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ORIGINAL RESEARCH

# Development of a Patient-Reported Outcome (PRO) Measure to Assess Emotional Impact of Treatment for Type 2 Diabetes

Kristina S. Boye · Katie D. Stewart · Louis S. Matza

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## ABSTRACT

***Introduction***: Patients receiving treatment for type 2 diabetes (T2D) may experience an emotional impact associated with treatment-related changes. A patient-reported outcome (PRO) measure assessing both positive and negative emotional impact of medication treatment for T2D is needed to better understand the patient experience of treatment. The purpose of this qualitative study was to explore the emotional impact of treatment for T2D and support the development of a questionnaire to assess the emotional impact of treatment for T2D.

***Methods***: Exit interviews were conducted with patients with T2D participating in the SURPASS-2 and SURPASS-3 trials for tirzepatide. The exit interviews included a concept elicitation section focusing on the emotional impact of their study treatment. Results were used to develop two questionnaires that were evaluated in cognitive interviews with patients with T2D.

***Results***: The concept elicitation interviews included 28 patients (mean age 57.6 years; 64.3% female). Most patients reported positive changes in emotions associated with tirzepatide, including increased confidence ($n$ = 23; 82.1%), hope ($n$ = 23; 82.1%), self-esteem ($n$ = 23; 82.1%), relief ($n$ = 22; 78.6%), optimism ($n$ = 21; 75.0%), sense of control ($n$ = 21; 75.0%), happiness ($n$ = 15; 53.6%), and motivation ($n$ = 15; 53.6%), as well as reduced worry/anxiety ($n$ = 19; 67.9%). Negative emotional impact was less commonly reported but included frustration ($n$ = 2; 7.1%), worry/anxiety ($n$ = 1; 3.6%), fear ($n$ = 1; 3.6%), and feeling depressed ($n$ = 1; 3.6%). Two new PROs, the Emotional Impact of Diabetes Treatment Questionnaires (EIDTQ, status and comparison versions), were developed based on these finding. The status version assesses the emotional impact of current treatment, while the comparison version allows for comparison of the current treatment to a previous treatment. The questionnaires were refined on the basis of cognitive interviews with 20 additional patients (mean age 58.3 years; 60.0% female), and results suggest that the final instruments were clear, comprehensible, and relevant to patients.

***Conclusion***: The EIDTQ-Status and Comparison measures can be used as a supplement to

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K. S. Boye
Eli Lilly and Company, Indianapolis, IN, USA
e-mail: boye_kristina_secnik@lilly.com

K. D. Stewart · L. S. Matza (✉)
Evidera, 7101 Wisconsin Avenue, Suite 1400, Bethesda, MD 20814, USA
e-mail: louis.matza@evidera.com

K. D. Stewart
e-mail: katie.stewart@evidera.com

clinical outcomes, such as hemoglobin A1c (HbA1c) and body weight, to provide a broader picture of the patient's emotional experience with medication treatment for T2D.

## PLAIN LANGUAGE SUMMARY

Medical treatment can have broad effects beyond symptom improvement, including an emotional impact. Emotional impact is subjective and therefore can only be assessed from the patient perspective. However, there is no previously published patient-reported outcome measure assessing both positive and negative emotional impact of medication treatment for type 2 diabetes. Thus, the purpose of this study was to conduct qualitative research to support the development of two new patient-reported outcome measures designed to assess the emotional impact of type 2 diabetes. Overall, the results add to previous research indicating that treatment for type 2 diabetes can have an emotional impact. The newly developed Emotional Impact of Diabetes Treatment Questionnaires were designed to assess this emotional impact, and current qualitative results support the content validity of these instruments in patients with type 2 diabetes. These instruments can be used as a supplement to clinical outcomes, such as HbA1c and body weight, to provide a broader picture of the patient's experience with medication treatment for type 2 diabetes.

**Keywords:** Type 2 diabetes; Patient-reported outcome; PRO; Concept elicitation; Qualitative research

**Key Summary Points**

***Why carry out this study?***

Patients receiving treatment for type 2 diabetes (T2D) may experience an emotional impact associated with treatment-related changes. However, there is no previously published patient-reported outcome (PRO) measure assessing both positive and negative emotional impact of medication treatment for T2D.

The purpose of this study was to conduct qualitative research to support the development of two new PRO measures designed to assess the emotional impact of T2D.

***What was learned from the study?***

After participating in the SURPASS-2 and SURPASS-3 trials, patients reported positive changes in emotions associated with their medication for T2D, including increased confidence, hope, self-esteem, relief, optimism, sense of control, happiness, and motivation, as well as reduced worry/anxiety. Negative emotional impact was less commonly reported but included frustration, worry/anxiety, fear, and feeling depressed.

The Emotional Impact of Diabetes Treatment Questionnaires (EIDTQ, status and comparison versions) may be useful for evaluating the emotional impact of treatment for T2D.

## INTRODUCTION

Medical treatment can have broad effects beyond symptom improvement, including effects on multiple aspects of quality of life [1–3]. In some cases, treatment can have an emotional impact as improvement in

symptoms and other aspects of disease can lead to improvement in mood disturbance [4], emotional role limitation [5–7], anxiety [8, 9], and depression [9, 10]. Because the emotional impact of disease and treatment is subjective, it must be measured using patient-reported outcomes (PROs) [11–13].

Many generic PRO instruments include items assessing emotional status. For example, the Short Form Health Survey-36 (v2) includes items in a role-emotional subscale related to "problems with work or other daily activities as a result of emotional problems (such as feeling depressed or anxious)" and additional items with emotional content such as "nervous," "calm and peaceful," "downhearted and blue," and "happy" [14]. The EQ-5D includes a single item on anxiety and depression [15–18]. However, it should be noted that the emotion-related items from these generic instruments assess one's overall emotional state, rather than the emotional impact of treatment or any specific medical condition. Across a range of medical conditions, condition-specific PROs have been designed to assess aspects of emotional functioning. For example, the Functional Assessment of Cancer Therapy scale includes a subscale for emotional well-being [19]. Measures developed for use in chronic cardiovascular and pulmonary diseases such as the Minnesota Living with Health Failure Questionnaire, the Cambridge Pulmonary Hypertension Outcome Review, and the Asthma Quality of Life Questionnaire also assess emotional functioning [20–23]. Compared to generic instruments, these condition-specific measures allow for a more targeted assessment of specific types of emotional impact that may be associated with particular medical conditions or treatments.

Type 2 diabetes (T2D) is a chronic illness that has been shown to have a broad impact on multiple areas of quality of life, including physical [24], psychological [25], and social domains [26]. Treatment for T2D has the potential to affect aspects of emotional functioning such as depression and diabetes-related distress [27–31]. A wide range of PRO measures have been developed specifically for use in T2D, including questionnaires assessing symptom severity [32, 33], quality of life [34, 35], treatment satisfaction [36–39], injection device experience [40, 41], treatment simplicity [42], and treatment burden [8, 38, 40]. Two measures have been developed to assess psychosocial adjustment to diabetes and diabetes-related distress including the Problem Area in Diabetes Survey [43] and the Diabetes Distress Scale (DDS) [44], but these instruments focus on negative emotions associated with diabetes and do not assess the positive emotional impact of treatment-related benefits [43, 44]. There is no previously published diabetes-specific PRO measure assessing both the positive and negative emotional impact of medication treatment.

The purpose of this study was to conduct qualitative research to support the development of two new PRO measures designed to assess the emotional impact of T2D. To generate content for the questionnaires, patients with T2D were asked to describe the emotional impact of medication treatment. Their responses were used to inform the development of draft questionnaires. One version of this instrument was designed to evaluate the emotional impact of current treatment (status version), while the other was designed to compare the emotional impact of current treatment to that of previous treatment (comparison version). These draft questionnaires were then examined in a cognitive interview study with a different group of individuals with T2D.

## METHODS

### Overview of Study Steps

The Emotional Impact of Diabetes Treatment Questionnaire—Status (EIDTQ-Status) and Emotional Impact of Diabetes Treatment Questionnaire—Comparison (EIDTQ-Comparison) were developed through a series of steps summarized in Fig. 1. The first step focused on identifying concepts related to the emotional impact of treatment for T2D via literature review and interviews with relevant experts. The concepts identified in this step were used to inform the development of the concept

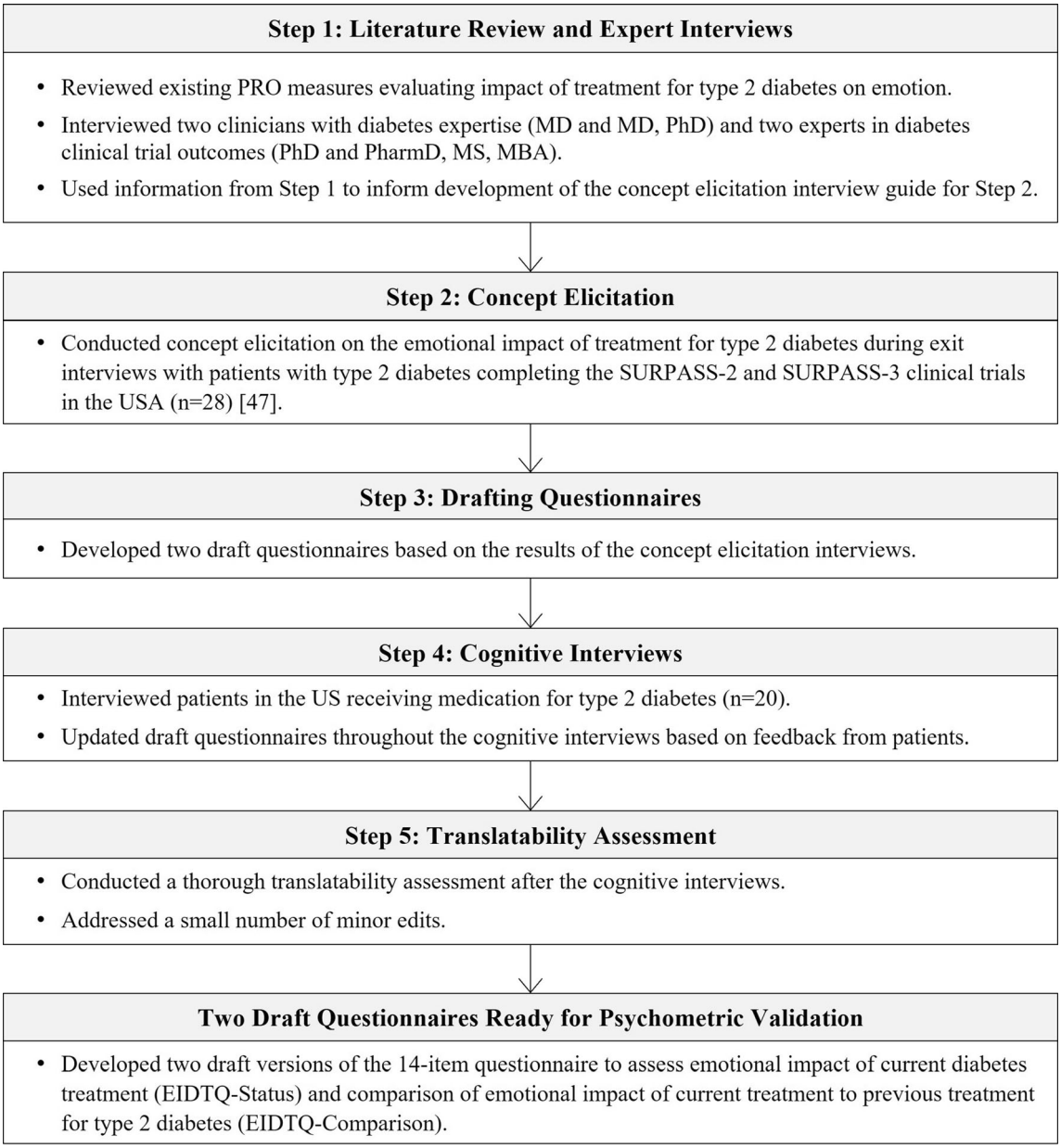


**Fig. 1** Summary of instrument development of the EIDTQ-Status and the EIDTQ-Comparison. *EIDTQ* Emotional Impact of Diabetes Treatment Questionnaire, *PRO* patient-reported outcome

elicitation interview guide and the initial drafts of the questionnaires.

Concept elicitation (step 2) was conducted during exit interviews with patients with T2D recently treated with tirzepatide in the SURPASS-2 or SURPASS-3 open-label phase III clinical trials [45, 46]. A description of these exit interviews has been published, but the published article does not report results on emotional impact, which is relevant to the current PRO measure development [47]. The concept elicitation results were used in step 3 to inform development of the two draft PRO instruments.

In step 4, the draft instruments were evaluated in cognitive interviews conducted with

patients receiving treatment for T2D. The cognitive interview participants were asked to complete the draft questionnaires and provide feedback on clarity, comprehensibility, comprehensiveness, redundancy, and relevance. The draft questionnaires were updated twice during the cognitive interview study based on patient feedback.

A translatability assessment was conducted (step 5) to ensure the resulting questionnaires would be suitable for translation. The two draft measures resulting from work in steps 1–5 were titled the Emotional Impact of Diabetes Treatment Questionnaire—Status (EIDTQ-Status) and the Emotional Impact of Diabetes Treatment Questionnaire—Comparison (EIDTQ-Comparison).

All study methods, materials, and clinical sites were approved by an independent review board (Ethical and Independent Review Services [E&I] study numbers 20122-01 and 21060-01). All participants provided informed consent prior to engaging in study procedures. All participants received remuneration for their time.

## Participants

### *Concept Elicitation (Step 2)*

Concept elicitation was conducted during clinical trial exit interviews, and detailed information on recruitment and inclusion criteria has previously been published [45–47]. All participants were required to have been treated for T2D with tirzepatide in either the SURPASS-2 or SURPASS-3 clinical trials. These patients were recruited from six clinical sites in the USA (California, Florida, North Carolina, Oklahoma, and Texas, which had two sites). All patients who received treatment with tirzepatide during the two trials were invited to participate at each site, including those who discontinued treatment prior to completing the full treatment period. Tirzepatide-treated patients were considered to be appropriate for this qualitative interview because the hemoglobin A1c (HbA1c) and weight changes generally associated with this treatment were theorized to have an emotional impact.

### *Cognitive Interviews (Step 4)*

All cognitive interview participants were required to be (1) diagnosed with T2D at least 6 months prior to the interview; (2) at least 18 years of age; (3) currently receiving treatment with medication for T2D; (4) residing in the USA; (5) able to speak, read, and understand English; (6) able and willing to give informed consent; (7) able to complete the protocol requirements; (8) willing to be audio-recorded; and (9) able to provide a mailing address to receive study materials for use during the interview. Potential participants were excluded if they (1) had a cognitive impairment, hearing difficulty, visual impairment, acute psychopathology, or insufficient knowledge of the English language that could interfere with their ability to provide consent and complete the interview; (2) were diagnosed with type 1 diabetes, latent autoimmune diabetes, or gestational diabetes; or (3) were employed by a pharmaceutical company or had a direct role in treating patients with diabetes.

The participants in step 4 were recruited from four of the clinical research sites used in the concept elicitation phase (Florida, North Carolina, Oklahoma, and Texas). A subset ($n$ = 7) of the cognitive interview participants in step 4 previously received treatment with tirzepatide in the SURPASS clinical trials. The other participants ($n$ = 13) were recruited from the same clinical sites, but they had not participated in the SURPASS clinical trials and did not have previous experience with tirzepatide. Efforts were made to obtain a clinically broad sample, including patients currently treated with only oral medication, insulin, and non-insulin injectable medications. In addition, the subset of seven patients with tirzepatide experience (in the SURPASS-2 or SURPASS-3 clinical trials) was recruited because the substantial HbA1c and weight changes generally associated with this treatment were theorized to have an emotional impact. None of the cognitive interview participants in step 4 participated in step 2.

## Data Collection

### *Concept Elicitation (Step 2)*

Concept elicitation interviews were conducted between September and November 2020 by telephone according to a semi-structured interview guide designed to elicit discussion of patients' experience with treatment and treatment-related changes during a trial of tirzepatide [47]. In addition to general questions about changes experienced during treatment ("Did you notice any changes due to the treatment?" "How did these changes impact your quality of life?"), concept elicitation participants were also asked specifically about the emotional impact of treatment ("Has treatment with the study medication affected you emotionally?" "Did you experience any positive or negative emotional changes related to treatment with the study medication?"). After discussing the emotions reported spontaneously, interviewers probed for the following emotions if they were not already spontaneously reported: worry, anxiety, fear, frustration, optimism, relief, comfort, confidence, self-esteem, hope, and sense of control.

### *Cognitive Interviews (Step 4)*

Cognitive interviews were conducted between May 2021 and September 2021 by telephone according to a semi-structured interview guide to assess the relevance, clarity, interpretation, ease of completion, and comprehensiveness of the draft questionnaires. Cognitive interview participants completed the EIDTQ-Status and EIDTQ-Comparison and were interviewed about their understanding of the instructions ("Are these instructions clear? If not, please explain what you would change and why"), items ("Did you have any difficulty understanding or responding to this item? If yes, what is confusing, and how would you suggest rewording the item?"), and response options ("Were the response options clear? Were these response options easy to use? If not, which ones were difficult? What did the response options mean to you?").

Each cognitive interview participant was also asked to describe their interpretation of the instructions ("In your own words, what are these instructions telling you to do?") and their interpretation of each item ("What does this item mean to you? What does 'hopeful' mean to you? How is 'feeling good about myself' different from 'self-confident'?"). In addition, they were asked how they selected each response ("What answer did you choose and why? What were you thinking about when answering this question?").

## Measures

All participants for both concept elicitation and cognitive interviews completed a background questionnaire including items on age, gender, race/ethnicity, marital status, education level, employment, and general health. Clinical site personnel completed a clinical information form for each participant to document duration of T2D, current medications for T2D, most recent HbA1c value, and the patient's height and weight for body mass index calculation. For concept elicitation participants, the clinical form also documented which SURPASS clinical trial the participant took part in (SURPASS-2 or SURPASS-3) and the duration of tirzepatide treatment. For cognitive interview participants, the clinical form documented whether the participant was previously treated with tirzepatide.

## Analysis Procedures

All concept elicitation and cognitive interviews were recorded and professionally transcribed. The transcripts were analyzed using a content analysis approach in ATLAS.ti (version 8 for concept elicitation; version 9 for cognitive interviews) [48]. The interview guides and interviewer notes were used to develop coding dictionaries of themes, concepts, and terms. To standardize the coding process, the dictionaries included a definition for each code and instructions for applying codes. The dictionaries were revised during coding to capture emerging concepts.

Transcripts from concept elicitation interviews were coded by selecting words and

phrases based on the coding dictionary and grouping these data into key concepts. The Food and Drug Administration has requested evidence of "saturation" in qualitative research that is carried out in the development of PRO instruments [11, 49]. Saturation is the point at which no substantially new information/concepts continue to emerge beyond what has been previously mentioned [11, 50, 51]. Saturation of concepts from concept elicitation interviews was demonstrated by organizing coded data in a saturation grid, with concepts listed along the *y*-axis and participants listed along the *x*-axis. This grid documents the number of individuals who received each code.

The analysis of data from the cognitive interviews includes assessment of the percentage of participants who understood each item, the percentage of participants who had difficulty understanding the instructions, the comprehensiveness of the instrument, and the appropriateness of the response scales and recall periods. The results are organized in an analysis grid.

Coders received training in qualitative analysis theory and practice, as well as study-specific training on each coding dictionary prior to coding transcripts. Concept elicitation transcripts were coded by three staff members, and cognitive interview transcripts were coded by two staff members. To establish consistency, the coders independently coded the first interview transcript in each phase, and a post-coding reconciliation occurred. All codes were compared, discussed, and reconciled wherever differences emerged. After reaching agreement, each coder coded a selection of the remaining transcripts. A quality review of all coding and analysis was performed by the same senior staff member for both the concept elicitation and cognitive interviews.

## RESULTS

### Step 1: Literature Review and Expert Interviews

The literature review performed to identify diabetes-specific PRO instruments that include items assessing emotional impact identified several relevant measures including the Diabetes Symptom Checklist—Revised [33], DDS [44], Treatment Related Impact Measure—Diabetes [40, 52], Diabetes Medication Satisfaction Questionnaire [38], Diabetes Therapy Related Quality of Life [53], Current Health Satisfaction Questionnaire [54], and Impact of Weight on Self-Perception [55, 56]. The instruments identified in this review tended to include a few items assessing emotions but did not focus on the emotional impact of diabetes treatment or evaluate the full range of emotions that may be impacted by treatment. Therefore, it was determined that a new measure could be useful for providing a detailed assessment of the emotional impact of treatment for T2D.

Two clinicians (MD and MD/PhD) and two diabetes clinical trial outcomes experts (PhD and PharmD, MS, MBA) provided input regarding potential emotional impact of treatment for T2D, including worry about hypoglycemia, worry about eating and diet, feeling in control of diabetes, fear, frustration, optimism, self-esteem, confidence, hope, improved outlook on life, embarrassment, willingness to do activities, and feeling energetic. Concepts identified by these experts were considered during development of the concept elicitation guide and the questionnaires.

### Steps 2 and 3: Concept Elicitation and Drafting Two Questionnaires

Concept elicitation on the emotional impact of diabetes treatment was conducted with 28 patients with T2D recently treated with tirzepatide in an open-label clinical trial (sample characteristics in Table 1). As reported previously [47], all concept elicitation participants completed the full treatment period of 40 weeks (SURPASS-2) or 52 weeks (SURPASS-3), except for one participant who discontinued treatment early (after 105 days in the SURPASS-2 trial). The interviews were conducted an average of 65.6 days after participants completed the 4-week follow-up safety period.

Participants reported a wide range of emotions associated with treatment during the

**Table 1** Summary of participant characteristics

| Characteristic | Concept elicitation interviews (*N* = 28) | Cognitive interviews (*N* = 20) |
|---|---|---|
| Age, mean years (SD) | 57.6 (10.0) | 58.3 (9.5) |
| Gender, *n* (%) | | |
| Male | 10 (35.7%) | 8 (40.0%) |
| Female | 18 (64.3%) | 12 (60.0%) |
| Ethnicity, *n* (%) | | |
| Hispanic or Latino | 9 (32.1%) | 7 (35.0%) |
| Not Hispanic or Latino | 19 (67.9%) | 13 (65.0%) |
| Race, *n* (%) | | |
| Black or African American | 7 (25.0%) | 2 (10.0%) |
| Native Hawaiian or other Pacific Islander | 1 (3.6%) | – |
| White | 16 (57.1%) | 17 (85.0%) |
| Multiple[a] | 1 (3.6%) | – |
| Other | 3 (10.7%) | 1 (5.0%) |
| Employment status, *n* (%) | | |
| Full-time work | 11 (39.3%) | 8 (40.0%) |
| Part-time work | 5 (17.9%) | 1 (5.0%) |
| Other[b] | 12 (42.9%) | 11 (55.0%) |
| Education level, *n* (%) | | |
| University degree | 6 (21.4%) | 6 (30.0%) |
| No university degree | 22 (78.6%) | 14 (70.0%) |
| Marital status, *n* (%) | | |
| Single | 5 (17.9%) | 3 (15.0%) |
| Married/cohabitating/living with partner | 16 (57.1%) | 12 (60.0%) |
| Other[c] | 7 (25.0%) | 5 (25.0%) |
| Duration of diabetes, mean years (SD) | 10.3 (5.0) | 11.8 (6.4) |
| Most recent HbA1c (%), mean (SD)[d] | 6.6 (1.1) | 7.2 (1.2) |
| BMI, mean kg/m$^2$ (SD) | 33.0 (6.9) | 33.3 (8.7) |
| Current treatment, *n* (%)[e] | | |
| Oral only | 23 (82.1%) | 11 (55.0%) |
| Injectable GLP-1 RA | – | 1 (5.0%) |
| Oral and insulin | – | 3 (15.0%) |
| Oral and injectable GLP-1 RA | 1 (3.6%) | 5 (25.0%) |

**Table 1** continued

| Characteristic | Concept elicitation interviews ($N$ = 28) | Cognitive interviews ($N$ = 20) |
|---|---|---|
| Oral and injectable medication (unknown) | 3 (10.7%) | – |
| Previous treatment with tirzepatide, *n* (%) | | |
| Previous experience with tirzepatide in trial[f] | 28 (100.0%) | 7 (35.0%) |
| No previous tirzepatide experience | – | 13 (65.0%) |

*BMI* body mass index, *GLP-1* glucagon-like peptide 1, *RA* receptor agonist, *SD* standard deviation

[a]Multiple includes one concept elicitation interview participant reporting race as "American Indian or Alaska Native" and "White"

[b]Other employment status includes the following for concept elicitation interviews: retired ($n$ = 7), disabled ($n$ = 2), homemaker ($n$ = 2), and unemployed ($n$ = 1); and the following for cognitive interviews: retired ($n$ = 5), disabled ($n$ = 1), homemaker ($n$ = 1), and unemployed ($n$ = 4)

[c]Other marital status includes divorced ($n$ = 5) and widowed ($n$ = 2) for concept elicitation interviews and divorced ($n$ = 4) and widowed ($n$ = 1) for cognitive interviews

[d]Result of most recent HbA1c test was unknown for two cognitive interview participants

[e]Current medication was not reported for one concept elicitation interview participant

[f]In the concept elicitation interviews, 27 participants were previously treated with tirzepatide in SURPASS-2, and one was treated with tirzepatide in SURPASS-3. In the cognitive interviews, seven participants were previously treated with tirzepatide in the SURPASS trials, but the specific trial number was not collected

concept elicitation interviews. See Table 2 for frequencies of participants who mentioned impact on each type of emotion and an example quotation for each concept. Statements regarding emotional impact were coded to reflect the participant's opinion about the change as positive (e.g., "Your improvements in your health also affects your attitude about how you approach things…You felt better. You had more confidence in yourself" [003-004]) or negative (e.g., "You're kind of frustrated about it because it is causing the mood swings and short-triggered sometimes" [004-003]). These categories were not mutually exclusive, and it was possible for a patient to have reported both positive and negative statements regarding the changes they experienced.

All concept elicitation interview participants reported positive emotional changes associated with treatment. Frequently reported areas of positive impact included increases in confidence (82.1%), hope (82.1%), self-esteem (82.1%), relief (78.6%), optimism (75.0%), sense of control (75.0%), happiness (53.6%), and motivation (53.6%). Respondents also reported decreases in worry/anxiety (67.9%), frustration (46.4%), fear (32.1%), and depression (10.7%). Positive emotional impacts were primarily associated with improved glycemic control, weight loss, and increased energy.

Four participants (14.3%) also reported negative emotional impact of their study medication. Negative changes in emotions included feeling frustration (7.1%), worry/anxiety (3.6%), fear (3.6%), depressed (3.6%), and less relieved (3.6%). Negative emotional impact was typically associated with treatment-related adverse events. For example, one participant (3.6%) reported feeling less "relieved" when vomiting began. Another participant was frustrated about experiencing diarrhea during treatment.

No new concepts related to emotional impact of treatment for T2D emerged in the final six concept elicitation interviews. Therefore, it was determined that concept saturation had been reached, and no additional concept elicitation interviews were needed. The concepts identified in the interviews with patients and clinical experts were used to draft two

**Table 2** Emotional changes frequently reported by concept elicitation interview participants when asked about treatment for type 2 diabetes in the SURPASS trials

| | Positive *n* (%) | Negative *n* (%) | Example quotation |
|---|---|---|---|
| Confidence | 23 (82.1%) | – | "When you have a little bit too much weight and you couldn't wear that sexy outfit that you wanted to wear when you went out and you end up in a moo-moo dress and staying home. So it did affect me sometimes. You'd look in the mirror and go, god, I hate this person over here, you know. With this medication, it kind of like gave you a sense of confidence… you could go out there and still have your sexy on." [001-001] |
| Hope | 23 (82.1%) | – | "Gave me a little hope and faith that I'm going to feel better, that it's going to help me get better because it's going to help me with my A1Cs and help me contain the issues with the weight problem and help bring it way down. Therefore, it's a two-prong attack on the problem and therefore it made me happier, just like I could actually say I'm doing something that is helping me, helping myself." [003-003] |
| Self-esteem | 23 (82.1%) | – | "The self-esteem is there and it's increasing because you're controlling this. You're on the right track. Again, you're adding years to your life." [004-003] |
| | | | "I mean just losing weight and having people tell you, 'you look great, you're doing great, what are you doing?' It makes you feel so much better, so absolutely, my self-esteem is many, many points higher than what it was." [005-001] |
| Relief | 22 (78.6%) | 1 (3.6%) | "There was really no emotional changes at all with the medication or anything like that, it was just more overall relief mentally, like I said, it was more of like not being stressed out about my glucose levels during the day, and I was able maybe to try other things that I wanted to try that I couldn't try because of having those negative high levels come up, but nothing—I guess you could say that it probably brought a little bit more joy knowing that I was able to do those things." [002-004] |
| | | | "I was relieved until I got the vomiting… Well, I felt like I was sick to my stomach all the time, and I didn't know why until I got the vomiting." [002-002] |
| Optimism | 21 (75.0%) | – | "I was very optimistic once I started seeing the positive results going towards the direction I wanted to go." [006-002] |
| Sense of control | 21 (75.0%) | – | "Well, I think it's because you were losing weight, your numbers are coming down. So, you're thinking oh I'm in control of this." [005-004] |

**Table 2** continued

| | Positive *n* (%) | Negative *n* (%) | Example quotation |
|---|---|---|---|
| Worry/ anxiety | 19 (67.9%) | 1 (3.6%) | "Oh, well I will say that the only thing that I can say is it let me live my life differently. I didn't have to be worrying about what my sugar was doing to my body because I know that it had the medicine and the medicine was helping me. So I didn't have to carry my metformin all the time and I didn't have to carry the, the meter all the time. I can, you know, just forget about it. You know what I'm saying?" [002-001] |
| | | | "I was anxious a couple times because I felt like I wasn't seeing it doing enough… The only thing I was worried about—you say anxious, anxiety, and worried or fear was what's it going to do to me in the long run. What kind of effect is it going to have on me and my pancreas, my liver, and everything in the long run?" [003-003] |
| Happy | 15 (53.6%) | – | "Well, I was definitely happier. I felt like there was a, there was a light at the tunnel. I mean I felt happy… It meant if I kept doing it, I'm going to reach my goals. I'm going to get down and I'm going to, you know, accomplish something, to feel better, get better health." [004-006] |
| Motivation | 15 (53.6%) | – | "I was able to go do what I needed to do. I had the desire to do stuff." [003-003] |
| | | | "Well now I have energy, I want to do things… I got a piece of paper and I write down everything that I want to do and I cross it out… I feel motivated." [002-001] |
| Frustration | 13 (46.4%) | 2 (7.1%) | "I don't get frustrated nearly as easily… And I have more patience. You know. I, I don't know. It's like it freed up space in my brain for me to have more patience or something. I don't know." [004-001] |
| | | | "Kind of frustrated about it because it [i.e., the medication] is causing the mood swings and short-triggered sometimes. That brings you down. You don't want to be short-triggered and snap at the smallest things." [004-003] |
| Fear | 9 (32.1%) | 1 (3.6%) | "I was afraid of the future, I guess, of what that held for me physically, but I don't really have much fear of that now." [005-001] |
| | | | "Before I got the vomiting, I didn't have that kind of feeling, but after that I was kind of nervous about injections after that." [002-002] |
| Perception by others | 7 (25.0%) | – | "I actually felt good about going out without being self-conscious that people were looking at me and judging." [003-005] |

**Table 2** continued

| | Positive *n* (%) | Negative *n* (%) | Example quotation |
|---|---|---|---|
| Depressed | 3 (10.7%) | 1 (3.6%) | "Just in a positive way. The emotions of course were—it took me out of some of my depression, just seeing the, you know, back to feeling good, starting to feel healthy, and then just actually seeing it physically like in a mirror, I mean for me it was all about—I mean it was just a good emotional feeling, just happy." [006-002] |
| | | | "The depression, at first, I'll say because I was sick and like golly, I just don't want to do this if it's going to make me like this." [003-003] |

The areas of emotional impact included in this table were discussed by participants in response to exit interview questions such as "Did you notice any change due to the treatment?" "How did these changes impact your quality of life?" "Has treatment with the study medication affected you emotionally? If yes, how?" and "Did you experience any positive or negative emotional changes related to treatment with the study medication?"

questionnaires. One draft measure focused on the emotional impact of current diabetes treatment (EIDTQ-Status), and the second was designed to compare the emotional impact of current treatment to previous treatment (EIDTQ-Comparison).

### Steps 4 and 5: Cognitive Interviews and Translatability Assessment

The draft PROs were evaluated in cognitive interviews with 20 people receiving treatment for T2D in the USA (see demographic and clinical characteristics in Table 1). These participants were receiving a range of treatments for T2D (Table 1). Eleven were receiving oral treatment only, while the other nine were treated with a regimen that included injectable medication such as insulin or glucagon-like peptide 1 (GLP-1) receptor agonists. Each participant was asked to complete the EIDTQ-Status and EIDTQ-Comparison and respond to a series of questions about the instruments. Cognitive interviews were conducted in three phases ($n = 8$, $n = 7$, and $n = 5$), and the instruments were updated after each phase.

Participants who had not received tirzepatide ($n = 13$) were instructed to complete the EIDTQ-Status based on perceptions of their current treatment and use the EIDTQ-Comparison to compare their current treatment regimen with their previous treatment regimen. The subset of participants previously treated with tirzepatide ($n = 7$) was asked to complete the questionnaires as if they were currently receiving treatment with tirzepatide in the clinical trial. Therefore, these seven participants used the EIDTQ-Status to rate the emotional impact of tirzepatide during the trial, and they used the EIDTQ-Comparison to compare tirzepatide to their pre-trial treatment regimen.

Cognitive interview participants consistently understood the item stems and emotional concepts in both versions of the EIDTQ. Table 3 presents example quotes illustrating participants' interpretations of each concept. Participants frequently interpreted the positive emotional concepts (such as hopeful, happy, self-confident) in relation to improvements in glycemic control, diet, or weight as a result of treatment. Interpretations of negative emotional concepts (fearful, frustrated, worried) were often related to lack of treatment efficacy, progression of diabetes, access to treatment, and treatment side effects.

Participants understood the response options of the EIDTQ-Status (never, rarely, sometimes, often, and almost always) and the EIDTQ-Comparison (much more, more, the same, less, and much less), and they were able to answer the items using these response

**Table 3** Example quotations of cognitive interview participants' interpretations of the EIDTQ item stems

| Item stem | Example quotation of participant interpretation of the item stem[a] |
|---|---|
| Hopeful | "Hopeful is a positive attitude, I guess forward-facing, and it's hard to describe hopeful without using the word 'hope,' but you sort of hope things will be better, you know, or are better… I would hope that it would improve, that my general overall health would get better." [102-201] |
| | "I was hopeful that it would control my diabetes better and give me a better life, better health." [102-105] |
| Optimistic | "Optimistic is when you're positive, when you be positive, you're optimistic, like you're looking forward to things." [103-106] |
| | "Your overall I guess outlook on the world and how you're feeling, and it being having some control over your diabetes." [102-103] |
| Happy | "Was I happy, did I find joy in what I was doing, what I was going through. Happy encompasses a lot to me, it's not just happy, joy, however you want to put it. There's peace tied to happiness, there is a sense of comfort tied to happiness." [101-105] |
| Relieved | "Relieved means that I wasn't as worried about the effects of diabetes on my body and my longevity, life longevity." [102-103] |
| Self-confident | "Self-confident I guess in this particular context sort of refers to my confidence in myself to do the right thing as far as regards my diabetes, and I used to be a lot more confident about it. I used to be really good at maintaining my weight and not eating the wrong stuff, etcetera, and now I am a lot less, well, somewhat less confident that I can do that." [102-201] |
| Good about myself | "When I answered this question, I felt like less worried about my medical condition, so for the most part that I have more control over my diet, therefore like my blood sugar levels, my fasting glucose and all of that stuff, more of like proud that I was able to control my blood sugar levels. Yeah, it was the medication, but I kind of felt good that I made that decision, that I feel like I made that decision." [101-207] |
| Motivated | "Yes, and that made me feel like looking forward to it that next day, because that makes you think, okay, I'm down so many numbers, and it keeps you like wishing and wanting to see those numbers keep going down, so that keeps you motivated, definitely, yes." [103-104] |
| Energetic | "Energetic is just having energy to get through the day and knowing that the medications that I'm on, and with the disease that I have can zap the energy at times, under certain situations. So that's how I saw energetic." [104-203] |
| In control of my diabetes | "An overall keeping my numbers down… my A1 and my daily whatever, now that I'm off of it, today is like 213 instead of, you know." [102-105] |
| In control of my eating | "Eating correctly and not splurging." [102-105] |
| In control of my weight | "Compared to before my medication, are you in more control of your weight, and the answer is yes, sure. I wasn't before, I didn't really control my weight at all, I never really had to. My weight primarily stayed the same no matter what I ate and how much I ate, and now that I took a lot of weight I off, I try to do the same thing, keep it where it is." [101-201] |

**Table 3** continued

| Item stem | Example quotation of participant interpretation of the item stem[a] |
|---|---|
| Fearful | "I take it as maybe being afraid that you can't control your diabetes and maybe, you know, being afraid of getting sick or more sick or your disease, you know, getting worse and worse and you can't control yourself." [104-201] |
| | "Fearful is the fear of adverse reactions, of not doing it the right way, of life itself to me." [102-204] |
| Frustrated | "I think frustrated for me is when you're doing all that you can do and it's still not working, there's a level of frustration. It's like, okay, I'm doing what the doctors are asking me to do. I'm doing what, you know, I'm told to do, but yet nothing is happening, and so there's a level of frustration there that kind of drives you crazy." [104-203] |
| Worried | "A feeling of maybe a little anxiety that you get over having diabetes and taking medication… there are times that I get worried that, you know, what if I can't afford my medication or what if, you know, I can't control my diabetes." [104-201] |
| | "Worried means that you just think that the pill is not going to work, that you're not going to get better, like I'd worry if something wasn't going to happen to me like in a good way, like get relief for my diabetes, that's what I think." [103-106] |

*EIDTQ* Emotional Impact of Diabetes Treatment Questionnaire

[a]The item interpretations were provided in response to questions from interviewers such as "What does this item mean to you?", "What is this item asking?", "What does 'hopeful' mean?", "What does 'optimistic' mean?", "What does 'in control of my diabetes' mean?", etc.

options. No participants expressed difficulty with the 1-week recall period.

Although the item stems listing the emotional concepts and the response options presented no apparent difficulty, there were some challenges with the instructions during the first two phases of cognitive interviews. In the first phase of interviews, some participants had difficulty understanding that their responses should be specifically related to their diabetes treatment. To address this difficulty, text was bolded to draw participants' attention to the part of the instructions telling them to think about emotions related to their diabetes treatment ("Think about how your current diabetes medication has affected you emotionally"). Some difficulty with this issue persisted in the second phase of cognitive interviews, so the item stem was revised to stress the relationship between emotions and diabetes treatment ("Because of your [medication], how often have you felt…"). These revisions were successful, and all cognitive interview participants completing the final version of the questionnaires considered the impact of their diabetes treatment on their emotions when responding.

When completing the EIDTQ-Status, some of the cognitive interview participants previously treated with tirzepatide in a clinical trial thought about the emotional impact of losing access to the medication at the end of a trial, rather than the emotional impact experienced during treatment. Therefore, optional instructions were developed that could be used in clinical trials to direct participants to think about emotions related to the medication rather than feelings about losing access to the medication after the study. These optional instructions were shown to participants in the final phase of cognitive interviews, and all understood the alternate language without difficulty.

With the EIDTQ-Comparison, some participants in the first two cognitive interview phases had difficulty understanding the comparative nature of the questionnaire. The final version of the questionnaire was revised to include the names of the participants' medications in the instructions. All cognitive interview

participants who completed this final version of the questionnaire understood the instructions as intended and compared the impact of their current and previous medications on their emotions.

After the cognitive interviews were completed, a translatability assessment was conducted to ensure the EIDTQ-Status and EIDTQ-Comparison are suitable for translation. One change was made to the EIDTQ instruments based on the translatability assessment. The instructions for both questionnaires originally included the phrase "when completing the questions below…", but the questionnaires contain one item stem and a list of emotional concepts rather than a series of complete questions. Although this inconsistency did not cause confusion in the cognitive interviews, it may complicate future translations. Therefore, the term "questions" was replaced with "items" in the instructions.

### Versions of the EIDTQ-Status and EIDTQ-Comparison Emerging from this Study

The resulting status and comparison versions of the EIDTQ each contain 14 items assessing the impact of treatment for T2D on emotions (see questionnaire content in Supplementary material 1 and 2). The EIDTQ-Status asks respondents to rate the frequency of experiencing emotions related to T2D treatment on a five-point scale ranging from "never" to "almost always." The EIDTQ-Comparison asks respondents to compare the intensity of the emotions experienced during current treatment to emotions experienced during previous treatment on a five-point scale ranging from "much more" to "much less."

The questionnaire instructions can be customized for the design and purpose of the study or situation in which the questionnaire is being used. For example, if the EIDTQ-Status is being used in a clinical trial, the instructions can be customized to direct respondents to think about how their diabetes study medication has affected them emotionally, and a statement can be included to think about emotions related to the diabetes study medication rather than feelings about losing access to the study medication after the trial (Supplementary material 1). The EIDTQ-Comparison can also be customized to include the names of the specific medications that participants should consider when responding. The customizable aspects of the instructions are presented in brackets (Supplementary material 2).

## DISCUSSION

In exit interviews with patients treated for T2D, concept elicitation interview participants reported a wide range of emotional impact associated with treatment. All patients reported at least one emotional benefit of their medication for T2D, including increased confidence, hope, self-esteem, relief, optimism, sense of control, happiness, and motivation, as well as reduced worry/anxiety. Negative emotional impact was less commonly reported, but included frustration, worry/anxiety, fear, and feeling depressed. Positive emotions tend to be associated with reductions in HbA1c and weight that were perceived to be a result of medication treatment, while negative emotions were most frequently linked to medication side effects or perceptions of efficacy that did not meet expectations. These results add to previous research suggesting that people with T2D may experience an emotional impact associated with treatment-related changes [27–31].

These concept elicitation results were used to inform the development of two draft questionnaires to assess the emotional impact of current diabetes treatment (EIDTQ-Status) and comparison with previous treatment (EIDTQ-Comparison). In the current qualitative study, the draft questionnaires were assessed in cognitive interviews with 20 patients with T2D in the USA. Nine of the 15 cognitive interview participants who completed the first two versions of the EIDTQ-Status initially had difficulty understanding that their responses should be specifically related to their diabetes treatment. With the first two versions of the EIDTQ-Comparison, eight of 15 participants had difficulty comparing two diabetes treatments. To address these difficulties, the draft questionnaires were

updated twice during the cognitive interview study to clarify the instructions, and all participants in the final set of cognitive interviews understood the items and instructions as intended, and they were able to complete both EIDTQ instruments without difficulty.

Although this qualitative research supports the content validity of the EIDTQ instruments, the study should be considered only the first step in the development and validation of these new questionnaires. Future research with larger samples is needed for quantitative analysis focusing on item performance, item reduction, identification of possible subscales, and development of scoring approaches. Then, psychometric analyses can examine reliability, validity, and sensitivity to treatment-related change. For example, the instruments could be included in a clinical trial to examine the extent to which improvement in body weight and glycemic control may be associated with emotional benefits.

Limitations associated with the study sample should also be acknowledged. Like most qualitative PRO research [57], this study was conducted with a relatively small sample that cannot be considered representative of the demographic and clinical characteristics in the broader population of people with T2D. For example, while the concept elicitation sample reported a wide range of emotional impact associated with treatment, this sample consisted entirely of patients treated with tirzepatide in two clinical trials. Generalizability to patients outside the clinical trial setting is unknown. In addition, tirzepatide has been shown to be associated with substantial weight reduction [45, 46, 58]. This impact on weight appeared to be an important factor contributing to the emotional reactions reported by patients in the concept elicitation interviews (Table 2). It is possible that patients receiving a different treatment could have fewer or different emotional benefits. Therefore, generalizability to patients receiving other types of treatments, such as oral medication or insulin, is unknown. Future research with larger and clinically diverse samples is needed to examine the varying emotional impact of various types of treatment.

Limitations associated with generalizability of the concept elicitation results are mitigated by the more clinically diverse sample in the cognitive interview phase of this study. Participants in the cognitive interviews were receiving a broad range of treatment, including oral medication, GLP-1 receptor agonists, and insulin. These patients reported that the items were relevant to their experience and comprehensive, regardless of the type of treatment they were receiving. Still, future research with larger samples is necessary to demonstrate the performance of the EIDTQ measures across a wider range of patients with T2D.

## CONCLUSION

Overall, this study adds to previous research indicating that treatment for T2D can have an emotional impact. The EIDTQ instruments were designed to assess this emotional impact, and current qualitative results support the content validity of these instruments in patients with T2D. After the instruments are refined based on quantitative research with larger samples and validated via psychometric analyses, they may be useful tools in clinical and observational research. These instruments can be used as a supplement to clinical outcomes, such as HbA1c and body weight, to provide a broader picture of the patient's experience with medication treatment for T2D.

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***Data Availability.*** For permission to reproduce or use the EIDTQ-Status or EIDTQ-Comparison, please contact copyright@lilly.com. After permission is obtained, there is no fee for using these instruments.



## REFERENCES

1. Acquadro C, Berzon R, Dubois D, et al. Incorporating the patient's perspective into drug development and communication: an ad hoc task force report of the patient-reported outcomes (PRO) harmonization group meeting at the Food and Drug Administration, February 16, 2001. Value Health. 2003;6(5):522–31.

2. Hareendran A, Gnanasakthy A, Winnette R, Revicki D. Capturing patients' perspectives of treatment in clinical trials/drug development. Contemp Clin Trials. 2012;33(1):23–8.

3. Leidy NK, Revicki DA, Geneste B. Recommendations for evaluating the validity of quality of life claims for labeling and promotion. Value Health. 1999;2(2):113–27.

4. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA. 1998;280(21):1837–42.

5. Freemantle N, Meneghini L, Christensen T, Wolden ML, Jendle J, Ratner R. Insulin degludec improves health-related quality of life (SF-36®) compared with insulin glargine in people with type 2 diabetes starting on basal insulin: a meta-analysis of phase 3a trials. Diabet Med. 2013;30(2):226–32.

6. Sahin S, Haliloglu O, Polat Korkmaz O, et al. Does treatment with sodium-glucose co-transporter-2 inhibitors have an effect on sleep quality, quality of life, and anxiety levels in people with type 2 diabetes mellitus? Turk J Med Sci. 2020;51(2):735–42.

7. Strand V, Kremer JM, Gruben D, Krishnaswami S, Zwillich SH, Wallenstein GV. Tofacitinib in combination with conventional disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: patient-reported outcomes from a phase III randomized controlled trial. Arthritis Care Res (Hoboken). 2017;69(4):592–8.

8. Ishii H, Niiya T, Ono Y, Inaba N, Jinnouchi H, Watada H. Improvement of quality of life through glycemic control by liraglutide, a GLP-1 analog, in insulin-naive patients with type 2 diabetes mellitus: the PAGE1 study. Diabetol Metab Syndr. 2017;9:3.

9. Langley RG, Feldman SR, Han C, et al. Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: results from a randomized, double-blind, placebo-controlled phase III trial. J Am Acad Dermatol. 2010;63(3):457–65.

10. Fleming P, Roubille C, Richer V, et al. Effect of biologics on depressive symptoms in patients with psoriasis: a systematic review. J Eur Acad Dermatol Venereol. 2015;29(6):1063–70.

11. Food and Drug Administration (FDA). 3. Patient-Focused Drug Development: Methods to identify what is important to patients. Guidance for industry, Food and Drug Administration staff, and other stakeholders Silver Spring, MD; 2022. https://www.fda.gov/media/131230/download. Accessed 26 Oct 2022.

12. Food and Drug Administration (FDA). 1. Patient-Focused Drug Development: Collecting comprehensive and representative input. Guidance for industry, Food and Drug Administration staff, and other stakeholders Silver Spring, MD; 2020. https://www.fda.gov/media/139088/download. Accessed 19 Mar 2021.

13. Walton MK, Powers JH 3rd, Hobart J, et al. Clinical outcome assessments: conceptual foundation-report of the ISPOR clinical outcomes assessment—emerging good practices for outcomes research task force. Value Health. 2015;18(6):741–52.

14. Ware J, Kosinski M, Bjorner J, Turner-Bowker D, Gandek B, Maruish M. Development. User's Manual for the SF-36v2 Health Survey. Lincoln: Quality Metric; 2007.

15. Brooks R. EuroQol: the current state of play. Health Policy. 1996;37(1):53–72.

16. EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199–208.

17. Kind P. The EuroQol Instrument: an index of health related quality of life. In: Spilker B, editor. Quality of life and pharmacoeconomics in clinical trials. 2nd ed. Philadelphia: Lippincott Raven; 1996. p. 191–201.

18. Rabin R, Gudex C, Selai C, Herdman M. From translation to version management: a history and review of methods for the cultural adaptation of the EuroQol five-dimensional questionnaire. Value Health. 2014;17(1):70–6.

19. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993;11(3):570–9.

20. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. Chest. 1999;115(5):1265–70.

21. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax. 1992;47(2):76–83.

22. McKenna SP, Doughty N, Meads DM, Doward LC, Pepke-Zaba J. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR): a measure of health-related quality of life and quality of life for patients with pulmonary hypertension. Qual Life Res. 2006;15(1):103–15.

23. Zlupko M, Harhay MO, Gallop R, et al. Evaluation of disease-specific health-related quality of life in patients with pulmonary arterial hypertension. Respir Med. 2008;102(10):1431–8.

24. Grandy S, Chapman RH, Fox KM, Group SS. Quality of life and depression of people living with type 2 diabetes mellitus and those at low and high risk for type 2 diabetes: findings from the Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD). Int J Clin Pract. 2008;62(4):562–8.

25. Peyrot M, Rubin RR, Lauritzen T, Snoek FJ, Matthews DR, Skovlund SE. Psychosocial problems and barriers to improved diabetes management: results of the Cross-National Diabetes Attitudes, Wishes and Needs (DAWN) Study. Diabet Med. 2005;22(10):1379–85.

26. Lopez JM, Annunziata K, Bailey RA, Rupnow MF, Morisky DE. Impact of hypoglycemia on patients with type 2 diabetes mellitus and their quality of

life, work productivity, and medication adherence. Patient Prefer Adherence. 2014;8:683–92.

27. Delahanty LM, Grant RW, Wittenberg E, et al. Association of diabetes-related emotional distress with diabetes treatment in primary care patients with type 2 diabetes. Diabet Med. 2007;24(1): 48–54.

28. Egede LE, Zheng D. Independent factors associated with major depressive disorder in a national sample of individuals with diabetes. Diabetes Care. 2003;26(1):104–11.

29. Peyrot M, Rubin RR. Persistence of depressive symptoms in diabetic adults. Diabetes Care. 1999;22(3):448–52.

30. Tanenbaum ML, Kane NS, Kenowitz J, Gonzalez JS. Diabetes distress from the patient's perspective: qualitative themes and treatment regimen differences among adults with type 2 diabetes. J Diabetes Complicat. 2016;30(6):1060–8.

31. Yang W, Zhuang X, Li Y, et al. Improvements in quality of life associated with biphasic insulin aspart 30 in type 2 diabetes patients in China: results from the A1chieve® observational study. Health Qual Life Outcomes. 2014;12:137.

32. Arbuckle RA, Humphrey L, Vardeva K, et al. Psychometric evaluation of the Diabetes Symptom Checklist-Revised (DSC-R)—a measure of symptom distress. Value Health. 2009;12(8):1168–75.

33. Grootenhuis PA, Snoek FJ, Heine RJ, Bouter LM. Development of a type 2 diabetes symptom checklist: a measure of symptom severity. Diabet Med. 1994;11(3):253–61.

34. Meadows K, Steen N, McColl E, et al. The Diabetes Health Profile (DHP): a new instrument for assessing the psychosocial profile of insulin requiring patients-development and psychometric evaluation. Qual Life Res. 1996;5(2):242–54.

35. The DCCT Research Group. Reliability and validity of a diabetes quality-of-life measure for the Diabetes Control and Complications Trial (DCCT). Diabetes Care. 1988;11(9):725–32.

36. Anderson RT, Skovlund SE, Marrero D, et al. Development and validation of the insulin treatment satisfaction questionnaire. Clin Ther. 2004;26(4):565–78.

37. Bradley C. Diabetes treatment satisfaction questionnaire. Change version for use alongside status version provides appropriate solution where ceiling effects occur. Diabetes Care. 1999;22(3):530–2.

38. Brod M, Skovlund SE, Wittrup-Jensen KU. Measuring the impact of diabetes through patient report of treatment satisfaction, productivity and symptom experience. Qual Life Res. 2006;15(3):481–91.

39. Cappelleri JC, Gerber RA, Kourides IA, Gelfand RA. Development and factor analysis of a questionnaire to measure patient satisfaction with injected and inhaled insulin for type 1 diabetes. Diabetes Care. 2000;23(12):1799–803.

40. Brod M, Hammer M, Christensen T, Lessard S, Bushnell DM. Understanding and assessing the impact of treatment in diabetes: the Treatment-Related Impact Measures for Diabetes and Devices (TRIM-Diabetes and TRIM-Diabetes Device). Health Qual Life Outcomes. 2009;7:83.

41. Matza LS, Boye KS, Stewart KD, Paczkowski R, Jordan J, Murray LT. Development of the Diabetes Injection Device Experience Questionnaire (DID-EQ) and Diabetes Injection Device Preference Questionnaire (DID-PQ). J Patient Rep Outcomes. 2018;2:43.

42. Matza LS, Stewart KD, Patel H, Boye KS. Patient perceptions of simplicity and complexity of treatment for type 2 diabetes. International Society for Pharmacoeconomics and Outcomes Research-European Congress (ISPOR-EU); Virtual; 30 November–3 December, 2021.

43. Polonsky WH, Anderson BJ, Lohrer PA, et al. Assessment of diabetes-related distress. Diabetes Care. 1995;18(6):754–60.

44. Polonsky WH, Fisher L, Earles J, et al. Assessing psychosocial distress in diabetes: development of the diabetes distress scale. Diabetes Care. 2005;28(3):626–31.

45. Frias JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med. 2021;385(6):503–15.

46. Ludvik B, Giorgino F, Jodar E, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. Lancet. 2021;398(10300):583–98.

47. Matza LS, Stewart KD, Lando LF, Patel H, Boye KS. Exit interviews examining the patient experience in clinical trials of tirzepatide for treatment of type 2 diabetes. Patient. 2022;15(3):367–77.

48. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res. 2005;15(9):1277–88.

49. Food Drug Administration (FDA). Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims. Fed Regist. 2009;74(235):65132–3.

50. Leidy NK, Vernon M. Perspectives on patient-reported outcomes: content validity and qualitative research in a changing clinical trial environment. Pharmacoeconomics. 2008;26(5):363–70.

51. Magasi S, Ryan G, Revicki D, et al. Content validity of patient-reported outcome measures: perspectives from a PROMIS meeting. Qual Life Res. 2012;21(5):739–46.

52. Brod M, Christensen T, Hammer M, Busk AK, Bushnell DM. Examining the ability to detect change using the TRIM-Diabetes and TRIM-Diabetes Device measures. Qual Life Res. 2011;20(9):1513–8.

53. Ishii H, Hansen BB, Langer J, Horio H. Effect of orally administered semaglutide versus dulaglutide on diabetes-related quality of life in Japanese patients with type 2 diabetes: the PIONEER 10 randomized, active-controlled trial. Diabetes Ther. 2021;12(2):613–23.

54. Traina SB, Colwell HH, Crosby RD, Mathias SD. Pragmatic measurement of health satisfaction in people with type 2 diabetes mellitus using the Current Health Satisfaction Questionnaire. Patient Relat Outcome Meas. 2015;6:103–15.

55. Hayes RP, DeLozier AM. Reliability, validity, and responsiveness of the Impact of Weight on Self-Perceptions Questionnaire (IW-SP) in individuals with type 2 diabetes and obesity. Diabetes Technol Ther. 2015;17(3):210–4.

56. Yu M, Brunt KV, Milicevic Z, Varnado O, Boye KS. Patient-reported outcomes in patients with type 2 diabetes treated with dulaglutide added to titrated insulin glargine (AWARD-9). Clin Ther. 2017;39(11):2284–95.

57. Turner-Bowker DM, Lamoureux RE, Stokes J, et al. Informing a priori sample size estimation in qualitative concept elicitation interview studies for clinical outcome assessment instrument development. Value Health. 2018;21(7):839–42.

58. Rosenstock J, Wysham C, Frias JP, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. Lancet. 2021;398(10295):143–55.