Evaluating the Appropriateness of the EQ-5D-5L Descriptive System and the Derived Health Utility Index Scores in Adults With Transfusion-Dependent β-Thalassemia: A Mixed-Methods Study

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Introduction and Objective

- Transfusion-dependent β-thalassemia (TDT) is a hereditary blood disorder requiring a lifelong regimen of frequent red blood cell transfusions (RBCTs) for survival,[1] leading to iron overload[2,3] and requiring chelation therapy
- Iron overload can result in progressive organ damage and life-threatening organ dysfunction.[4-6] Numerous secondary problems that arise from RBCTs have the potential to greatly impair health-related quality of life (HRQoL) and functional status and are major causes of morbidity and mortality in patients with TDT[2-4]
- The EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) is commonly used to derive health utility index scores for use in cost-effectiveness analyses. The EQ-5D-5L is a generic, preference-based measure of HRQoL, composed of 5 descriptive system (DS) dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression[7-8]
- The National Institute for Health and Care Excellence (NICE) Guide to the Methods of Technology Appraisal specifies a preference for using the EQ-5D-5L to derive health utility index scores to maintain "consistency" across their health technology appraisals[9]
- Despite the range of symptoms and functional impacts of TDT, studies in TDT show that EQ-5D-5L health utility index scores are often comparable to the general population scores (indicating good HRQoL),[10-13] which suggests that the EQ-5D-5L and derived health utility index scores may not adequately capture the impact of TDT or be responsive to changes in this population

Objective:

To examine the appropriateness of the EQ-5D-5L DS for use in adults with TDT

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Methods: Study Design

- This was a mixed-methods study of adults with TDT in the United States, the United Kingdom, and France, which included 60-minute 1:1 semi-structured qualitative interviews, administering both the EQ-5D-5L DS and a background questionnaire
- Key eligibility criteria included:
  - Self-reported TDT diagnosis and ≥8 RBCTs/year in each of the 2 years prior to enrollment
  - Aged 18 to 35 years
- Participants were recruited via patient panels and patient advocacy groups
- Participants completed the background questionnaire and EQ-5D-5L DS prior to their interviews. Participants completed the EQ-5D-5L DS twice: first, based on a typical day when they felt "**at their worst**" and second, based on a typical day when they felt "**at their best**"
- The qualitative interviews had 2 parts:
  - Part 1: Concept elicitation questions on the symptoms of TDT and the impacts of the disease and associated treatment on HRQoL
  - Part 2: Completion of the EQ-5D-5L DS for participants' current status, as well as questions on the perceived relevance of the EQ-5D-5L DS in capturing HRQoL
- Participant demographics/clinical characteristics and their quantitative valuations of the EQ-5D-5L DS were summarized using descriptive statistics

EQ-5D-5L DS, EuroQol 5 Dimensions 5 Levels descriptive system; HRQoL, health-related quality of life; RBCT, red blood cell transfusion; TDT, transfusion-dependent β-thalassemia.

Methods: Qualitative and Mixed-Methods Analysis

- Concept elicitation data were analyzed using thematic analysis, a qualitative method of identifying, analyzing, and reporting themes (disseminated separately)
- Cognitive debrief data were analyzed using qualitative content analysis, which provides a summary of responses to specific questions of interest
- A mixed-methods analysis was used to compare qualitative descriptions relating to the EQ-5D-5L DS dimensions and quantitative responses to determine the level of concordance/discordance
- A concept mapping exercise was also carried out, which involved determining whether concepts identified in the concept elicitation data were measured by the EQ-5D-5L DS

EQ-5D-5L DS, EuroQol 5 Dimensions 5 Levels descriptive system.

Results: Demographics

Category	Total (N = 30)
Age (years), mean (SD)	28 (5.1)
Sex, n (%)	
Female	22 (73.3)
Male	8 (26.7)
Country, n (%)	
United States	14 (46.7)
United Kingdom	12 (40.0)
France	4 (13.3)
Race, n (%)	
Asian or Pacific Islander	8 (26.7)
Other	8 (26.7)
Indian	5 (16.7)
Pakistani	5 (16.7)
White or Caucasian	5 (16.7)
Bangladeshi	2 (6.7)
Employment status, n (%)	
Employed full-time	15 (50.0)
In education/training	5 (16.7)
Employed part-time	4 (13.3)
Unemployed	4 (13.3)
Full-time homemaker/caregiver	1 (3.3)
Sick leave	1 (3.3)
Education, n (%)	
Bachelor's degree and above	27 (90.0)
No degree	3 (10.0)

SD, standard deviation.

A total of **30 adults** participated in the study: **46.7%** were from the United States and **53.3%** were from Europe (i.e., France and the United Kingdom)

73.3% of participants were **female**

90.0% of participants had a **bachelor's degree** or **higher**

Only 50.0% of participants were working full-time (≥32 hours/week)

Results: Clinical Characteristics

Category	Total (N = 30)
Age at diagnosis (years), mean (SD)	1 (2.1)
Age at first RBCT (years), mean (SD)	2 (3.4)
Number of RBCTs in past year, mean (SD)	18 (8.2)
Number of RBCTs in year before last, mean (SD)	18 (7.7)
Symptoms present in the past 3 months, n (%)	
Tiredness or fatigue	30 (100)
Weakness	27 (90.0)
Pain or discomfort	26 (86.7)
Shortness of breath	22 (73.3)
Tachycardia	15 (50.0)

Participants reported receiving a mean of **18** (SD: 8.2) RBCTs in the **past 12 months**

The key reported symptoms (≥50% frequency) **present in the past 3 months** were:

- Tiredness/fatigue (100%)
- Weakness (90.0%)
- Pain/discomfort (86.7%)
- Shortness of breath (73.3%)
- Tachycardia (50.0%)

RBCT, red blood cell transfusion; SD, standard deviation.

Results: Cognitive Debriefing – EQ-5D-5L DS Did Not Always Capture TDT Experience

- Overall, 42.9% of participants (n = 12/28) reported negative or neutral overall impressions about the EQ-5D-5L DS
  - 17.9% (n = 5) participants were neutral and did not express any opinions about the EQ-5D-5L DS
  - 25.0% (n = 7) participants held negative overall impressions about the EQ-5D-5L DS

- In addition, 45.8% of participants (n = 11/24) felt the EQ-5D-5L DS did not capture their experience of living with TDT, for reasons including:
  - The questions were not always relevant, because their TDT symptoms fluctuated
  - The EQ-5D-5L DS was too simple and did not capture nuances in disease
  - A missing concept was reported (i.e., social support and broader aspects of mental health)
  - The EQ-5D-5L DS had a poor layout
  - It would be better for the EQ-5D-5L DS to ask about average experiences with TDT rather than about experiences with TDT on a single day

"They're asking the questions that sometimes affect me and sometimes they don't affect me."

– Participant 116, United Kingdom

"It's just very minimalistic … it's not as nuanced."

– Participant 248, United States

EQ-5D-5L DS, EuroQol 5 Dimensions 5 Levels descriptive system; TDT, transfusion-dependent β-thalassemia.

Results: Cognitive Debriefing – EQ-5D-5L DS Did Not Capture Important Aspects of Living With TDT

- Overall, 74.1% of participants (n = 20/27) reported that the EQ-5D-DS did not capture **important aspects** of their experience of living with TDT
- 29.6% of participants (n = 8/27) commented that the EQ-5D-5L DS did not capture how their experience of living with TDT changes depending on where they were in their RBCT cycle
- Other reported examples of **important aspects** of the experience that the EQ-5D-5L DS did not capture included:
  - Social support and relationships (22.2% [n = 6/27])
  - Fatigue (22.2% [n = 6/27])
  - Broader aspects of mental health other than depression and anxiety (14.8% [n = 4/27])
  - Practical impacts relating to the requirement to have ongoing RBCTs (11.1% [n = 3/27])
  - Education/work (7.4% [n = 2/27])
  - Finances (7.4% [n = 2/27])

"Today's a good day so you're not getting my truest answers when it comes to transfusion dependant stuff."

– Participant 207, United States

"It would be good to have a question on what social support…from my own experience and you know, learning about it from other people who've lived with thalassemia, a few of my friends, the social support is a huge aspect."

– Participant 252, United States

EQ-5D-5L DS, EuroQol 5 Dimensions 5 Levels descriptive system; RBCT, red blood cell transfusion; TDT, transfusion-dependent β-thalassemia.

Results: Mixed Methods – Some Discordance Between Qualitative Descriptions and EQ-5D-5L DS Dimension Scores Was Observed

- Overall, some participants reported more severe qualitative descriptions of their TDT than what their EQ-5D-5L DS scores indicated
- Some participants reported **no problems** on the EQ-5D-5L DS when feeling at their **worst**, **but the qualitative description indicated more severe impairment**. Select participant quotes are summarized below

Mobility

"If it's on flat ground, there's no problem, but... there you go. If I start to... to "climb", between quotation marks, it becomes... it becomes difficult."

– Participant 319, France

Self-care

"I would say self-care on bad days it's harder to get ready for the day, when you're feeling really tired or you're feeling depressed because of it. It's really like such a chore to even like get ready for the day, you feel so tired. So, it does impact self-care."

– Participant 205, United States

Anxiety/depression

"When you're feeling at your worst, you tend to…, you sleep more, you're sort of less energetic, you sort of… feel down in the dumps as such, you sometimes question… what- why do I have to go through with this and you can sometimes get yourself a little bit worked up."

– Participant 107, United Kingdom

EQ-5D-5L DS, EuroQol 5 Dimensions 5 Levels descriptive system; TDT, transfusion-dependent β-thalassemia.

Results: Concept Mapping – Qualitative Data to EQ-5D-5L DS Domains

	Concepts Identified in Qualitative Interviews[a]															
EQ-5D-5L DS Dimension	**Fatigue**	**Pain**	**Shortness of breath**	**Headaches**	**Heart palpitations**	**Dizziness**	**Weakness**	**Sleep problems**	**Concentration difficulties**	**Reduced appetite**	**Mobility**	**Time and planning**	**Self-care**	**Emotional wellbeing**	**Daily activities**	**Relationships**
Mobility																
Self care																
Usual activities																
Pain/discomfort																
Anxiety/depression																
Overall																

- The EQ-5D-5L DS did not capture **11 of 16 (68.8%)** symptoms/functional impacts elicited across all interviews (N = 30)
  - **No coverage (n = 8/16 [50.0%]):** shortness of breath, heart palpitations, dizziness, weakness, sleep problems, concentration difficulties, reduced appetite, and relationships
  - **Partial coverage (n = 3/16 [18.8%])**: fatigue, time and planning, emotional wellbeing

EQ-5D-5L DS, EuroQol 5 Dimensions 5 Levels descriptive system.

[a]**Pink**: **concept covered** by EQ-5D-5L domain. **Blue**: **concept partially covered** by EQ-5D-5L domain. **Blank**: **concept not covered.**

Limitations

- Study participants were self-selected and needed access to the Internet and email, which may impact the generalizability of these results

Conclusions

- The EQ-5D-5L DS does not capture most of the symptoms or functional impacts of TDT
  - Most notably, fatigue was not captured, which is a key symptom of TDT
- There were notable examples where the qualitative descriptions were worse than patient reports on the EQ-5D-5L DS
- The EQ-5D-5L DS lacks the capacity to capture fluctuating symptoms over time (i.e., given the recall period of “today”). In TDT, EQ-5D-5L DS responses are highly dependent on where patients are in their RBCT cycle – likely a reflection of fluctuating hemoglobin levels
- Overall, the findings from this mixed-methods study question the content validity of the EQ-5D-5L DS, and the ability of the derived health utility index score to fully represent the burden of disease in TDT

EQ-5D-5L DS, EuroQol 5 Dimensions 5 Levels descriptive system; RBCT, red blood cell transfusion; TDT, transfusion-dependent β-thalassemia.

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CME, continuing medical education.

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