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## RESEARCH ARTICLE

# Development of a patient-reported outcomes symptom measure for patients with nontransfusion-dependent thalassemia (NTDT-PRO<sup>©</sup>)

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## Abstract

$\beta$ -Thalassemia, a hereditary blood disorder caused by reduced or absent synthesis of the  $\beta$ -globin chain of hemoglobin, is characterized by ineffective erythropoiesis, and can manifest as nontransfusion-dependent thalassemia (NTDT) or transfusion-dependent thalassemia (TDT). Many patients with NTDT develop a wide range of serious complications that affect survival and quality of life (QoL). Patient-reported outcomes (PRO), including health-related QoL (HRQoL), are important tools for determining patient health impairment and selecting appropriate treatment. However, there are currently no disease-specific PRO tools available to assess symptoms related to chronic anemia experienced by patients with NTDT. This study aimed to develop a new, US Food and Drug Administration (FDA)-compliant PRO of chronic anemia symptoms, the NTDT-PRO<sup>©</sup> tool, for use in patients with NTDT. Participants had a median age of 36 years (range, 18-47) and 60% were female. The initial development of the NTDT-PRO tool involved concept-elicitation interviews with 25 patients from 3 centers (in Lebanon, Greece, and Canada); subsequent interview discussions and clinical input resulted in the generation of 9 items for inclusion in the draft NTDT-PRO. Following a round of cognitive interviews involving 21 patients from 2 centers (in Lebanon and Greece), 4 items (Pain, Headaches, Ability to Concentrate, and Paleness) were removed from the draft NTDT-PRO. The final NTDT-PRO comprises 6 items that measure Tiredness, Weakness, and Shortness of Breath, with or without Physical Activity. The NTDT-PRO is a new disease-specific HRQoL tool for patients with NTDT, developed using a thorough methodology based on FDA 2009 PRO development guidelines.

## 1 | INTRODUCTION

$\beta$ -Thalassemia is a hereditary blood disorder caused by reduced or absent synthesis of the  $\beta$ -globin chain of hemoglobin and is characterized by ineffective erythropoiesis.<sup>1</sup> Patients with  $\beta$ -thalassemia may

be classified as having either nontransfusion-dependent thalassemia (NTDT) or transfusion-dependent thalassemia (TDT). Overall, the treatment options for  $\beta$ -thalassemia patients are limited and focus on symptomatic relief. For patients with TDT, this involves regular and lifelong red blood cell (RBC) transfusions from the first months of life along with iron chelation therapy. In contrast, treatment options for patients with NTDT largely focus on the management of the long-

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term complications of ineffective erythropoiesis, which are not eliminated through suppression of erythropoiesis by chronic transfusion protocols, as in TDT patients.<sup>2,3</sup> Treatment options targeting NTDT and its complications are limited and include splenectomy, RBC transfusions, iron chelation therapy, and hydroxyurea in some cases.<sup>4</sup> A novel therapeutic agent, luspatercept (under development by Celgene Corporation, Summit, NJ, USA) is in phase 3 clinical development for the treatment of patients who require regular RBC transfusions due to  $\beta$ -thalassemia (Piga et al., manuscript submitted for publication).

Despite the increased transfusion burden associated with TDT and perception of increased disease severity in comparison with NTDT, most patients with NTDT also develop an array of serious complications that compromise survival and health-related quality of life (HRQoL). Such complications include activity-limiting anemia, bone pain, low bone density, leg ulcers, pulmonary hypertension, silent cerebral ischemia, and renal disease.<sup>4,5</sup> These patients may also have low levels of hemoglobin, which is associated with a reduced HRQoL,<sup>6</sup> compounding the fact that the therapy required to treat NTDT and its complications may also have a negative impact on patient HRQoL.<sup>3</sup>

Patient-reported outcome (PRO) measures, including HRQoL, are important tools for determining patient health impairment and selecting appropriate treatment. Although disease-specific PRO questionnaires have been developed for patients with TDT (TranQoL<sup>7</sup>; Specific Thalassemia Quality of Life Instrument, STQOLI<sup>8</sup>), there are currently no disease-specific PRO tools available to assess symptoms related to chronic anemia experienced by patients with NTDT.

Regulatory agencies, such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have expressed interest in the use of disease-specific PROs in establishing product efficacy and safety, as well as in documenting the patient's experience of their illness and treatment. The qualitative research described here is a first step in generating a NTDT-specific symptom PRO tool and it follows 2009 FDA industry guidelines for the development of PRO tools.<sup>9</sup> It is also consistent with expert guidelines for the development of PRO tools in the medical product development context.<sup>10</sup>

The objective of the present study was to develop a new PRO tool, the NTDT-PRO<sup>®</sup>, for use in patients with NTDT.

## 2 | METHODS

### 2.1 | Development of the NTDT-PRO tool

A qualitative study was carried out to develop the NTDT-PRO tool, consistent with regulatory and expert guidance. Development was carried out in four stages: concept elicitation, item generation, cognitive interviews, and modification (Figure 1).

Interviews were conducted in the native language of each patient by trained interviewers and audio-recorded. Transcripts were subsequently translated into English for analysis.

#### 2.1.1 | Stage 1: Concept elicitation

To identify symptoms associated with NTDT and determine the impact of those symptoms on patients with NTDT, a cross-sectional, qualitative,

concept-elicitation-interview study was carried out with patients recruited from 3 centers in Lebanon, Greece, and Canada; local institutional review board (IRB) approval was obtained for all 3 centers. Patients who were  $\geq 18$  years of age and presented with a NTDT diagnosis, confirmed by clinical chart review, were eligible to participate; eligible patients were invited to participate in a face-to-face interview at their local clinical center. Interviews were conducted by trained interviewers and were carried out using a standardized, semi-structured discussion guide, which was developed based on a literature review and findings from a Delphi panel of 7 clinical experts. The patient interviews were conducted in 2 parts: during the first part, patients were asked open-ended questions to gather information about their symptom experiences and the impact of NTDT on their symptoms and functioning; the second part of the interview focused on specific symptoms, identified by the Delphi panel and a literature review, which had not been mentioned during the first part of the interview. Clinical center staff completed a form for each patient, recording pertinent data of their clinical history, including the date of diagnosis, medication history, and complications of NTDT. Each interview lasted approximately 90 min.

#### 2.1.2 | Stage 2: Item generation and data analysis

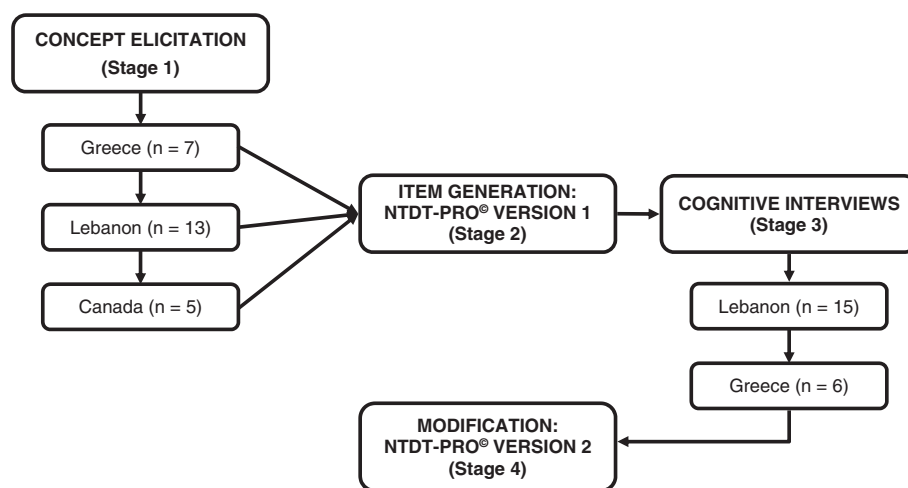
The aim of stage 2 was to develop a draft NTDT-PRO instrument, based on the concept-elicitation interviews conducted during stage 1. Quantitative data (sociodemographic and clinical data, 36-Item Short Form Health Survey version 2 [SF-36v2], and Functional Assessment of Cancer Therapy-Anemia [FACT-An]) responses were stored in a database that was developed, tested, and validated using DataFax (an optical character-recognition software; Clinical DataFax Systems, Inc., Hamilton, ON, Canada) and reviewed by project scientific staff. Data discrepancies were identified and resolved prior to being summarized using descriptive statistics.

Qualitative data from the transcripts were summarized using ATLAS.ti qualitative data analysis software (ATLAS.ti v.7.1.8; ATLAS.ti GmbH, Berlin, Germany). A content-analysis approach was used to analyze qualitative data, and a coding scheme was created based on the structure and content of the discussion guide. Concepts identified during each concept-elicitation interview were analyzed with the aim of comparing and quantifying the amount of novel information observed in each subsequent interview; overall saturation occurred when no novel information emerged from subsequent interviews. Key symptoms were identified based on prevalence and perceived importance for patients interviewed. Based on these data, the NTDT-PRO version 1 (NTDT-PRO.v1) was created to assess the severity of NTDT from a patient perspective.

A conceptual framework, depicting domains and possible scoring, was developed and modified during the development of the NTDT-PRO instrument.

#### 2.1.3 | Stage 3: Cognitive interviews

Cognitive interviews were carried out using the NTDT-PRO.v1 to ensure the content of the tool captured all relevant symptoms, was understandable by patients, and included suitable response options and recall period. This stage was also designed to identify any necessary modifications required to produce a final version of the



**FIGURE 1** Study chronology. NTDT-PRO<sup>®</sup>, nontransfusion-dependent thalassemia patient-reported outcomes symptom measure

NTDT-PRO. A cross-sectional qualitative interview study was conducted with patients from 2 clinical centers in Lebanon and Greece; these were the same centers used in the concept-elicitation phase, and IRB approval was obtained for both centers.

To ensure consistency between stages, the same eligibility criteria, patient recruitment methods, and data collection processes were used as during stage 1 (concept elicitation). Eligible patients were invited to a face-to-face interview at their local clinical center. Due to the rarity of the disease, patients were permitted to participate in both concept-elicitation interviews and cognitive interviews, although different patients were preferred. Patients were subsequently asked to complete the NTDT-PRO.v1. Interviews were then conducted using a standardized semi-structured discussion guide focusing on the discussion of instructions, content and formatting of individual items, response options, and recall period.

Sociodemographic and clinical information was collected as in the concept-elicitation interviews. Descriptive statistics were used to summarize clinical characteristics, and quantitative data from the NTDT-PRO.v1 and the sociodemographic questionnaire.

Qualitative data from cognitive interviews were assessed using ATLAS.ti; a programming workflow was generated to analyze the structure and content of the discussion guide; understanding of the instructions, questionnaire content, symptom recall period, and question response options were evaluated for each item. Degree of understanding was assessed for each item; patients' comments for improvement were coded separately.

#### 2.1.4 | Stage 4: Modification based on cognitive interviews

The final stage involved identification and implementation of updates to the NTDT-PRO.v1, based on findings from cognitive interviews and clinical input.

## 3 | RESULTS

### 3.1 | Concept-elicitation interviews

A total of 25 patients from the centers in Lebanon ( $n = 13$ ), Greece ( $n = 7$ ), and Canada ( $n = 5$ ) were included in the concept-elicitation interviews; demographic and clinical characteristics are presented in Table 1.

The most frequent complications included bone disease ( $n = 16$ ), cholelithiasis ( $n = 10$ ), deep vein thrombosis ( $n = 7$ ), extramedullary hematopoiesis ( $n = 4$ ), and ulcers on the lower extremities ( $n = 4$ ); 2 patients (8%) did not report complications. Splenectomy was reported in 20 patients.

Based on the concept-elicitation interviews, a total of 11 distinct symptoms were identified among patients (descending order of reported frequency): tiredness/fatigue (88%), weakness (80%), breathlessness (80%), pain (72%), headaches (72%), skin pallor (68%), sleep problems (60%), cognitive impairment (52%), dizziness/lightheadedness (32%), chest problems (28%), and sexual problems (19%).

Of the 25 patients interviewed, 21 (84%) patients reported physical impacts as a result of their disease, and 18 (72%) patients reported that their daily activities were limited as a result; impact on work or school life was reported by 17 (68%) patients. Additionally, 15 (60%) patients reported anxiety and 15 (60%) patients reported that their disease had an impact on their social life.

### 3.2 | Item generation

Based on findings from the concept-elicitation interviews, the NTDT-PRO.v1 was developed. The NTDT-PRO.v1 included 9 items assessing the following symptoms: Tiredness without Physical Activity, Tiredness with Physical Activity, Weakness, Shortness of Breath (SoB)

**TABLE 1** Demographic and clinical characteristics

Patient characteristic	Concept-elicitation cohort (n = 25)	Cognitive-interview cohort (n = 21)
Median age (range), years	36 (18–47)	37 (23–45)
Female, n (%)	15 (60.0)	11 (52.4)
Thalassemia diagnosis, n (%)		
β-Thalassemia intermedia	23 (92.0)	21 (100)
HbE/β-thalassemia	2 (8.0)	0
Median time since diagnosis (range), years	29.0 (17–47)	28.0 (12–45)
Hospitalization in last 3 months, n (%)	2 (8.0)	2 (9.5)
Number of NTDT complications, n (%)		
<3	14 (56.0)	14 (66.7)
3–5	9 (39.1)	5 (23.8)
≥6	0	2 (9.5)
Highest education level, n (%)		
Primary/elementary	2 (8.0)	2 (9.5)
Secondary/high school	7 (28.0)	8 (38.1)
College/university	14 (56.0)	8 (38.1)
Unknown/other	2 (8.0)	3 (14.3)

Abbreviations: HbE, hemoglobin E; NTDT, nontransfusion-dependent thalassemia.

without Physical Activity, SoB with Physical Activity, Worst Pain, Headaches, Ability to Concentrate, and Paleness. An 11-point numerical rating scale, ranging from 0 (“no symptom”) to 10 (“very extreme symptom”) was used for each item. The items asked the patient to consider their experience over the past 24 hours when responding.

### 3.3 | cognitive interviews

A total of 21 patients, 15 from 1 center in Lebanon and 6 from 1 center in Greece, participated in 2 rounds of cognitive interviews; summarized demographic and clinical characteristics are presented in Table 1. A total of 13 patients (8 of the 15 patients recruited in Lebanon and 5 of the 6 patients recruited in Greece) took part in both the concept-elicitation stage and the cognitive-interview stage of the study.

The items covering Worst Pain and SoB without Physical Activity showed a notable floor effect—47% and 62% of patients rating these outcomes as 0, respectively. The remainder of items showed a good distribution of reported values across the 0–10 range, with responses in the lower two-thirds of the scale seen most frequently.

Mean item scores for the NTDT-PRO.v1 ranged from 1.2 (Headaches) to 4.2 (Tiredness with Physical Activity) (Table 2). All patients reported that the instructions in the NTDT-PRO.v1 were clear and easy to understand. The 24-hr recall period was understood and easily adhered to by all patients who were specifically asked the question (n = 21).

Overall, patient comprehension reflected the intended meaning of the items. However, 5 patients did not understand the question relating to “SoB while not engaging in physical activity,” largely due to variation in patient definitions of “no physical activity” (eg, from “not

**TABLE 2** NTDT-PRO<sup>®</sup>.v1 item scores

	Cognitive-interview Cohort (n = 21)
Tiredness without Physical Activity	3.2 (2.7)
Tiredness with Physical Activity	4.2 (2.6)
Weakness	3.4 (2.6)
Shortness of Breath without Physical Activity	2.0 (3.1)
Shortness of Breath with Physical Activity	3.3 (2.4)
Worst Pain	2.4 (2.5)
Ability to Concentrate	2.7 (2.5)
Headaches	1.2 (2.0)
Paleness	3.9 (2.9)

Values shown are mean (SD) NTDT-PRO.v1 item scores; severity range 0 (no) to 10 (high).

NTDT-PRO<sup>®</sup>.v1, nontransfusion-dependent thalassemia patient-reported outcomes measure, version 1; SD, standard deviation.

doing anything” to “not running errands”). A few patients (3/21, 14%) found the question on weakness ambiguous, due to a lack of clarity regarding whether the item referred to physical weakness, or emotional, psychological, intellectual, social, or personality weakness; some patients also highlighted that they were already weak (ie, “Weak physically. We are already weak, I mean we are not healthy, we do not have a strong body”). Additionally, although the majority of the patients understood the question on skin pallor, several patients erroneously reported “yellowness” due to jaundice, rather than “paleness” due to anemia.

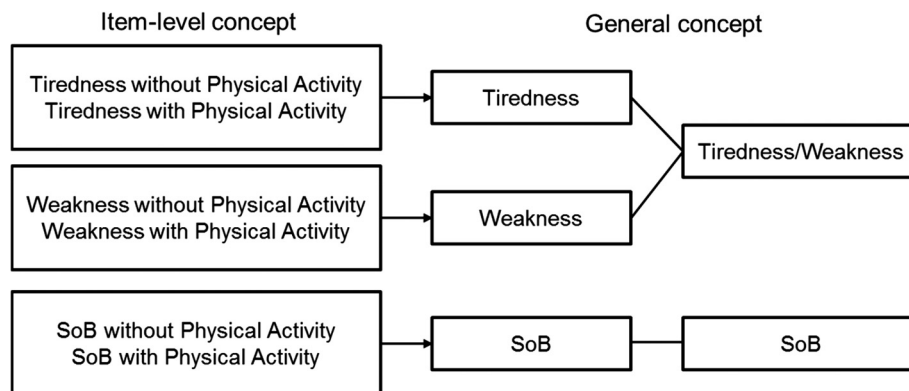
No additional symptoms were identified during the cognitive interviews.

### 3.4 | Modifications based on cognitive interviews

Based on patient and clinical input gained during the cognitive-interview stage, the NTDT-PRO.v1 was revised as follows: attribution of the symptoms to NTDT was removed from the patient instructions, as FDA guidance states that patients may not be able to attribute symptoms to their condition; items related to tiredness and SoB were removed or rephrased to include reference to physical activity; Weakness was revised to Physical Weakness for improved clarity; 4 items were deleted (Worst Pain, Headaches, Ability to Concentrate, and Paleness). Worst Pain was removed from the NTDT-PRO.v1 as it was unclear whether this was a symptom of NTDT or a complication related to treatment, and it was felt that this would be better captured as an adverse event. Headaches, Ability to Concentrate, and Paleness were removed as tool items as they were not considered to be core symptoms (ie, distal to NTDT). These symptoms were also less frequently reported by patients, which contributed to the decision to exclude these 4 items initially included in the conceptual framework.

#### 3.4.1 | NTDT-PRO and conceptual framework

Based on the findings of the patient interviews, a 6-item revised NTDT-PRO.v2<sup>®</sup> instrument was developed (Appendix and Table S1 of the Supporting Information). The NTDT-PRO was designed as a daily diary with recall of thalassemia-related symptoms over the previous 24 hr. The relatively short recall period was chosen due to the high



**FIGURE 2** Conceptual framework. SoB, shortness of breath

level of day-to-day variation in symptoms experienced by patients with NTDT.

The 6 NTDT-PRO items assessed the presence or severity of specific symptoms using a numerical rating scale ranging from 0 ("absent/minimal") to 10 ("extreme/high"): Tiredness with or without Physical Activity, Weakness with or without Physical Activity, and SoB with or without Physical Activity.

NTDT-PRO items were grouped a priori into 2 domains, based on the conceptual framework (Figure 2): Tiredness/Weakness (Tiredness with Physical Activity, Tiredness without Physical Activity, Weakness with Physical Activity, and Weakness without Physical Activity) and SoB (SoB with Physical Activity, SoB without Physical Activity).

## 4 | DISCUSSION

General anemia/HRQoL instruments may not be useful for patients with NTDT as they do not include the individual patient experience of symptom severity. Disease-specific HRQoL PRO tools are currently available for patients with TDT.<sup>7,8</sup> However, available TDT tools, such as the TranQol<sup>7</sup> and STQOLI,<sup>8</sup> are not appropriate for patients with NTDT; patients with TDT receive transfusions more frequently, and report a higher frequency of hospitalization, resulting in a different impact on HRQoL and perceived burden of disease. Furthermore, the treatment pathways and disease progression are not equal for patients with TDT and NTDT. As the impact of thalassemia on HRQoL is perception-based, there is a need for a PRO HRQoL tool to determine NTDT patients' individual physical and social requirements.

The primary objective of this study was to develop the first disease-specific PRO tool to assess reported symptom severity in patients with NTDT. In the present study, we defined the item selection and evaluated the appropriate analyses for NTDT-PRO. Patients were recruited from multiple geographic and socioeconomic backgrounds to increase the generalizability of the tool content, demonstrating evaluation and testing of this tool on a diversified patient cohort. Patients who received RBC transfusions (<5 units in the previous 24 weeks to allow for RBC degradation) were excluded, as they may not exhibit the full symptom range seen in NTDT patients. In addition, a threshold of less than 10 g/dL hemoglobin was set to ensure faithful recapitulation of low tissue oxygen delivery. To ensure applicability, the NTDT-PRO was developed in multiple languages

(Italian, Greek, Arabic, and English); however, this may have contributed to the misunderstanding in physical versus emotional weakness. Modifications were also required to account for nonmedical interpretation of skin pallor, as this was interpreted by some patients as jaundice. To ensure clarity and understanding among the target patient population, 2 rounds of cognitive interviews were conducted among patients with NTDT in Greece and Lebanon. While findings from these cognitive interviews indicated that participants understood the items as intended, there may be a need for future translations that take more account of cultural considerations.

The NTDT-PRO was developed using concept-elicitation interviews, interview discussions, cognitive interviews, and clinical input. Compared with existing tools for evaluating HRQoL in patients with TDT (ie, TranQol), the NTDT-PRO is considerably shorter, comprising 6 items across 2 domains (Tiredness/Weakness and SoB) in addition to an overall severity score, versus 37 items over 4 domains for the adult form of the TranQol,<sup>7</sup> and 28 items over 4 domains for the STQOLI.<sup>8</sup> This is important as it provides patients with a PRO tool to quickly report on their disease severity, allowing symptom reporting with higher sensitivity for the prescribing physician. One of the key findings from the development of the TranQol was the difference in the reported HRQoL priorities between patients with TDT and other patient groups, that is, relating to the disease-specific impact of thalassemia, and to the impact and risks associated with frequent transfusions.<sup>7</sup> There are a number of limitations associated with this study. As this was a noninterventional study, there are no data on the performance of the NTDT-PRO tool in response to treatment interventions. There are also limited data on the performance of the tool in different settings, such as community-based centers versus academic research centers, and how the tool can be generalized to a real-world setting (ecological validity).

Quantitative analysis to support the reliability and validity of the NTDT-PRO tool has been performed in an observational, noninterventional study (NCT02626689) (Taher et al, manuscript submitted for publication); however, future studies will be required to confirm the psychometric properties of the NTDT-PRO and its sensitivity in capturing changes. Additional assessment of what constitutes a minimal clinically important difference in interventional clinical trials is currently ongoing. We hope this tool will provide researchers with a more appropriate measure of the impact NTDT has on the HRQoL of

patients affected, both in daily clinical practice and in multicenter trials of novel interventions for patients with NTDT.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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