Preference weights for quality-adjusted life-years estimation for treatments of paroxysmal nocturnal hemoglobinuria in five countries

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BACKGROUND

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare hematologic disorder caused by uncontrolled activation of the terminal complement pathway.
- PNH manifests with intravascular hemolysis, hemolytic anemia and thrombosis, and is associated with a high burden of disease and impaired health-related quality of life.
- Previously, the only approved treatment for PNH was eculizumab, administered every 2 weeks (q2w).[1–3]
- Ravulizumab is a new approved treatment for PNH, administered every 8 weeks (q8w) with a comparable clinical effectiveness and safety profile to eculizumab.[4]
- Therefore, the decision maker is faced with two treatments that may be equally effective but vary in terms of their burden to patients.
- Stated preference research can be used to understand the value that people place on different treatments and provide preference weights for quality-adjusted life-year (QALY) estimation in cost-effectiveness analyses.
- In this study, a stated preference survey was designed to estimate disutilities for the experience of hemolysis, the risk of meningitis-type infections, treatment administration (frequency and duration of infusions) and the need for a blood transfusion.

OBJECTIVES

- In cost-effectiveness analyses for health technology assessment, there is a normative view that outcomes such as quality of life should be weighted by the preferences of the general public.
- In this study, in the absence of EQ-5D data, a stated preference survey was designed to estimate disutilities for the experience of hemolysis, the risk of meningitis-type infections, treatment administration (frequency and duration of infusions) and the need for a blood transfusion.

METHODS

Participants

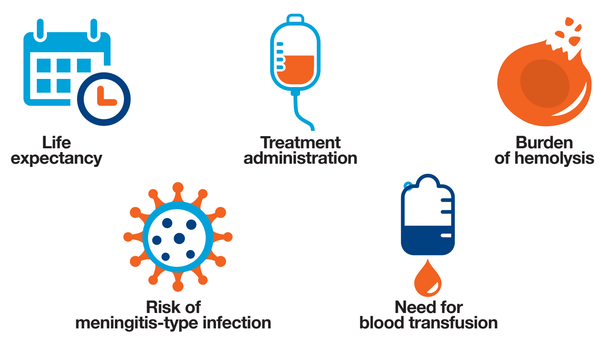
- The survey was administered to general public participants (age ≥ 18 years) from Australia, Canada, the Netherlands, Sweden and the UK recruited through specialist recruitment panels (online panels consisting of members of the public with an interest in participating in research studies).

Survey

- The survey included background details regarding PNH without naming the condition, including symptoms and how it affects people. The disease was anonymized so that participants did not look up the disease to obtain more information.

Discrete choice experiment

- A stated preference discrete choice experiment (DCE) survey was used to evaluate the relative importance of the following treatment attributes to the participants and to assess their willingness to trade these attributes with each other.



- In the DCE, participants were presented with choice sets referring to two hypothetical treatments (Treatment A and Treatment B) and asked to select one treatment based on their preference.
  - The survey consisted of 16 choice sets.
  - The survey was initially presented to participants in the UK.
  - As a test that participants in the UK understood the survey, in one of the 16 choice sets, one treatment was logically better on all attributes than the other.
  - An example of a choice set is shown in **Figure 1**.
- The updated survey completed by participants in Australia, Canada, the Netherlands and Sweden included an additional logical choice test and required participants to confirm that they had read and understood each treatment attribute.
- Participants were excluded if they failed one of the logical choice tests (selected the logically worse treatment as the better treatment).
- Attributes and defined levels were combined into choice sets using a published orthogonal array.

Analysis

- DCE data were analyzed using the mixed effects logit regression model, which estimates preference strength and disutilities for each attribute and accounts for preference heterogeneity between respondents.
- Marginal rates of substitution (MRS) were used to indicate the extent to which people are willing to trade a year of life in order to avoid episodes of hemolysis, increases in treatment administration frequency, increases in risk of infection or the need for a blood transfusion.
  - Average remaining life expectancy for participants from each country was estimated by subtracting the mean age of the population from the average life expectancy in each country.
  - Disutilities were estimated by dividing the MRS estimates by the average life expectancy.

Figure 1. Sample choice set included in the DCE survey

Please imagine that you have been told that you have PXH disease and you need to start a treatment. For each choice below, please indicate whether you prefer treatment A or B.

	Treatment A	Treatment B
Treating PXH disease		
On average how much is life expectancy reduced by PXH disease with treatment?	Life expectancy reduced by 8 years	Life expectancy reduced by 4 years
Administering treatment		
Treatment is via an intravenous infusion into your arm	Treatment is every 8 weeks (6–7 times a year)	Treatment is every 2 weeks (26 times a year)
	It is delivered at home	It is delivered at home
	Treatment takes about 3 hours	Treatment takes about 1 hour
Risk of meningitis-type infection	One additional person per thousand will develop meningitis a year	One additional person per thousand will develop meningitis in 2 years
Return of symptoms		
Red blood cell destruction	Patients **never** experience destruction of red blood cells	**Severe** red blood cell destruction
Causes abdominal pain, dark urine, swallowing difficulties		Requires treatment in hospital
Need for a blood transfusion	**Never** need a transfusion	Need a blood transfusion **once a year**

Which treatment is best? Please tick A or B **A** ☐ **B** ☐

PXH, paroxysmal nocturnal hemoglobinuria (undisclosed to participants).

RESULTS

Demographics

- Across countries, after exclusion of 754 participants who failed at least one of the logical choice tests, 1764 participants were included in the analyses (52.6% female).

Discrete choice experiment

- The results of the DCE are presented in **Table 1**.

Life expectancy

- In all countries, potential reduction in life expectancy was a significant predictor of choice, with a significant aversion to a reduction in life expectancy of 4 or more years.

Treatment administration

- Participants in all countries preferred six or seven infusions a year to 26 infusions a year.

Risk of meningitis-type infection

- Participants in all countries showed a significant preference for no risk of infection compared with a low (1 in 1000) risk of infection every year.
- However, low risk of infection every 2 or 5 years was not considered by participants to be significantly different from no risk of infection.

Burden of hemolysis

- Participants showed a significant preference for no hemolysis compared with severe hemolysis requiring admission to hospital. In all countries, mild hemolysis with treatment at home was not valued by participants over no hemolysis.

Blood transfusions

- Participants in all countries preferred to avoid the need for annual transfusions but showed no preference for one blood transfusion every 2–5 years over no transfusions.

Marginal rates of substitution

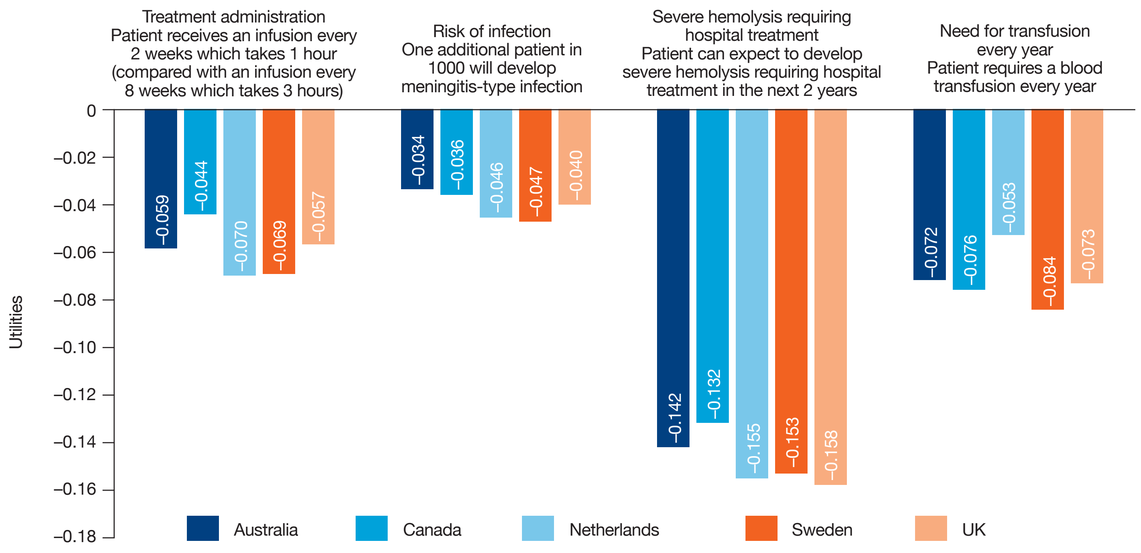
- The MRS data (**Figure 2**) indicate the extent to which participants are willing to forego a unit of one attribute in order to gain a unit in a different attribute.
- For instance, UK participants had an average life expectancy of 31.17 years and were willing to trade 4.93 years of life for avoidance of severe hemolysis requiring hospitalization. Hence, disutility = –4.93/31.17 = –0.158.
- Across countries, participants were willing to trade years of life to avoid annual blood transfusions and increases in treatment administration frequency, risk of infection and severity of hemolysis.

Table 1. Results of mixed logit model depicting preferences for DCE survey attributes

Attributes and levels	Odds ratios (CI)				
	Australia	Canada	Netherlands	Sweden	UK
Life expectancy (reference: not reduced)					
Reduced by 4 years	**0.405** (0.343–0.479)	**0.341** (0.283–0.411)	**0.386** (0.319–0.468)	**0.379** (0.314–0.458)	**0.452** (0.393–0.520)
Reduced by 8 years	**0.153** (0.121–0.193)	**0.099** (0.077–0.127)	**0.138** (0.107–0.179)	**0.127** (0.099–0.161)	**0.189** (0.157–0.226)
Reduced by 12 years	**0.021** (0.015–0.030)	**0.010** (0.007–0.014)	**0.010** (0.007–0.015)	**0.011** (0.008–0.016)	**0.030** (0.023–0.040)
Treatment administrations (reference: 6–7 times a year at home, takes 3 hours)					
26 times a year at home, takes 1 hour	**0.470** (0.392–0.563)	**0.541** (0.444–0.659)	**0.392** (0.315–0.488)	**0.413** (0.335–0.509)	**0.594** (0.516–0.683)
Risk of meningitis-type infection (reference: no risk)					
1 in 1000: every 5 years	1.128 (0.939–1.355)	1.033 (0.837–1.276)	1.047 (0.846–1.296)	1.008 (0.825–1.232)	1.029 (0.879–1.204)
1 in 1000: every 2 years	1.226 (0.984–1.529)	1.025 (0.803–1.309)	1.278 (0.983–1.662)	1.160 (0.908–1.482)	1.164 (0.966–1.401)
1 in 1000: every 1 year	**0.644** (0.537–0.772)	**0.607** (0.500–0.738)	**0.541** (0.440–0.666)	**0.548** (0.449–0.669)	**0.696** (0.597–0.812)
Return of symptoms in 2 years (reference: no hemolysis)					
Mild hemolysis, treated at home for a few days	0.909 (0.767–1.077)	0.998 (0.825–1.208)	0.828 (0.673–1.018)	0.882 (0.725–1.073)	1.013 (0.878–1.170)
Mild hemolysis, treated at home for a few weeks	1.095 (0.871–1.376)	1.173 (0.903–1.522)	1.245 (0.934–1.660)	0.963 (0.741–1.250)	1.095 (0.901–1.330)
Severe hemolysis, treated in hospital	**0.162** (0.128–0.205)	**0.159** (0.123–0.205)	**0.128** (0.099–0.166)	**0.141** (0.111–0.179)	**0.238** (0.199–0.284)
Need for transfusion (reference: never needed)					
Every 5 years	0.918 (0.773–1.090)	0.805 (0.664–0.976)	1.099 (0.905–1.335)	1.118 (0.931–1.342)	0.960 (0.828–1.113)
Every 2–5 years	0.953 (0.764–1.190)	1.123 (0.879–1.435)	**1.542** (1.177–2.019)	1.182 (0.919–1.520)	0.967 (0.803–1.163)
Every year	**0.395** (0.328–0.476)	**0.345** (0.277–0.430)	**0.495** (0.402–0.610)	**0.341** (0.279–0.416)	**0.515** (0.446–0.593)

Numbers in bold indicate statistical significance of $p < 0.05$. CI, confidence interval.

Figure 2. Estimate MRS (expressed as a disutility) for differences in attribute levels



MRS, marginal rates of substitution.

CONCLUSIONS

- This study estimated disutilities for events that are rarely measured in clinical studies.
- This study showed the value that the general public places on attributes of treatment for PNH.
- In each country, life expectancy, treatment administration, risk of meningitis-type reactions, hemolysis and the need for blood transfusions were all important to participants.
- A limitation of the study is that it was not possible to confirm that participants had read and fully understood all information received.
- However, we believe that this is a useful method for generating preferences from the perspective of the general public and estimating disutilities for economic modeling where EQ-5D data are not available.

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DISCLOSURES

KJM, JRS, KA, AH and IT are employees of and hold stock in Alexion Pharmaceuticals, Inc. AL and KG are full-time employees of Acaster Lloyd Consulting Ltd, who were paid a fixed fee by Alexion Pharmaceuticals, Inc. for their work on this project. SA has no conflicts of interest to declare. CJP has received speaking honoraria, advisory board honoraria, and travel grants from and is site investigator for clinical trials with Alexion Pharmaceuticals, Inc.

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