.08-1.00)	2.01 (1.19-2.84)
	Injection at hospital	Oral tablets at home	2.81 (2.24-3.37)	4.25 (3.49-5.01)
	IV at hospital	Oral tablets at home	3.35 (2.69-4.00)	4.92 (4.04-5.80)

CI = confidence interval; IV = intravenous infusion; MAR = maximum acceptable risk.

Other Possible Marginal Rates of Substitution

- Willingness to Pay (WTP)

$$WTP = - \text{Benefit} / \beta[\text{cost} * \log(\text{average income})]$$

- Maximum Acceptable Benefit (MAB)

$$MAR = - \text{disutility} / (\text{unit change in benefit})$$

- Others … people can be inventive…

NOTE:

In general, you need a unit change at the denominator!

Minimum Acceptable Benefit (for a given disutility, i.e. to accept to IV or injection instead of tablet)

Baseline Efficacy	From	To	Assuming continuous linear (95% CI)	Assuming categorical effect coded (95% CI)
12 months until the cancer gets worse	Oral tablets at home	Injection at hospital	3.59 (2.93-4.25)	5.01 (3.78-6.25)
	Oral tablets at home	IV at hospital	4.29 (3.54-5.05)	6.17 (4.75-7.59)
18 months until the cancer gets worse	Oral tablets at home	Injection at hospital	3.59 (2.93-4.25)	4.68 (3.73-5.63)
	Oral tablets at home	IV at hospital	4.29 (3.54-5.05)	5.76 (4.61-6.91)
24 months until the cancer gets worse	Oral tablets at home	Injection at hospital	3.59 (2.93-4.25)	1.35 (1.06-1.64)
	Oral tablets at home	IV at hospital	4.29 (3.54-5.05)	1.66 (1.31-2.01)

CI = confidence interval; IV = intravenous infusion; MAR = maximum acceptable risk.

Next – an example of client madness … or a clever move ☺

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Instead of MAB, Client Wanted the Reduction in Efficacy Respondents Are Willing to Accept to Receive Oral Tablets at Home

Baseline Efficacy	From	To	Assuming continuous linear (95% CI)	Assuming categorical effect coded (95% CI)
24 months until the cancer gets worse	Injection at hospital	Oral tablets at home	3.59 (2.93-4.25)	5.01 (3.78-6.25)
	IV at hospital	Oral tablets at home	4.29 (3.54-5.05)	6.17 (4.75-7.59)
18 months until the cancer gets worse	Injection at hospital	Oral tablets at home	3.59 (2.93-4.25)	4.68 (3.73-5.63)
	IV at hospital	Oral tablets at home	4.29 (3.54-5.05)	5.76 (4.61-6.91)
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	IV at hospital	Oral tablets at home	4.29 (3.54-5.05)	1.66 (1.31-2.01)

Same results

CI = confidence interval; IV = intravenous infusion; MAR = maximum acceptable risk.

Alternative Approaches to Exploring Benefit Risk Tradeoffs in Discrete Choice Experiments

Tradeoff Calculations

- Ratio-based calculation:

$$MAR = -\frac{h(\beta, \Delta X^*)}{\alpha} \quad (1)$$

- CV-based calculation:

$$CV = -\frac{\ln(e^{V_i}) - \ln(e^{V_0})}{\alpha} \quad (2)$$

Where $h(\beta, \Delta X^*)$ is the utility generated by improving the attribute X, α is the risk coefficient (marginal disutility), V_0 is the opt-out (or basis scenario) and V_i is the alternative scenario (either with 1 risk only or including multiple attributes attribute levels).

- If only one benefit varies, and the opt-out effect is not included in the calculation, MAR and CV are equivalent.

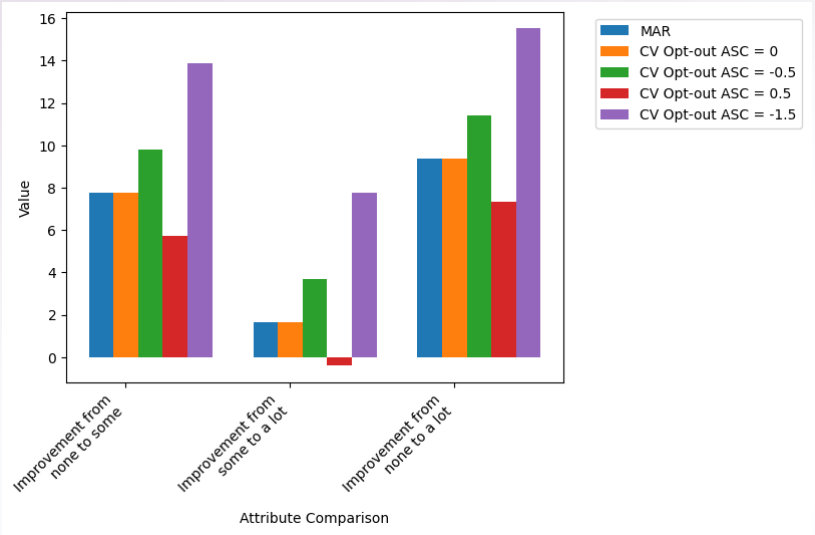

Figure 1. Comparing Maximum Acceptable Risks on Marginal Variations and Compensating Variation varying the opt-out effect

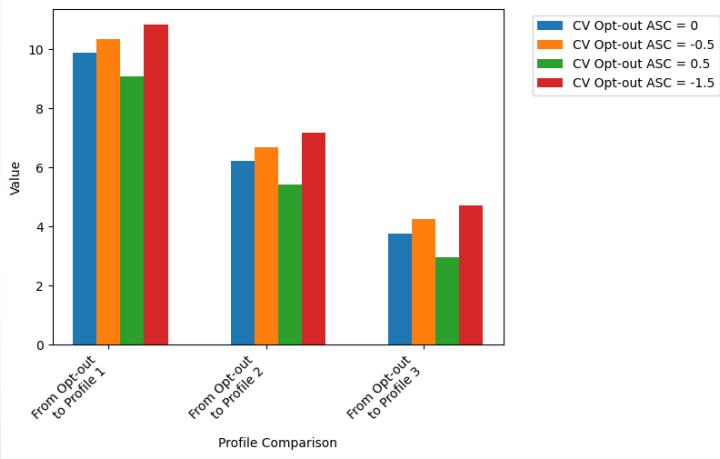

Figure 2. Compensating Variation to Evaluate Total Improvement (Rather Than Marginal) on Alternative Treatment Profiles

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NOT REAL DATA

PROTECTED FILE TO UNLOCK, PW: ISPOR2025 (suggestion: make a copy)

Attribute	Level code	Level Description	Coefficient	Robust std. err	95% CI	
Efficacy	1	Lev1 (worst)	-0.30	0.052	-0.40	-0.20
	2	Lev2	-0.07	0.040	-0.15	0.01
	3	Lev 3 (best)	0.37	0.051	0.27	0.47
Onset of action	1	Slow	-0.59	0.094	-0.78	-0.41
	2	Mid	-0.36	0.068	-0.50	-0.23
	3	Fast	0.53	0.094	0.35	0.72
Adverse event	1	Mild	1.29	0.111	1.07	1.51
	2	Moderate	0.16	0.049	0.07	0.26
	3	Severe	-0.82	0.094	-1.00	-0.64
Risk of mild AE	Const.	0-75%	-0.03	0.004	-0.04	-0.02
Risk of severe AE	Const.	0-15%	-0.30	0.122	-0.54	-0.06
Mode of administration	1	Infusion	-0.82	0.074	-0.96	-0.67
	2	Injection	0.25	0.047	0.15	0.34
	3	Oral Pill	0.57	0.065	0.44	0.70
OPT-out constant	1	Opt out alternative	0.30			

ONLY CHANGE THIS AND THE CONSTANT

Select Level Code for Alternative A	Select Level Code for Alternative B
Efficacy	Efficacy
1	2
Onset	Onset
1	1
AE	AE
1	1
Mode	Mode
1	1
1	0 (Cannot change)

Profiles		
	A	B
Efficacy	1	0
	0	1
	0	0
Onset	1	1
	0	0
	0	0
AE	1	1
	0	0
	0	0
	0	0
	0	0
Mode	1	1
	0	0
	0	0
	1	0

utility A: -0.12316

NOTE: s.e. can be calculated by delta method or using the variance covariance matrix (but it gets complex really quickly).

Compensating Variation from A to B Mild AE: -2.36

Compensating Variation from A to B Severe AE: -0.24

Share A	Share B
51.8%	48.2%

Note: the variation c other coul consider t

Tradeof

- Ratio-b
- CV-bas

Where *h* risk coef is the alt attribute

- If o calc

MAR mild AE

Improvements		MAR in %
Efficacy 1-2	Improvement from Lev 1 to lev2	7.55
Efficacy 1-3	Improvement from Lev 1 to lev3	22.29
Efficacy 2-3	Improvement from Lev 2 to lev3	14.74
oncet 1-2	Improvement from Slow to Mid	7.60
Oncet 1-3	Improvement from Slow to Fast	37.24
Oncet 2-3	Improvement from Mid to Fast	29.64

MAR severe AE

Improvements		MAR in %
Efficacy 1-2	Improvement from Lev 1 to lev2	0.76
Efficacy 1-3	Improvement from Lev 1 to lev3	2.25
Efficacy 2-3	Improvement from Lev 2 to lev3	1.49
oncet 1-2	Improvement from Slow to Mid	0.76
Oncet 1-3	Improvement from Slow to Fast	2.25
Oncet 2-3	Improvement from Mid to Fast	1.49

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6

Preference Research in Clinical Settings

Implications of the FDA Patient Focused Drug Development

- Patient focused drug development guidelines from FDA drew a lot of attention to this type or data
  - Guidance 1: Collecting Comprehensive and Representative Input
  - Guidance 2: Methods to Identify What is Important to Patients
  - Guidance 3: Selecting, Developing or Modifying Fit-for-Purpose Clinical Outcomes Assessments
  - Guidance 4: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making

- Potentially, more patient data required (costs↗, # studies↗, timelines↗)
  - Need synergies to avoid waste of resources and replication
- How can we gather multiple information in one study?
  - Collect preferences in prospective data collection (clinical settings, clinical trials, obs. studies…)

https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

Collecting Preference Data in a Clinical Setting

Advantages:

- Integrated patient experience data collection (PFDD)
- Patients **recruited once** (always valid, but crucial in rare diseases)
- **Sites are trained once**
- **Cost effective**
- **Population of interest** defined once
- Allows to integrate and compare patient and HCPs preferences

Challenges:

- Collecting PPI in clinical settings:
  - Might require **additional steps in ethics approval**
  - **Does not use** standard instruments (NOT a PRO)
  - Often cannot be administered using ePRO standard software (integration across systems)
    - Although simpler methodologies exist
  - Additional patient and site coordinator burden
  - Challenges recruiting and retention
- Risk cross talk between PRO and Preference
- Good planning is crucial!

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Stated Preference in Clinical Setting: Two examples

- Nicotinamide: are patients willing to accept risk and cost to reduce the risk of non-melanoma skin cancer recurrence?
  - No sponsor, curiosity driven study implemented by researchers
  - Survey designed to be simple and administered with “pen and paper”
  - Low budget → long execution time

Boeri et al. 2023. Journal of Dermatological Treatment, doi: 10.1080/09546634.2023.2247105.

- Patient and physician tradeoffs in antiseizure medication monotherapy choices: a discrete choice experiment eliciting preferences in real-world study "VOTE"
  - Pharma Sponsored (started in 2016)
  - Included in an observational study since its inception
  - Complex design, complex idea, required modifications (protocol amendment)

Rosenow et al., 2022. Epilepsia. doi: 10.1111/epi.17137

Case Study 1

Nicotinamide: Introduction and Background

- Non-melanoma skin cancers (NMSCs)
  - More than 3 million diagnosed annually in the US[1]
  - 2,000 annual deaths, substantial morbidity, high treatment costs[2]
  - Effective and safe interventions to reduce NMSC incidence are desirable
- Phase 3 randomized placebo-controlled trial (ONTRAC) on Patients with history of NMSC
  - Nicotinamide resulted in 23% reduction in NMSC compared to placebo[3]
  - Severe infections risk higher in nicotinamide (5.2%) compared to placebo (2.6%)[3]

QUESTION:

- Is a 23% risk reduction enough to offset risks or costs?

1. cancer.net. Skin Cancer (Non-Melanoma): Statistics. https://www.cancer.net/cancer-types/skin-cancer-non-melanoma/statistics. Accessed 15 November 2018.
2. United States Department of Health and Human Services. The Surgeon General's Call to Action to Prevent Skin Cancer. Washington, DC: Office of the Surgeon General; 2014.
3. Chen AC, Martin AJ, Choy B, Fernández-Peñas P, Dalziell RA, McKenzie CA, et al. A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention. N Engl J Med. 2015;373(17):1618-26

Nicotinamide: Study Objectives

- Primary objective:
  - To determine patients' willingness to trade off benefits (reduced NMSC recurrence risk linked to oral nicotinamide), risk of severe infection and out-of-pocket cost
- Secondary objective:
  - To explore preference heterogeneity across the sample

Nicotinamide: Data Collection and Sample

- Data collection: November 2019 – September 2021 (Covid19 Pandemic)
- Survey completed on site (pen and paper, not assisted by staff)
  - Patients recruited at clinic between stages of Mohs surgery to treat their NMSC
    - During Mohs surgery the surgeon removes thin layers of skin one at a time and examines each layer to determine if any cancer remains.
      - Lots of spare time, let's administer a preference survey! ☺
- Sample:
  - Patients:
    - Adult (>18) patients able to read and understand English to consent and complete the survey
    - History of ≥2 NMSC within the past 5 years
    - Undergoing Mohs procedure for treatment of NMSC
  - 4 sites:
    - Chevy Chase, MD; Austin, TX; Hagerstown, MD; Fort Atkinson, WI

Nicotinamide: Attributes and Levels and Experimental Design

Attributes and Levels

Attributes	Levels
Reduction in risk of non-melanoma skin cancer	10% reduction in skin cancers
	20% reduction in skin cancers
	30% reduction in skin cancers
	50% reduction in skin cancers
Increased risk of severe infection each year	25% increase in the risk of severe infection
	50% increase in the risk of severe infection
	100% increase in the risk of severe infection
	150% increase in the risk of severe infection
Increased cost	$0.10 per day ($3.00 per month)
	$0.20 per day ($6.00 per month)
	$0.50 per day ($15.00 per month)
	$2.00 per day ($60.00 per month)

Benefit

Risk

Cost

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Nicotinamide: Attributes and Levels and Experimental Design

Attributes and Levels

Attributes	Levels
Reduction in risk of non-melanoma skin cancer	10% reduction in skin cancers
	20% reduction in skin cancers
	30% reduction in skin cancers
	50% reduction in skin cancers
Increased risk of severe infection each year	25% increase in the risk of severe infection
	50% increase in the risk of severe infection
	100% increase in the risk of severe infection
	150% increase in the risk of severe infection
Increased cost	$0.10 per day ($3.00 per month)
	$0.20 per day ($6.00 per month)
	$0.50 per day ($15.00 per month)
	$2.00 per day ($60.00 per month)

Example of Choice Question

	Option 1 Supplement A	Option 2 Supplement B	Option 3 No Supplement
Reduction in Risk of Non-melanoma Skin Cancer	**20% reduction** in skin cancers	**10% reduction** in skin cancers	None
Increased Risk of Severe Infection	**50% increase** in the risk of severe infection	**25% increase** in the risk of severe infection	None
Increased Cost	$0.10 per day ($3.00 per month)	$0.20 per day ($6.00 per month)	None
Which option would you choose? ***(Check only one)***	**Supplement A** ☐	**Supplement B** ☐	**No Supplement** ☐

- The experiment included 24 DCE questions divided into 2 blocks of 12 questions (efficient design in SAS)
  - Respondents were randomly assigned to 1 of the 2 blocks

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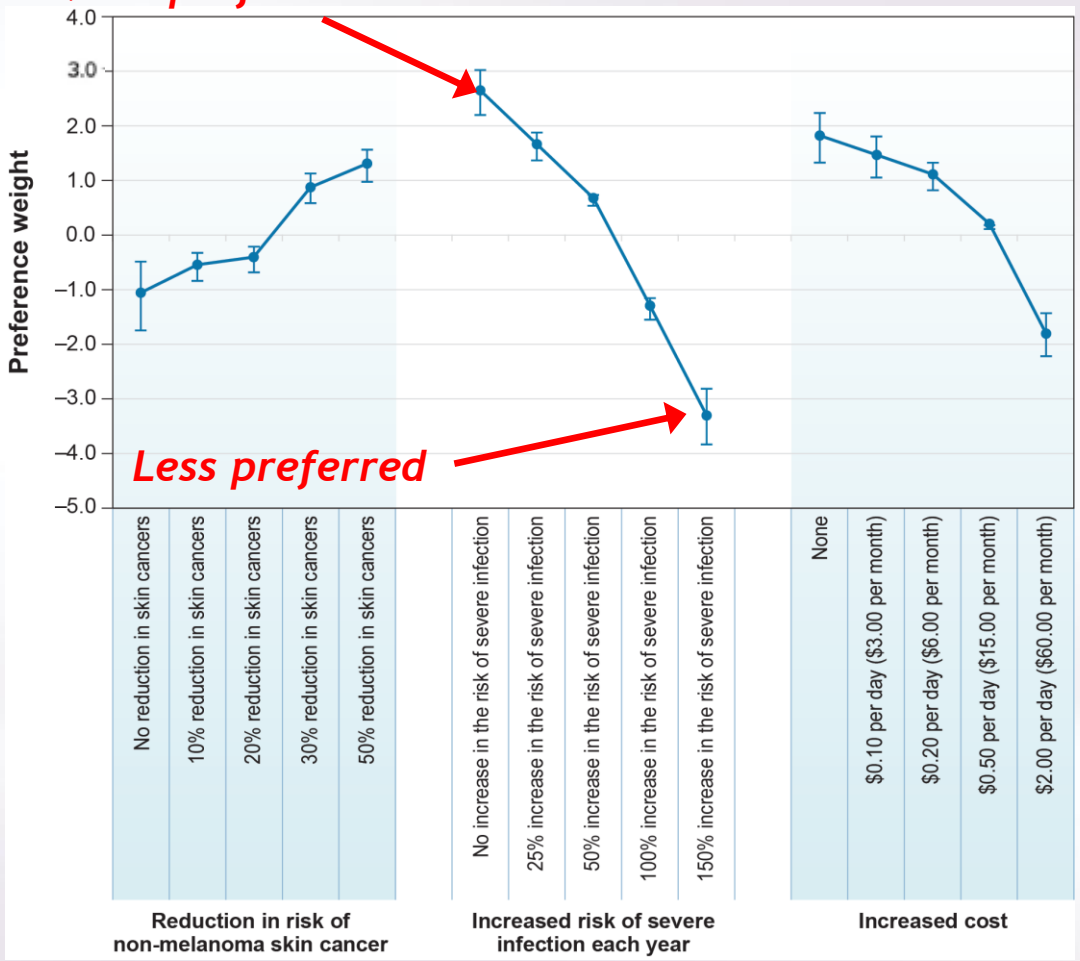
Nicotinamide: Preference Analysis



No reduction in skin cancer represents the opt-out alternative specific constant

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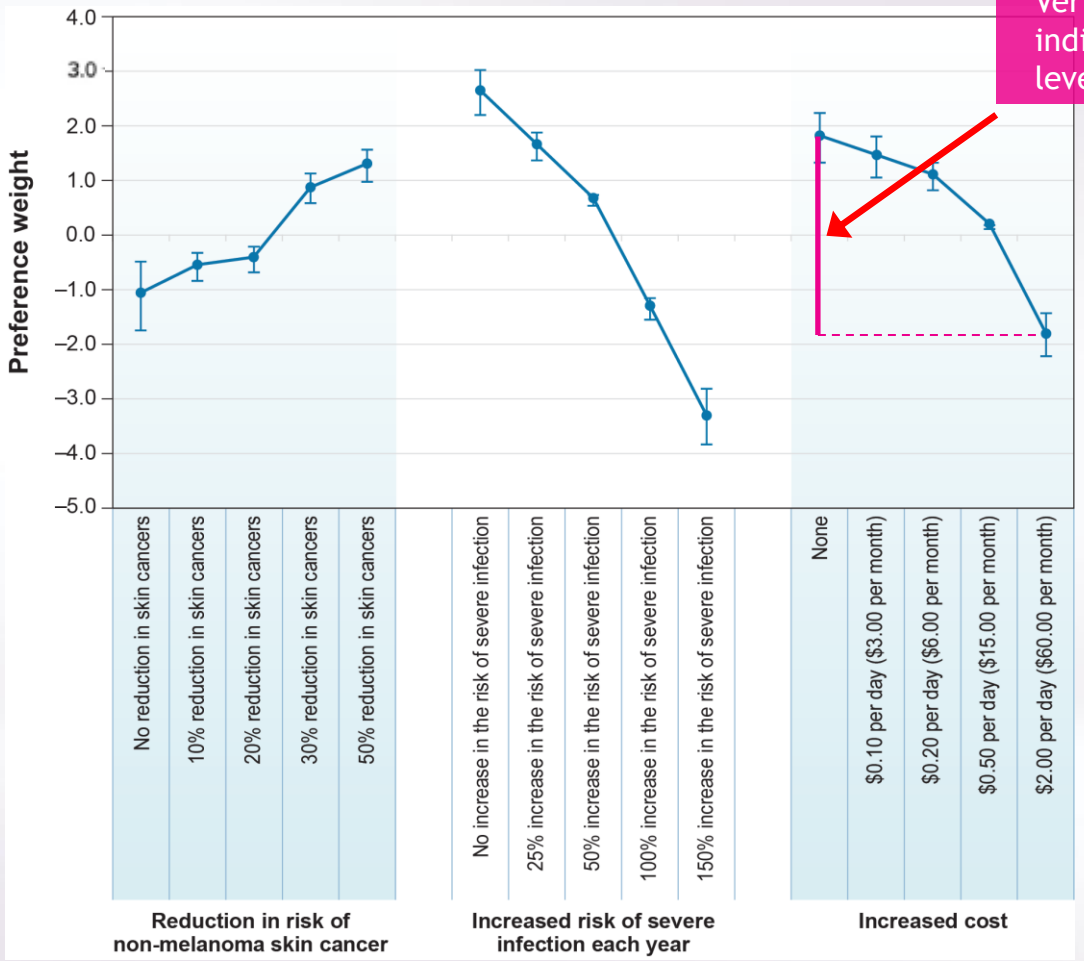
Nicotinamide: Preference Analysis



Vertical distance between preference weights indicates strength of preference for changes between levels

The difference between the most and least preferred level is known as the conditional relative importance

No reduction in skin cancer represents the opt-out alternative specific constant

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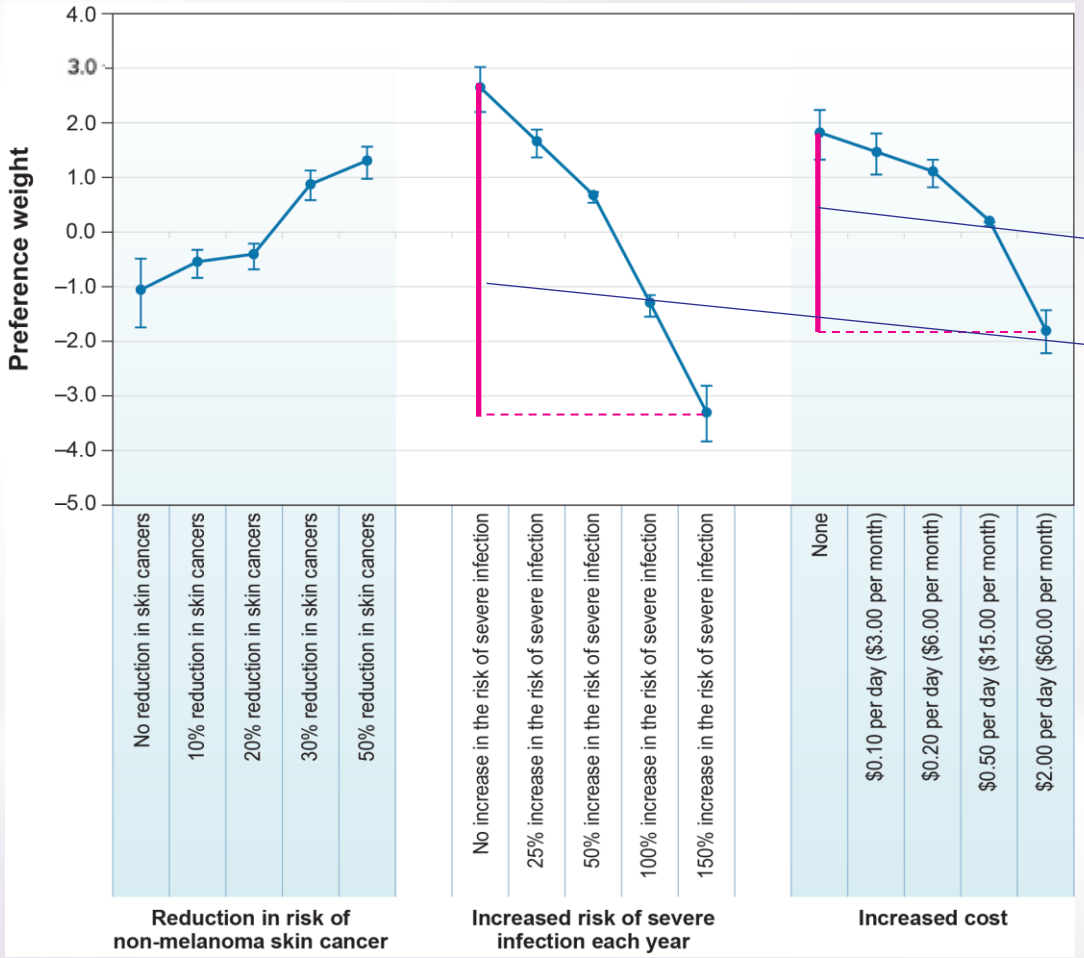
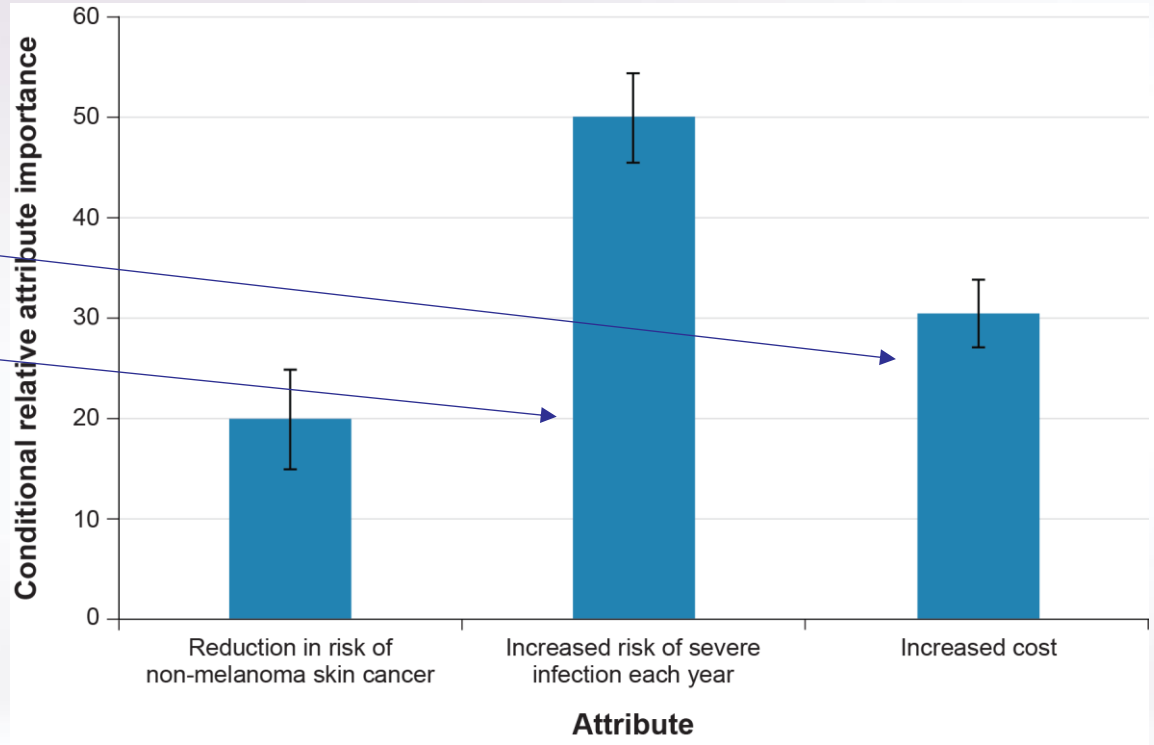
Nicotinamide: Preference Analysis





- Risk of severe infection 2 ½ times as important as efficacy and 2/3 more important than cost
- Cost 1/3 more important than efficacy
- Efficacy is the least important attribute

No reduction in skin cancer represents the opt-out alternative specific constant

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Nicotinamide: Tradeoffs

- Maximum acceptable risk (MAR) of (annual) severe infection was 26.4% (CI 7.5-45.2)
  - Observed risk in ONTRAC was higher (from 2.6% to 5.2%→ 100%)
  - However, absolute risk was lower (if respondents misinterpreted the attribute levels)

- Willingness to pay (WTP) for 23% risk reduction was $8.41 per month (CI $2.45-$14.37)
  - Observed nicotinamide retail cost $3 to $14.40 per month at a dose of 500 mg

Nicotinamide: Preference Heterogeneity

Three subgroups explored:

1. Pre vs. during COVID19 pandemic
2. Site of interview (high income vs. lower income)
3. History (lifetime number of NMSC)

- No statistically significant differences between the first two subgroup sets
- Statistically significantly differences found between patients with history of ≤ 5 NMSCs and those with ≥ 6 NMSCs (Wald test P value = 0.03)
  - Respondents with more lifetime NMSCs placed more importance on cost, though differences were small

Nicotinamide: Lessons Learned and Challenges

- Study fielded by 2 clinician in 4 sites. No sponsor.
  - Limited resources
  - Only four locations (can we generalize to population?)
  - Simple design (limited by pen and paper in clinic administration
    - Other adverse side effects associated with nicotinamide (diarrhea and flushing) not analysed
    - Other potential benefits of nicotinamide may persuade patients to take supplement
- Very long timeline (started in 2015)
  - Sponsored studies are (usually) faster

Case Study 2

Epilepsy Preference Study: Main Results

- DCE administered within a prospective observational study in Europe (VOTE)
  - Survey administered to adult patients with focal seizures changing their monotherapy
  - DCE done before and after doctor visit
  - DCE also completed by the visiting doctor (referring to the patient visited, up to 3)

- Results:
  - Efficacy (chance of becoming seizure free) most important attribute
  - Preferences differ before and after visit
    - Efficacy was more important after the visit compared to before the visit
  - Compared to patients, doctors placed more importance on efficacy

Epilepsy Preference Study: Lessons learned

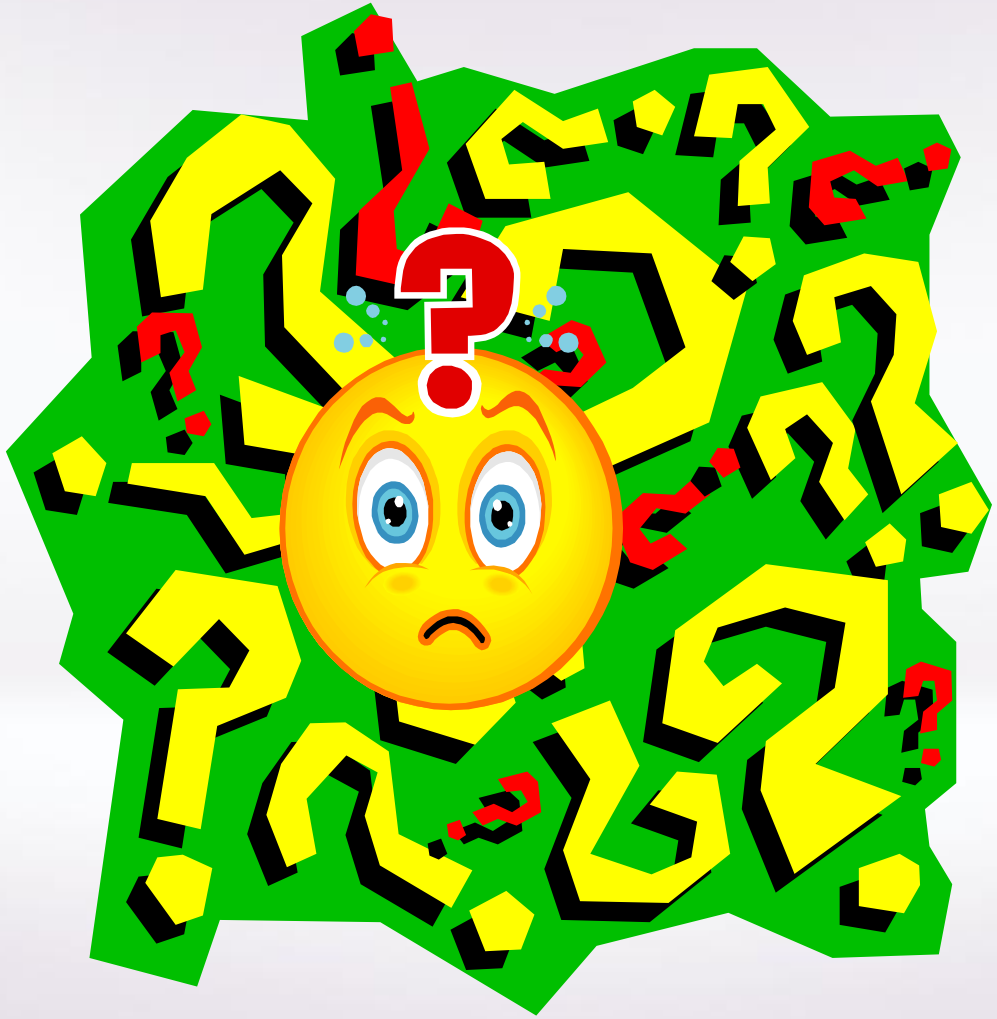
- Complex ambitious design (8 countries with 7 different languages) **unrealistic**
  - Several protocol amendments required with study ongoing
- Study must be well **integrated** in the trial/clinical settings
  - Set clear responsibilities and clear expectations
  - Reduce potential burden to staff and patients
  - Reduce potential mistakes
- Allowed to study effects of **interaction** between **patients and physicians**
- Potentially can be used to observe AE

Discussion and Conclusions

Is it worth optimizing study costs by collecting PPI in clinical settings?

- Planning is crucial
- Simpler is better
- Clear research question and target population
- Choice of appropriate SP methods
  - e.g., DCE, thresholding, multiple thresholding, best worst scaling, ranking,
- Patient engagement and inclusion throughout the study process
- Could add value (more research questions can be answered)

Question?



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Thank you for your attention

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