Cross-referencing and aggregating multiple independent sources to estimate subgroup-level values

The EQ-5D utility of emicizumab in severe haemophilia A

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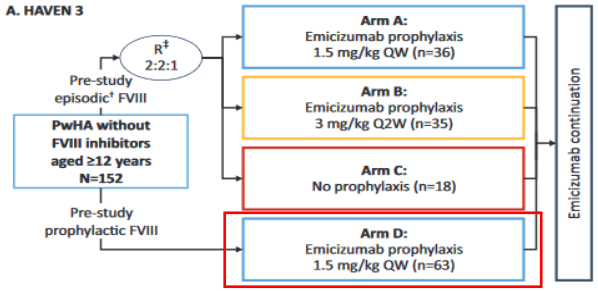
Context: Emicizumab for severe haemophilia

- Emicizumab is a monoclonal antibody that bridges activated factor IX and factor X to restore function of missing activated factor VIII (FVIII), for the treatment of haemophilia A

- The efficacy and safety of emicizumab prophylaxis for treating severe haemophilia A in patients without FVIII inhibitors was evaluated in the HAVEN-3 study, which enrolled 152 patients:
  - 89 patients who received prior episodic FVIII were randomised to two dosing schedules (Arm A and Arm B) and placebo (Arm C)
  - 63 patients who received prior prophylactic treatment were assigned to the Arm D dosing schedule

- Later, the HAVEN-4 study was also conducted to evaluate a different dosing regimen, which enrolled 48 patients:
  - 7 patients were enrolled in the run-in cohort
  - 41 patients were enrolled in the expansion cohort



Source: "*The effect of emicizumab prophylaxis on long-term, self-reported physical health in persons with haemophilia A without factor VIII inhibitors in the HAVEN 3 and HAVEN 4 studies*", Skinner et al., 2021

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Context: Utility of patients with severe haemophilia

- Utility data has been collected and reported for comparisons between Arm A, Arm B, and Arm C
- While utility data for Arm D was collected, it has not been reported explicitly
- This information is desirable for performing indirect treatment comparisons to establish the comparative effectiveness in prophylaxis patients

Our aim is to estimate the unreported Arm D EQ-5D utilities to understand the impact of prophylaxis emicizumab in patients with severe haeomphilia

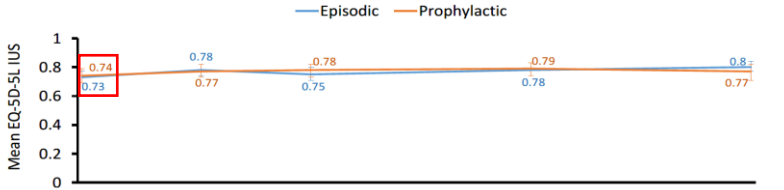
Context: The available information

- To estimate the missing Arm D utilities, we can make use of information reported across several documents, including:
  - Published articles: Pipe et al. (2019), Skinner et al. (2021), Kiialainen et al. (2022), Mahlangu et al. (2023)
  - Clinical trials documents: EudraCT, clinicaltrials.gov, EMA, G-BA

- These documents report a range information that could help to identify and estimate the missing Arm D utilities, from patient characteristics to change in utility. This includes…

Examples: Available information

Utilities aggregated on selected patient characteristics:



Utilities at selected individual time points:

Arm/Group Title	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W
Arm/Group Description	Participants who had received episodic treatment with FVIII prior to study entry were randomized to... + Show more	Participants who had received episodic treatment with FVIII prior to study entry were randomized to... + Show more	Participants who had received episodic treatment with FVIII prior to study entry were randomized to... + Show more
Overall Number of Participants Analyzed	14	34	29
Mean (Standard Deviation) | Unit of Measure: units on a scale	0.63 (0.20)	0.76 (0.24)	0.76 (0.18)

Patient characteristics by study arm:

Reporting group values	Arm C (Control): No Prophylaxis	Arm A: Emicizumab 1.5 mg/kg QW	Arm B: Emicizumab 3 mg/kg Q2W	Arm D: Emicizumab 1.5 mg/kg QW (Pre-study FVIII Prophylaxis)	Total
Number of subjects	18	36	35	63	152
Age categorical					
Units: Subjects					
In utero	0	0	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0	0	0
Newborns (0-27 days)	0	0	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0	0	0
Children (2-11 years)	0	0	0	0	0
Adolescents (12-17 years)	1	0	0	7	8
Adults (18-64 years)	17	34	34	54	139
From 65-84 years	0	2	1	2	5
85 years and over	0	0	0	0	0
Age Continuous					
Units: years					
arithmetic mean (standard deviation)	37.8 ± 12.9	39.8 ± 14.0	40.4 ± 11.4	36.4 ± 14.4	-
Sex: Female, Male					
Units: participants					
Female	0	0	0	0	0
Male	18	36	35	63	152

Patients who report/fail to report over time:

	Arm A		Arm B		Arm C_{Emi}*		Arm D	
Zeitpunkt	**In Studie n/N (%)**	**Rücklauf n/N (%)**	**In Studie n/N (%)**	**Rücklauf n/N (%)**	**In Studie n/N (%)**	**Rücklauf n/N (%)**	**In Studie n/N (%)**	**Rücklauf n/N (%)**
Beginn	36 / 36 (100)	36 / 36 (100)	35 / 35 (100)	33 / 35 (94,3)	17 / 17 (100)	17 / 17 (100)	63 / 63 (100)	59 / 63 (93,7)
Woche 13	36 / 36 (100)	34 / 36 (94,4)	34 / 35 (97,1)	29 / 34 (85,3)	14 / 17 (88,2)	15 / 17 (88,2)	63 / 63 (100)	60 / 63 (95,2)
Woche 25	35 / 36 (97,2)	34 / 36 (94,4)	34 / 35 (97,1)	31 / 34 (91,2)	10 / 17 (0,0)	8 / 10 (80,0)	63 / 63 (100)	58 / 63 (92,1)
Woche 49	24 / 36 (66,7)	21 / 24 (87,5)	23 / 35 (65,7)	21 / 23 (91,3)	-	-	49 / 63 (77,8)	45 / 49 (91,8)

Figure 1 taken from "*The effect of emicizumab prophylaxis on long-term, self-reported physical health in persons with haemophilia A without factor VIII inhibitors in the HAVEN 3 and HAVEN 4 studies*", Skinner et al., 2021

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Can we just use simultaneous equations?

- From the available information, we have several overlapping estimates which resemble **simultaneous equations**

- For example:
  - The mean utility value across all prophylaxis patients reporting at baseline is 0.74
  - There are 52 prophylaxis patients from Arm D [68%] and 24 from the HAVEN 4 expansion cohort [32%]
  - As an equation: $0.68x_{3D} + 0.32x_{4E} = 0.74$

- Repeating this process for multiple patient characteristics, we end up with a system-of-equations. For example:

$$0.2x_{3A}, 0.1x_{3B}, 0.3x_{3C} + 0.3x_{3D} + 0.1x_{4E} = 0.74$$
$$0.1x_{3A}, 0.1x_{3B}, 0.4x_{3C} + 0.2x_{3D} + 0.2x_{4E} = 0.71$$
$$0.4x_{3A}, 0.1x_{3B}, 0.2x_{3C} + 0.1x_{3D} + 0.2x_{4E} = 0.70$$

- We attempted to solve with qr.solve, but this had two issues:
  1. **Solution plausibility:** The solutions were unbounded and could therefore yield implausible utility values
  2. **Rounding**: In some cases, rounding would obfuscate the true solution

Source: "*The effect of emicizumab prophylaxis on long-term, self-reported physical health in persons with haemophilia A without factor VIII inhibitors in the HAVEN 3 and HAVEN 4 studies*", Skinner et al., 2021

Proposed solution: Linear programming!

Linear programming has the potential to mitigate both issues and can be easily implemented in R

1. **Implausible values**: In linear programming, we can place upper and lower bounds on the solution, forcing the approach to consider only defined utility values (i.e., no negative utilities or utilities over one)
   - **E.g.,** $0 < x \leq 1$ for all $x \in (x_{3A}, x_{3B}, x_{3C}, x_{3D}, x_{4E})$

2. **Rounding**: In linear programming, we can replace equalities with a pair of inequalities, forcing the approach to search for solutions in a range that would **round up** or **round down** to the reported value.
   - **E.g.,** $0.68x_{3D} + 0.32x_{4E} = 0.74$ can be replaced with $0.68x_{3D} + 0.32x_{4E} \geq 0.735$ and $0.68x_{3D} + 0.32x_{4E} < 0.745$

GLPK (GNU Linear Programming Kit)

Package 'Rglpk'

January 13, 2024

Version 0.6-5.1

Title R/GNU Linear Programming Kit Interface

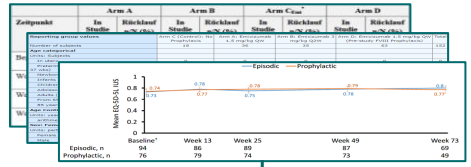
Description R interface to the GNU Linear Programming Kit.
'GLPK' is open source software for solving large-scale linear programming (LP), mixed integer linear programming ('MILP') and other related problems.

GLPK: https://www.gnu.org/software/glpk/
Rglpk: https://r-forge.r-project.org/projects/rglp/

Proposed solution: summary of implementation

Overall, our proposed solution to estimate the HAVEN-3 Arm D utilities is as follows:

1. Identify the aggregate utility for each patient characteristic from published sources
2. Establish the percentage of patients in each arm that contribute to this estimate using published sources
3. Capture 1 and 2 as a system of equations expressed in terms of the arm-specific utilities $(x_{3A}, x_{3B}, x_{3C}, x_{3D}, x_{4E})$
4. Replace each equation with a pair of inequalities that round to the aggregate utility
5. Solve using linear program (`Rglpk::Rglpk_solve_LP`) with a solution boundary that yields plausible utilities



Mean EQ-5D in prophylaxis patients = 0.74

Mean EQ-5D in episodic patients = 0.73

Prophylaxis patients by arm (%)				
H3A	H3B	H3C	H3D	H4E
0	0	0	68	32

Episodic patients by arm (%)				
H3A	H3B	H3C	H3D	H4E
38	35	17	0	10

$$0.68x_{3D} + 0.32x_{4E} = 0.74$$

$$0.38x_{3A} + 0.35x_{3B} + 0.17x_{3C} + 0.10x_{4E} = 0.73$$

$$0.68x_{3D} + 0.32x_{4E} \geq 0.735$$
$$0.68x_{3D} + 0.32x_{4E} < 0.745$$
$$0.38x_{3A} + 0.35x_{3B} + 0.17x_{3C} + 0.10x_{4E} \geq 0.725$$
$$0.38x_{3A} + 0.35x_{3B} + 0.17x_{3C} + 0.10x_{4E} < 0.735$$

$$\widehat{x_{3A}}, \widehat{x_{3B}}, \widehat{x_{3C}}, \widehat{x_{3D}}, \widehat{x_{4E}}$$

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Simulation of pseudo patient-level data

- Before we can apply our solution, there are two sources of variance we need to account for in our data:
  1. **Inconsistent reporting:** At each week, a subset of patients fail to report in each arm
  2. **Dosing regimens may change:** At certain weeks, a small number of patients switch dosing regimen in each arm

- To account for variance in the data, we generated 100,000 data frames containing pseudo patient-level data for each study arm that included simulated switches in dosing regimen and failures to report

- We discarded any simulated data that disagreed with published sources, leaving us with only "valid" data for solving:

Category	Week 0		Week 13		Week 25		Week 49	
	All	HAVEN 3, Arm D	All	HAVEN 3, Arm D	All	HAVEN 3, Arm D	All	HAVEN 3, Arm D
In-study	176	56	176	56	176	56	176	56
Observed	170	52	165	55	163	[53,54]	160	[51,54]
< 9 bleeds	83	[44,45]	85	[46,48]	80	[44,46]	82	[43,48]
≥ 9 bleeds	87	[7,8]	80	[7,9]	83	[8,9]	78	[3,10]
≥ 1 target joints	121	[24,25]	114	[24,25]	114	[23,25]	113	[20,25]
0 target joints	49	[27,28]	51	[30,31]	49	[29,31]	47	[26,31]
Prophylaxis	76	52	79	55	74	[53,54]	73	[51,54]
Episodic	94	0	86	0	89	0	87	0
QW	88	52	89	55	86	[52,53]	84	[51,54]
Q2W	49	0	43	0	45	0	45	0

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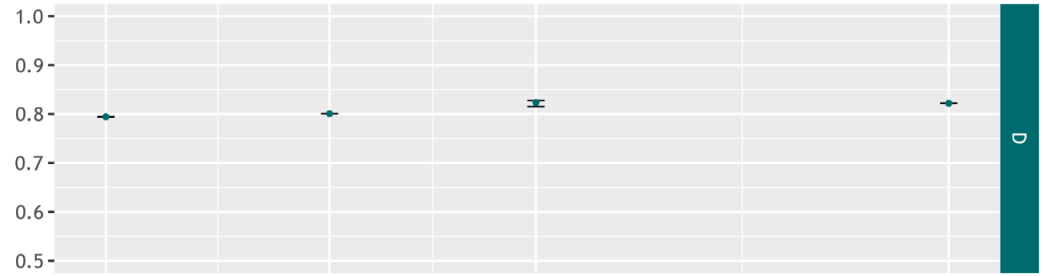
Results: Estimated HAVEN 3 Arm D utilities



Week 0 EQ5D, mean (range)	Week 13 EQ5D, mean (range)	Week 25 EQ5D, mean (range)	Week 49 EQ5D, mean (range)
0.79 (0.79, 0.79)	0.80 (0.80, 0.80)	0.82 (0.82, 0.83)	0.82 (0.82, 0.82)

- We initially configured the linear program solver to impose solution boundaries of [0.55, 0.85]
  - This reflects our expectation over the plausible range of utility solutions
- The results show that:
  - From Week 0 to Week 49, the mean EQ-5D HAVEN-3 Arm D utility increased by 0.03
  - The estimated utilities were largely unaffected by remaining variance in patient characteristics

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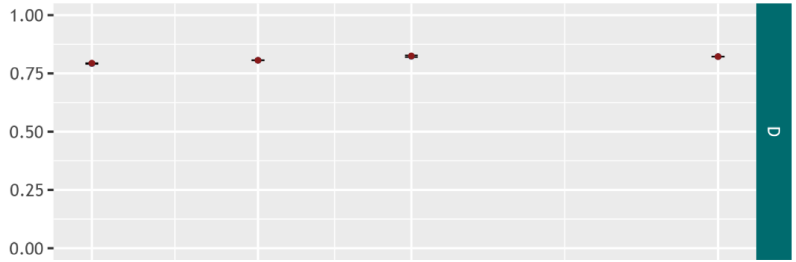
Results: Estimated HAVEN 3 Arm D utilities



Boundaries	Week 0 EQ5D, mean (range)	Week 13 EQ5D, mean (range)	Week 25 EQ5D, mean (range)	Week 49 EQ5D, mean (range)
[0.55, 0.85]	0.79 (0.79, 0.79)	0.80 (0.80, 0.80)	0.82 (0.82, 0.83)	0.82 (0.82, 0.82)
[0.5, 0.9]	0.79 (0.79, 0.79)	0.81 (0.81, 0.81)	0.82 (0.82, 0.83)	0.82 (0.82, 0.82)
[0.4, 0.1]	0.79 (0.79, 0.79)	0.81 (0.81, 0.81)	0.82 (0.82, 0.83)	0.82 (0.82, 0.82)

- To explore the robustness of our results to the imposed solution boundaries, we then explored two additional, more relaxed scenarios ([0.5, 0.9] and [0.4, 1.0])

- These additional scenarios show that:
  - Only the Week 13 utility changed by 0.01 from 0.80 to 0.81
  - This gives us confidence that the predicted Arm D utilities were largely robust the solution boundaries

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Future work and conclusions

- There are several limitations that present opportunities for future work:
  - Constraints are only placed at the aggregate-level, but not at the patient-level
  - Rounding to two decimal place sounds reasonable but results in meaningful omission of information
  - Potentially different estimates used (e.g., modelled versus observed), where it is not always clear

- Despite these limitations, we were able to estimate the following increases in HAVEN-3 Arm D utilities:
  - **Week 0 to Week 13:** An increase of 0.01 from 0.79 to 0.80
  - **Week 0 to Week 25:** An increase of 0.03 from 0.79 to 0.82
  - **Week 0 to Week 49:** An increase of 0.03 from 0.79 to 0.82

Questions?

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