Contextualizing Health-State Utilities in Patients with Transfusion-Dependent β-Thalassemia

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BACKGROUND

- Transfusion-dependent β-thalassemia (TDT) is a rare genetic disease caused by mutations in the β-globin gene (*HBB*) that impair the production of adult hemoglobin (HbA), resulting in inefficient erythropoiesis and severe anemia.[1]
- Patients with TDT require lifelong regular blood transfusions and consequently develop complications from prolonged periods of high iron levels.[1]
- Because of the complexity of managing this condition and the potential for serious complications, patients with TDT often experience substantial impacts on their quality of life (QoL).[2]
- The transfusion-dependent quality of life (TranQoL) questionnaire is a validated, TDT-specific measure of health related QoL (HRQoL).[2]
- The work-productivity assessment inventory (WPAI) is a non-disease-specific measure of work and activity impairment over the past 7 days prior to the evaluation and has been used for TDT as it measures aspects of daily life that are affected by the disease, such as school or work attendance.[3,4]
- The EuroQoL 5 Dimensions Youth Version (EQ-5D-Y) (for younger patients) and the EuroQoL 5 Dimensions 3 Level Version (EQ-5D-3L) (for adult patients)[5,6] are generic, health-related questionnaires that are used to derive health state utility scores.
- Cost-utility analyses (CUA) are needed to assess the value of therapies for TDT.
  - — However, CUA in TDT often use health-state utility values that have not been compared with disease-specific QoL measures[7-9]
  - — Comparison of these generic health-state utility values with disease-specific measures is necessary to perform and interpret CUA for current and new TDT therapies

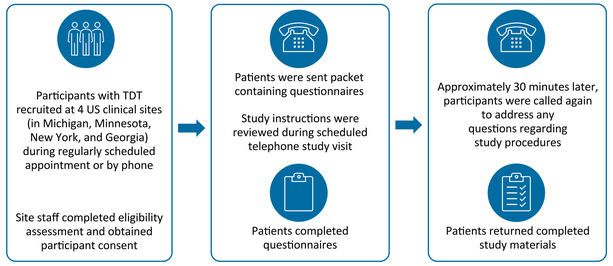
OBJECTIVES

- This study aimed to contextualize utility-value estimates for TDT with disease-relevant data.
- The analysis reported here aimed to understand the relationship between generic utility-value estimates and TDT-specific HRQoL measures, as well as their relationship with disease-relevant data.

METHODS

- This was a cross-sectional study designed to collect health-state utilities using the EQ-5D questionnaire, as well as patient-reported outcomes using tools that are relevant (WPAI) or specific (TranQoL) to TDT.
- Patients with TDT who were >12 years old and required >8 transfusion episodes per year were recruited from 4 clinical sites in the US (**Figure 1**).

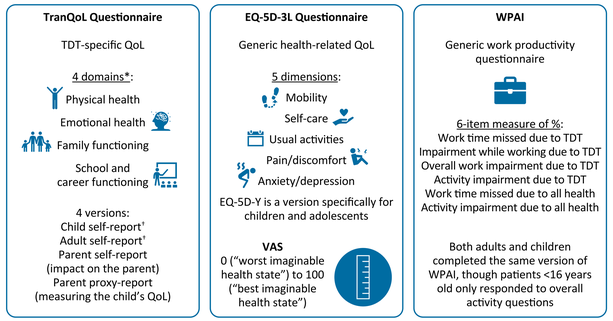
Figure 1. Study design



TDT, transfusion-dependent β-thalassemia.

- Patients completed the EQ-5D-3L (for patients >16 years old)[5,6], the EQ-5D-Y (for patients 12–15 years old), the TranQoL questionnaire (adult or child self-report version), and the WPAI questionnaire (**Figure 2**).[2]

Figure 2. Patient-reported outcome measures



*An additional domain of sexual health is included in the adult and parent self-report versions, but is not included for pediatric patients. †Versions used in this study (12 to <16 years [child] and ≥16 years [adult]).
EQ-5D-3L, EuroQoL 5 Dimensions 3 Level Version; EQ-5D-Y, EuroQoL 5 Dimensions Youth Version; TDT, transfusion-dependent thalassemia; TranQoL, transfusion-dependent quality of life; VAS, visual analog scale; WPAI, work-productivity assessment inventory.

- Clinical data collected included: timing of last transfusion, number of transfusions during the past year, and hemoglobin levels during the past 6 months.
- As a US value set for EQ-5D-Y does not exist, scores were derived using the value set for Spain.[10]
- Correlations between the EQ-5D instruments, TranQoL, and days since last transfusion were assessed.
- Statistical analyses were completed using SAS (version 9.4).
- Statistical significance for all analyses was α = 0.05, and all tests were two-tailed.
- P-values were generated for all correlations.
- Floor and ceiling effects were assessed. These effects occur when many patients score the minimum or maximum values, limiting the ability of the test to differentiate within groups of patients at either end of the scale.

RESULTS

Demographics and clinical characteristics

- 9 patients 12–15 years old (mean age: 13.0 years old) and 23 patients >16 years old (mean age: 36.9 years old) completed the study (**Table 1**).

Table 1. Baseline demographics and clinical characteristics by questionnaire completed[a]

Characteristic	Patients Aged 12–15 N=9	Patients Aged ≥16 N=23	All patients N=32
Age, years (mean, SD)	13.0 (1.2)	36.9 (12.3)	30.2 (15.1)
Sex, n (%)			
Male	4 (44.4)	9 (39.1)	13 (40.6)
Female	5 (55.6)	14 (60.9)	19 (59.4)
Age at TDT diagnosis, months (mean, SD)	20.8 (18.0)	13.9 (15.1)	15.2 (15.6)
Number of days since last transfusion (mean, SD)	33.6 (32.6)	43.5 (29.5)	40.7 (30.2)
Number of transfusion episodes in the past year (mean, SD)	14.9 (2.8)	18.0 (4.5)	17.1 (4.3)
Highest Hb over the past 6 months, g/dL (mean, SD)	11.8 (2.4)	11.0 (0.7)	11.3 (1.4)
Lowest Hb over past 6 months, g/dL (mean, SD)	8.5 (0.9)	8.6 (1.0)	8.6 (0.9)

EQ-5D, TranQoL, and WPAI scores

- The mean (SD) EQ-5D-3L index score was 0.86 (0.15), with 9 (42.9%) patients at the ceiling (**Table 2**).
- The mean (SD) EQ-5D-Y visual analog scale score was 90.56 (10.73), with 3 (33.3%) at the ceiling (**Table 2**).

Table 2. EQ-5D Scores

Item	N	Mean	SD	Range	95% CI	Floor,[a] n (%)	Ceiling,[b] n (%)
EQ-5D-3L (patients aged ≥16)							
Mobility	23	-	-	1.00–2.00	-	18 (78.3)	0
Self-care	23	-	-	1.00–2.00	-	22 (95.7)	0
Usual activities	23	-	-	1.00–2.00	-	17 (73.9)	0
Pain/discomfort	21	-	-	1.00–3.00	-	12 (57.1)	0
Anxiety/depression	23	-	-	1.00–2.00	-	13 (56.5)	0
Index score	21	0.86	0.15	0.45–1.00	0.79–0.93	0	9 (42.9)
VAS	23	73.91	15.30	35.00–100.00	67.30–80.53	0	1 (4.3)
EQ-5D-Y (patients aged 12-15)							
VAS	9	90.56	10.73	70.00–100.00	82.31–98.80	0	3 (33.3)

[a]The floor refers to the lowest possible score on any given scale or item. [b]The ceiling refers to the highest possible score on any given scale or item.
CI, confidence interval; EQ-5D-3L, EuroQoL 5 Dimensions 3 Level Version; EQ-5D-Y, EuroQoL 5 Dimensions Youth Version; SD, standard deviation
VAS, visual analog scale.

- Mean (SD) TranQoL score was 77.58 (9.07) among patients aged 12–15 years old (**Table 3**) and 67.12 (17.53) among patients aged >16 years old (**Table 4**).

Table 3. TranQoL scores for patients aged 12–15 years old (N=9)

Domain	N	Mean	SD	Range	95% CI	Floor,[a] n (%)	Ceiling,[b] n (%)
Physical health	9	80.56	16.00	58.33–100.00	68.26–92.86	0	2 (22.2)
Emotional health	9	70.37	7.98	55.56–80.56	64.24–76.50	0	0
Family health	9	86.73	6.48	77.78–94.44	81.75–91.71	0	0
School and career health	9	68.75	14.66	50.00–93.75	57.48–80.02	0	0
Overall score	9	77.58	9.07	63.39–90.18	70.61–84.55	0	0

[a]The floor refers to the lowest possible score on any given scale or item. [b]The ceiling refers to the highest possible score on any given scale or item.
CI, confidence interval; SD, standard deviation; TranQoL, transfusion-dependent quality of life.

Table 4. TranQoL scores for patients aged ≥16 years old (N=23)

Domain	N	Mean	SD	Range	95% CI	Floor,[a] n (%)	Ceiling,[b] n (%)
Physical health	23	69.34	19.80	25.00–97.50	60.77–77.90	0	0
Emotional health	23	67.33	17.46	25.00–98.21	59.78–74.88	0	0
Sexual health	17	57.35	24.63	0–100.00	44.69–70.02	1 (5.9)	1 (5.9)
Family health	22	65.68	23.21	20.00–100.00	55.39–75.97	0	1 (4.5)
School and career health	23	65.36	24.67	20.00–100.00	54.69–76.03	0	2 (8.7)
Overall score	23	67.12	17.53	26.39–95.83	59.54–74.70	0	0

- None of the 12–15 year-old participants had paid employments; these group reported a mean of 20% impairment in regular daily activities.
- 18/23 (78.3%) of participants ≥16 years old were employed (**Table 5**).
  - — Employed participants missed an average of 8.65% of work time in the past week because of problems associated with TDT (e.g., disease symptoms and transfusion appointments) and experienced 31.46% overall work impairment due to TDT
  - — Across both employed and unemployed participants, a mean of 25.65% impairment in regular daily activities other than working at a job was reported

Table 5. WPAI score in participants aged ≥16 years old (N=23)

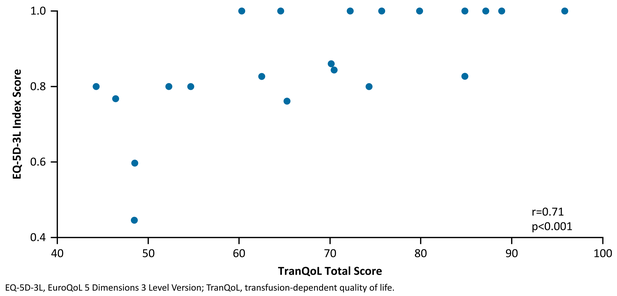
Item	N	Mean	SD	Range	95% CI	Floor, n (%)
Percent work time missed due to TDT[a]	17	8.65	15.74	0.00–50.00	0.56–16.75	9 (52.9)
Percent impairment while working due to TDT	18	25.56	26.62	0.00–70.00	12.32–38.79	6 (33.3)
Percent overall work impairment due to TDT[a]	17	31.46	29.35	0.00–75.00	16.37–46.55	4 (23.5)
Percent activity impairment due to TDT	23	25.65	25.91	0.00–90.00	14.45–36.85	6 (26.1)

[a]One participant marked that they were employed, however wrote that they worked 0 hours in the previous week.
Ceiling score was 0 for all items assessed.
CI, confidence interval; SD, standard deviation; TDT, transfusion dependent β-thalassemia; TranQoL, transfusion-dependent quality of life; WPAI, work-productivity assessment inventory.

Comparison of health-state utility and TDT-specific measures

- The EQ-5D-3L was correlated with the TranQoL (r=0.71; p<0.001) (**Figure 3**), however patients with a wide range of TranQoL scores had EQ-5D utilities of 1, suggesting that EQ-5D was not sensitive to QoL differences that were detected with the TDT-specific measure.

Figure 3. Correlation analysis of EQ-5D-3L versus TranQoL scores



EQ-5D-3L, EuroQoL 5 Dimensions 3 Level Version; TranQoL, transfusion-dependent quality of life.

- Neither EQ-5D version correlated significantly with the number of days since last blood transfusion.
  - — EQ-5D-3L: r=-0.097 (p=0.676)
  - — EQ-5D-Y: r=-0.345 (p=0.362)

LIMITATIONS

- Limitations of this study included:
  - — The small sample size, particularly for the subgroup aged 12–15 years, although this reflects the challenges of recruiting participants with rare conditions such as TDT
  - — Data were only collected at one timepoint; longitudinal data would allow more robust assessment of the sensitivity of QoL measures
  - — The 3-level version of the EQ-5D was used rather than the 5-level version, which is considered more sensitive to changes and differences in QoL

CONCLUSIONS

- TranQoL scores were generally consistent with what has been reported in the literature.[2]
- The substantial ceiling effect of the EQ-5D suggests it may not be sensitive to QoL impact in TDT.
- The lack of correlation between EQ-5D scores and days since last transfusion (a TDT clinical burden indicator) raises questions about the sensitivity of the EQ-5D to clinical burden.
- Additional research on EQ-5D and TranQoL correlation is warranted to create a foundation for more robust CUA of newer therapies for TDT, including gene therapies.

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DISCLOSURES

KG and **CP** are employees of bluebird bio and own bluebird bio stock/stock options. **TAH, JJ,** and **LSM** are employees of Evidera. **JB** has received consulting fees from bluebird bio, Accelleron, and Celgene, lecture payments from Clinical Care Options, and has served on a drug safety monitoring board role for Chiesi, and a medical advisory board role for Cooley's Anemia Foundation. **SAFS** has been an advisor for Focusvision, Vertex, and Sobi and a presenter for Agios and Gather Ed. **AKG** has received honoraria from Bausch Health and Global Blood Therapeutics. **SS** has received consulting fees from Agios Pharmaceuticals, bluebird bio, Bristol Myers Squibb, Forma, and Chiesi and has served on a clinical trial steering committee for CRISPR/Vertex CTX001 for thalassemia.

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