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ORIGINAL RESEARCH

A Mixed-Methods Study to Better Measure Patient-Reported Pain and Fatigue in Soft Tissue Sarcoma

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ABSTRACT

Introduction: Pain and fatigue are commonly reported by patients with soft tissue sarcoma (STS) as distressing symptoms, yet no patient-reported outcome (PRO) measures have been validated or developed specifically for STS. This study aimed to develop novel PRO scales using existing item banks to measure pain and fatigue in STS.

Methods: A three-stage mixed-methods approach was used. Stage 1: a literature review examined the development and validation of the European Organization for Research and Treatment of Cancer (EORTC) library, Patient-Reported Outcomes Measurement Information System (PROMIS) pain/fatigue item banks, Functional Assessment of Cancer Therapy-General, and FACIT-Fatigue. Conceptual models were developed for pain and fatigue. Stage 2: semi-structured interviews were conducted with clinical experts (n = 3) and STS patients (n = 28) to ensure conceptual coverage and cognitively debrief the selected PRO items. Stage 3: exploratory Rasch measurement theory (RMT) analyses were performed to examine the measurement properties of the proposed scales.

Results: Stage 1: The conceptual model for fatigue was organized into two overarching domains: fatigability and fatigue, further split into two subdomains: symptoms and impact. The conceptual model for pain had one overarching domain split into two subdomains: descriptors and impact. Pain (n = 56) and fatigue (n = 40) items were selected from the EORTC item library. Stage 2: qualitative findings ensured conceptual coverage, provided insight into the relevance and comprehension of the items, and informed subsequent item reduction. Stage 3: The total item number was reduced to 43 (pain n = 18, fatigue n = 25). Exploratory RMT analyses supported the final scales' psychometric properties.

Conclusions: This mixed-methods research generated important information on the experience of pain and fatigue in specific subtypes of STS. Five novel PRO scales have been developed through careful item selection in consultation with experts and supported by qualitative and quantitative evidence. These scales may be of value to future clinical trials for STS.

Keywords: EORTC; Fatigue; Mixed-methods research; Oncology; Pain; Patient-centered

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outcome measurement; Patient-reported outcomes; Rare disease; Rasch measurement theory; Soft tissue sarcoma

Key Summary Points

Soft tissue sarcomas (STS) are a group of rare cancers, representing less than 1% of all types of adult cancer. Pain and fatigue were identified as the most distressing symptoms by patients.

Conceptual frameworks of the patient experience of pain and fatigue in STS were developed from existing patient-reported outcome (PRO) item content, key opinion leader consultation, and qualitative interviews with patients.

Using mixed-methods research and the European Organization for Research and Treatment of Cancer (EORTC) item library, we developed five content-valid PRO scales to measure pain and fatigue in patients with STS.

Further psychometric evaluation in larger samples is recommended to determine that the PRO scales are fit for purpose to evaluate treatment benefit in future STS trials.

INTRODUCTION

Soft tissue sarcomas (STS) are a group of rare cancers, representing less than 1% of all types of adult cancer [1] and characterized by malignancy in any connective, supportive, or surrounding tissue of the body. There are more than 50 identified subtypes of STS, the clinical presentation of which is largely dependent on the subtype and the tumor location in the body [2]. The overall 5-year survival for STS varies widely depending on subtype, ranging from 94% in fibroblastic liposarcoma to 49% in the dedifferentiated subtype [3]. Moreover, factors such as sex, age, and size of the tumor can negatively affect mortality, with male sex, aged over 35 years, and larger tumors more closely associated with poor prognoses and decreased survival rates [4]. Early diagnosis is key; without treatment, almost half of all patients will develop metastatic disease, a nearly incurable stage of STS, with a median survival rate of less than 1 year [5].

Many patients with STS report symptoms such as pain, lack of energy, difficulty sleeping, feeling bloated, shortness of breath, and difficulty concentrating [6], with increased frequency of these symptoms accompanying disease progression [7]. However, due to its many subtypes and locations in the body, STS manifestations can be diverse, making it difficult to generalize all the symptoms patients with STS may experience [6]. Although nearly all patients with STS will report pain, the type of pain can differ depending on the location of their tumor [6]. For instance, patients with the chordoma subtype (cranial location) describe headaches and palsy as the most common symptoms, whereas patients with dedifferentiated liposarcoma of the gastroesophageal junction often report abdominal pain (retroperitoneal location) [8].

Treatment options for inoperable STS are limited [9], but systemic therapy options are increasing [10]. Surgery and chemotherapy are the general standard treatment for STS; however, the heterogeneity of the disease can require varied treatment modalities based on the type and location of the tumor in the body [11]. Management of inoperable, advanced, or metastatic STS remains challenging [12] and lacks sufficient high-quality evidence to support its effectiveness. While these treatments aim to improve survivability, patients often experience significant sequelae related to their treatment, reporting increased pain and fatigue that limits their ability to function [13].

Indeed, in a 2017 study describing symptom prevalence and severity in patients with STS by Gough et al., patients with STS identified pain and fatigue to be the most distressing part of both their disease and treatment [13]. This finding was further supported by a 2022 study by Eliason et al., which found pain and fatigue were the most-mentioned symptoms in patients

with metastatic synovial sarcoma [14]. Unfortunately, as there are no subtype-specific studies on either pain or fatigue in patients with STS, the true depth of the effect of pain and fatigue on this population's quality of life is unknown.

As with other rare diseases, there is scant patient-centered research on STS; however, the impact of the disease and its treatment on the patient's quality of life warrants investigation [8]. Examining qualitative data related to patients' needs can provide insights into concepts that may otherwise remain unnoticed in the clinical context, including treatment benefit. Patient-reported outcomes (PRO) instruments are essential to this process, but none have been developed specifically for this context of use (COU) [15, 16]. While sarcoma research commonly includes scales such as the Toronto extremity salvage score (TESS) [17], Short form-36 [18], European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 [19], and the EQ-5D [20], their ability to measure pain and fatigue in STS is limited [21]. Given the heterogeneity of STS and the multifaceted nature of pain and fatigue, single-item scales would likely result in an incomplete view of these important symptoms. Therefore, multi-item scales are required to capture the complexity of the total patient experience of pain and fatigue.

However, developing an STS-specific PRO does not necessarily require starting from scratch; Hollander et al. (2020) suggest using the EORTC Item Library to build appropriate scales tuned to the needs of the study population [21]. Therefore, the aim of this study was to develop new PRO scales, using an existing item bank, to measure the patient experience of pain and fatigue in STS clinical research.

METHODS

A non-interventional, mixed-methods research design was used consisting of three stages. First, a literature review examined the three most commonly used item banks in oncology research: EORTC, Patient-Reported Outcomes Measurement Information System (PROMIS), and the Functional Assessment of Chronic Illness Therapy (FACIT). Following this review, and consultations with key opinion leaders (KOLs), conceptual models of pain and fatigue were developed.

Second, concept elicitation and cognitive debriefing interviews were conducted with participants diagnosed with STS. Third, exploratory Rasch measurement theory (RMT) analyses examined the measurement performance of the selected PRO items.

Stage 1: Literature Review and Development of Conceptual Models

Literature Review

The literature review examined the EORTC item library, PROMIS item banks, Functional Assessment of Cancer Therapy-General (FACT-G), and FACIT-Fatigue.

The EORTC item library consists of over 850 unique items in 110 languages, which can be used as supplements to the core QLQ-C30 questionnaire to provide more detailed evaluations of health-related quality of life in patients with cancer [22, 23]. The PROMIS library includes over 300 measures that assess various aspects of physical, mental, and social health [24, 25]. The FACT-G measures general cancer quality of life and can be supplemented by other FACIT quality-of-life instruments, including the FACIT-F, a 40-item measure of self-reported fatigue [26].

PubMed was searched to identify studies examining the psychometric properties of the FACIT/PROMIS/EORTC, including validity and reliability, in an STS population using the following search terms:

1. (Sarcoma) AND (PROMIS OR "Patient-reported Outcomes Measurement Information System")
2. (Sarcoma) AND (FACIT OR "Functional Assessment of Cancer Therapy" OR "Functional Assessment of Chronic Illness Therapy")
3. (Sarcoma) AND (EORTC OR "European Organisation for Research and Treatment of Cancer")

Data on the psychometric properties of the scales were extracted. Clinicaltrials.gov was searched to review use of these instruments in liposarcoma trials (phases 2–4).

Conceptual Models

PRO items related to pain and fatigue were extracted from the three sources (EORTC, PROMIS, FACIT) by searching through the existing scales and libraries with the terms pain and fatigue. Each item was examined and assigned a conceptual label to describe its content (e.g., "trouble taking a walk because of pain" was assigned a label of "mobility"). The concepts were then grouped into higher level domains (e.g., pain impact) and organized to create conceptual models.

Selection of PRO Item Library

The literature review results informed the selection of either EORTC, PROMIS, or FACIT items to be taken forward into stage 2.

Stage 2: Clinician and Patient Interviews

Key Opinion Leader (KOL) Consultation

Online interviews were conducted with three expert oncologists with a minimum of 14 years' experience in STS. A semi-structured guide was used to discuss the conceptualization of pain and fatigue in STS and obtain feedback on the EORTC PRO items. Interviews lasted approximately 1 h and were recorded following verbal consent.

Participants and Data Collection

Participants were recruited by two global recruitment companies and were included if they were aged $\geq$ 18 years, had a current diagnosis of one of the following STS types (liposarcoma, leiomyosarcoma, undifferentiated pleomorphic sarcoma, synovial sarcoma, or myxofibrosarcoma) or had been in remission for 6 months or less, were able to participate in a 1-h-long online interview, and were fluent in English. These specific STS subtypes were targeted due to murine double minute clone 2 (MDM2) amplification. Participants were excluded if they had any impairment that would prevent participation in interviews. All criteria were self-reported.

Open-ended, semi-structured interviews consisting of concept elicitation and cognitive debriefing were conducted, audio recorded and transcribed verbatim. Concept elicitation aimed to gather information about participants' experiences of pain and fatigue, including descriptions, severity, and variation in concepts from their perspectives. Cognitive debriefing, which is used to ascertain if a patient understands the items of an instrument as intended by the developers [27], aimed to identify any issues spontaneously reported by participants and those specifically probed by the interviewer (see supplementary material, Table S1, for further details on the interview questions).

Compliance with Ethics Guidelines

Study documents were reviewed by Advarra institutional review board (IRB), and the study was deemed exempt from IRB oversight (IRB number Pro00054657). Informed consent was obtained before proceeding with the interviews, and participants consented to have their responses included in this research and any resulting publication. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Qualitative Data Analysis

De-identified transcripts were analyzed thematically [28] with detailed line-by-line open and inductive coding [29–31] using ATLAS.ti software [32]. The first two transcripts were coded in parallel by two researchers to ensure consistency in coding methods and to develop a coding guide. The remaining transcripts were coded by the research team and cross-checked by a senior researcher. For concept elicitation analysis, coding was tailored to the research objectives of the study (i.e., focused on the symptoms of pain and fatigue), and standard analytical techniques of conceptual model development were used [29, 31, 33]. Codes and, where necessary, quotations are compared with the rest of the data and inductively categorized into higher-order overarching categories (referred to as concepts, subdomains, and domains) reflecting their conceptual content.

Cognitive debriefing analysis focused on the following issues: relevance of items to experience of STS, clarity, conceptual overlap, and missing concepts. Coding involved multiple-level codes containing information on (i) the item/response scale/instruction and (ii) the corresponding issue, e.g., clarity/relevance/interpretation.

Stage 3: Psychometric Evaluation

Participants and Data Collection

Qualitative interview participants provided quantitative data by responding to the PRO items via an online REDcap survey.

Exploratory RMT Analysis

Rasch measurement theory (RMT) analysis was performed to evaluate the measurement properties of the items. Due to the small sample size, the primary focus of this analysis was to review scale targeting. Targeting refers to the match between the distribution of the concepts of interest (COI) (e.g., pain and fatigue) in the sample and the range of COI measured by a PRO instrument [34]. In addition to scale-to-sample targeting, other RMT analyses included examination of item thresholds, item fit, local dependency, and person separation to examine whether the observed data "fit" the requirements specified by the Rasch model.

Findings of the RMT analyses were reviewed in conjunction with the qualitative work, as well as with a review of scale content to inform the potential for item reduction. RMT analysis was then performed on the final reduced scales. All RMT analyses were conducted using RUMM2030 software (RUMM Laboratory; Perth, Australia).

RESULTS

Stage 1: Literature Review and Development of Conceptual Models

Literature Review

A total of 338 articles were identified from PubMed, but only five articles reported on psychometric properties and were included (four using EORTC-QLQ-C30 and one using FACIT). A flow diagram detailing reasons for exclusion is provided in Figure S1 in the online supplementary materials. A total of 92 trials were identified from clinicaltrials.gov; no trials used PROMIS/FACIT, and two trials included the EORTC-QLQ-C30. A total of 158 pain items and 166 fatigue items were extracted from the EORTC item library, PROMIS item banks, and subscales from the FACIT measurement system.

Conceptual Models

The conceptual models consist of a number of domains and subdomains that conceptualize the experience of pain and fatigue in STS. These are further detailed in Fig. 1.

Selection of PRO Item Library

On the basis of the literature review results and review of item content, the EORTC item library was selected. A total of 56 pain items and 40 fatigue items were taken forward to stage 2.

Stage 2: Clinician and Patient Interviews

KOL Consultation

Clinicians expressed support for the conceptual frameworks and provided useful feedback on EORTC PRO items, suggesting key questions, missing concepts, and items that could be removed. Importantly, they described that pain was usually due to tumor location; however, some locations of pain are more likely to be due to treatment (e.g., pain in the throat, mouth, and rectum). Regarding fatigue, clinicians reported that treatment-related fatigue varied and that it can also be impacted by tumor location and bulk. Clinicians emphasized that the key aspects to capture in clinical trials were pain severity, impact of pain on activities of daily living, and day-to-day functioning, as well as pain causality, duration, and the amount of pain medication taken.

Patient Interviews

The study sample comprised 29 participants. Demographic and health data are presented in Table 1. Of the sample, 73% were female, 41%

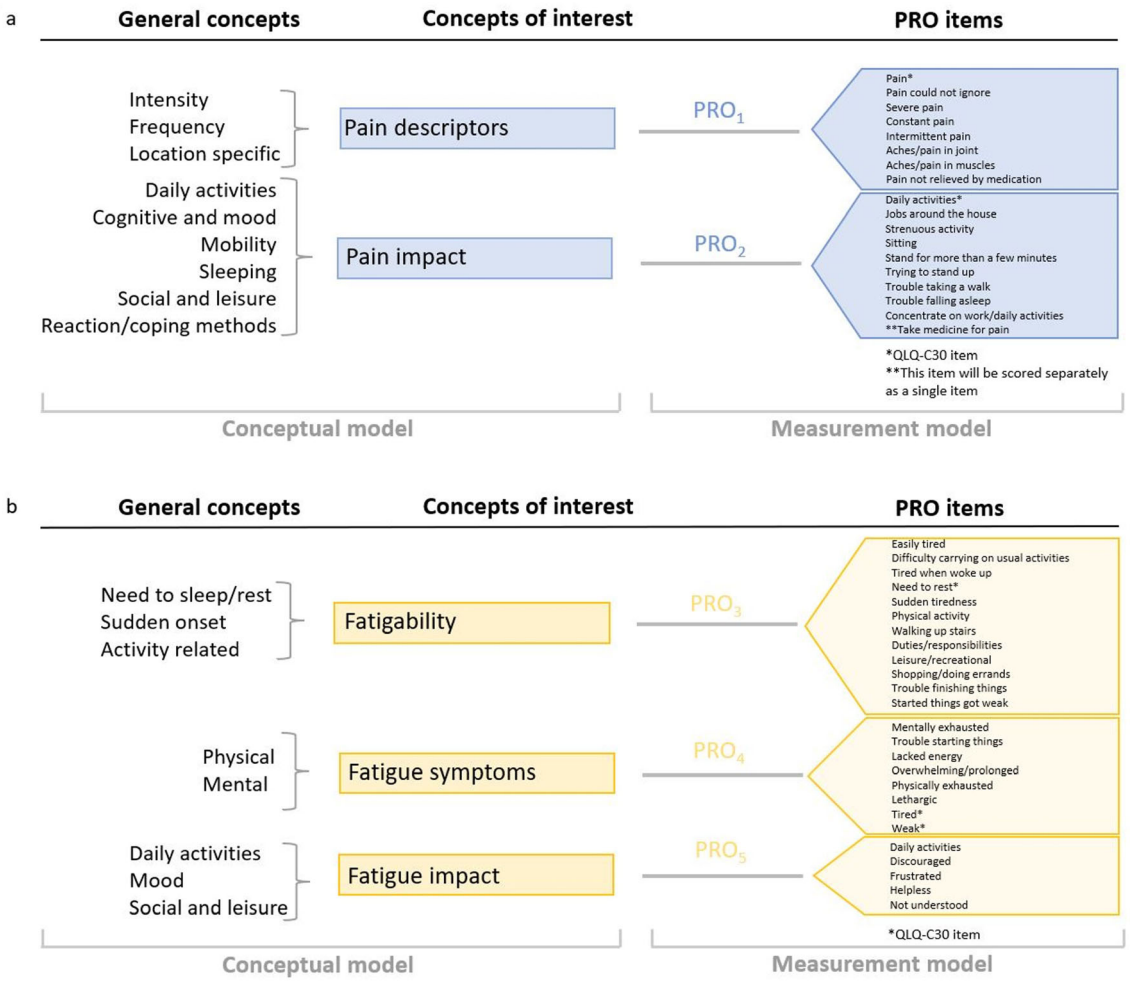


Fig. 1 Pain conceptual framework (**a**) and fatigue conceptual framework (**b**) in STS patients. This figure shows the conceptual models for pain and fatigue and their corresponding measurement models. **a** shows the conceptual model for pain and the items in the measurement model for the two pain PRO scales: pain descriptors and pain impact; and **b** shows the conceptual model for fatigue and the items in the measurement model for the three fatigue PRO scales: fatigability, fatigue symptoms, and fatigue impact. PRO items from the core EORTC QLQ-30 scale are indicated with an asterisk

had a diagnosis of STS within the previous 12 months, and 31% were diagnosed with liposarcoma. One participant with leiomyosarcoma completed the EORTC PRO questions but did not take part in the interview, making qualitative data available for $n = 28$.

Concept Elicitation

Line-by-line coding of the 28 transcripts resulted in 324 unique codes related to pain and fatigue symptoms and impacts. Data from concept elicitation showed coverage of all concepts in the conceptual framework developed from the literature review stage and no missing concepts.

Pain Some patients reported pain due to treatment, such as in the location of surgery or radiation therapy. Chemotherapy-related therapy included neuropathy, sore skin, and edema. Others reported pain due to the tumor. Concepts related to pain and their associated participant quotes can be found in supplementary materials.

Table 1 Sample characteristics

Participant group	Patient sample (n = 29)
Age (years)	
Mean (SD)	43 (14)
Range	22–79
Sex, n (%)	
Female	22 (73%)
Type STS, n (%)	
Liposarcoma	9 (31%)
Undifferentiated pleiomorphic sarcoma	4 (14%)
Leiomyosarcoma	7 (24%)
Synovial sarcoma	7 (24%)
Myxofibrosarcoma	2 (7%)
STS location, n (%)	
Head	3 (10%)
Arms	4 (14%)
Neck	3 (10%)
Legs	14 (48%)
Abdomen	13 (45%)
Other	10 (34%)
Time since diagnosis, n (%)	
Within the past 12 months	12 (41%)
1–2 years	5 (17%)
Over 2 years	12 (41%)
Currently in remission, n (%)	
0–6 months	6 (21%)
6–8 months[a]	1 (3%)
Treatments received, n (%)	
Surgery	26 (90%)
Chemotherapy	16 (55%)
Radiotherapy	17 (59%)
Supportive care	1 (3%)
Other	5 (17%)
Performance status, n (%)	
0	3 (10%)
1	19 (66%)
2	5 (17%)
3	2 (7%)
4	0 (0%)

[a]By the time the interview was scheduled, one participant had been in remission for 8 months

Performance status descriptions: 0—I am fully active and able to carry out activities the same as before my cancer diagnosis, without any restrictions; 1—I have difficulty with physically strenuous activity, but I can walk and carry out work that is light or based in one location, such as light housework or office work; 2—I can walk and take care of myself, but I am not able to carry out work activities, I am up and about more than half the hours that I am awake; 3—I am capable only of limited self-care and spend more than half the hours that I am awake in bed or in a chair; 4—I am completely disabled, cannot carry on any self-care, and am totally confined to a bed or chair

Fatigue Both the tumor and treatment, such as chemotherapy, surgery, and radiation therapy, were mentioned by patients as the cause of their fatigue. Exemplary quotes from the interviews are provided for each concept in the fatigue conceptual framework in supplementary materials.

Cognitive Debriefing

Line-by-line coding of the 28 transcripts resulted in 1887 unique codes, which were organized and assigned to the following categories: most important; less important; not relevant at all; not relevant in the past week; item clarity; conceptual overlap; and potential missing concepts.

Pain Questionnaire Items Item 49 "concentrate on work/daily activities" was reported as the most important (n = 7) and item 52

"vagina" as the least important (n = 4). Item 48 "trouble sleeping" (n = 3), item 7 "stomach" (n = 2), and item 16 "groin" (n = 2) were reported as having potential clarity issues.

Fifty-two items were reported as having relevance issues with item 30 "urinated" most frequently mentioned (n = 14). Fifty-three items were reported as not being relevant in the past week but had been at some point. Patients suggested adding a "not applicable" response option to some items, most frequently for item 38 "strenuous activity" (n = 2). Conceptual overlap was reported most frequently for items 4 and 2 (severe/extreme, n = 6), items 15 and 16 (genital area/groin, n = 5), and items 43 and 42 (sitting/sit more than 1 h, n = 3).

Pain location items reported as being treatment related included item 27 (sore/painful skin), items 23 and 29 (mouth/throat pain), item 19 (headaches), item 14 (eyes), and items 18 and 28 (shooting pains in hands/toes/feet).

Fatigue Questionnaire Items Item 2 "mentally exhausted" and item 39 "not understood" were reported as the most important (n = 9), and item 1 "confused" as the least important (n = 6). Items reported as lacking clarity included item 1 "confused" (n = 6), item 20 "sleep for long periods" (n = 5), item 33 "simple things" (n = 4), item 19 "need to rest" (n = 4), and item 13 "tired" (n = 4).

Thirty items were reported as having relevance issues, with item 8 "shower" being most frequently mentioned (n = 8). Thirty-seven items were reported as not being relevant in the past week, with item 9 "sleep for long periods" being the most mentioned.

Patients suggested adding a "not applicable" response option to some items, most frequently for item 25 "walking up stairs" (n = 3). Conceptual overlap was reported most frequently for items 14 and 15 (weak/worn out, n = 6), items 13 and 14 (tired/weak, n = 5), and items 6 and 11 (drowsy/sleepy during the day, n = 5).

Causes of fatigue mentioned included, low blood count, dehydration, pain, not sleeping well, and treatment. Some missing concepts were also mentioned by one participant each: depression, employment, embarrassed, how many days did you feel fatigued, interactions with others, outside help, parenting, too tired to drive, and difference between physical/mental fatigue.

Stage 3: Psychometric Evaluation

Sample

Analyses were conducted on scale responses from n = 29 participants; n = 28 of these also participated in the qualitative interview stage. For sample characteristics, see Table 1.

Exploratory RMT Analysis

The RMT analysis findings are reported in Table 2 and summarized below.

Pain Descriptors The pain descriptors scale was found to have excellent coverage (Fig. 2a) and reliability. All items fit the Rasch model, and item response thresholds were ordered for all but one of the items, supporting the four-level response category. One item pair, P01 "pain" and P06 "intermittent pain," had residual correlations > 0.30, implying that a response to one item influenced the response to the other.

Pain Impact The pain impact scale was found to have good coverage (Fig. 2b) and excellent reliability. All items fit the Rasch model, and item response thresholds were ordered for 6/9 of the items, supporting the four-level response category. One item pair, P31 "daily activities" and P34 "jobs around the house," had residual correlations > 0.30.

Fatigue Symptoms The fatigue symptoms scale was found to have excellent coverage (Fig. 3a) and reliability. All items fit the Rasch model, and item response thresholds were ordered for all the items, supporting the four-level response category. Two item pairs had residual correlations > 0.30.

Fatigability The fatigability scale was found to have excellent coverage (Fig. 3b) and reliability. One item, F18 "tired when woke up," displayed fit residuals outside of the recommended range of ± 2.5; however, it did not display significant

Table 2 Summary of RMT measurement properties and findings

Scale	Targeting[a] (%)	Response scale[b] (%)	Item fit[c] (%)	Dependency[d]	Reliability[e]
Fatigue symptoms (8 items)	90	100	100	2/28	(0.89/0.89)
Fatigability (12 items)	90	100	92	5/66	(0.92/0.92)
Fatigue impact (5 items)	79	60	100	0/10	(0.74/0.70)
Pain descriptors (8 items)	97	88	100	1/28	(0.88/0.87)
Pain impact (9 items)	76	67	100	1/36	(0.85/0.86)

Higher percentages indicate better findings

[a]Estimated using the percentage of individual sample measurements (n = 29) covered by the scale range

[b]Estimated on the basis of the percentage of items displaying ordered response thresholds

[c]Estimated on the basis of the percentage of items displaying significant chi-square estimates suggesting item misfit

[d]Number of item pairs that are locally dependent on the basis of > 0.3 residual correlations indicating > 9% shared variance

[e]PSI (person separation index) is reported on a scale from 0 to 1: 0 represents all error; 1 represents no error

chi-square probabilities (differences between observed scores and expected values did not exceed chance expectations). Item response thresholds were ordered for all items, supporting the four-level response category. Five item pairs had residual correlations > 0.30.

Fatigue Impact

The fatigue impact scale was found to have reasonable coverage (Fig. 3c) and good reliability. All items fit the Rasch model and item response thresholds were ordered for 60% of the items, supporting the four-level response category. No item pairs displayed residual correlations > 0.30.

Final Conceptual Frameworks

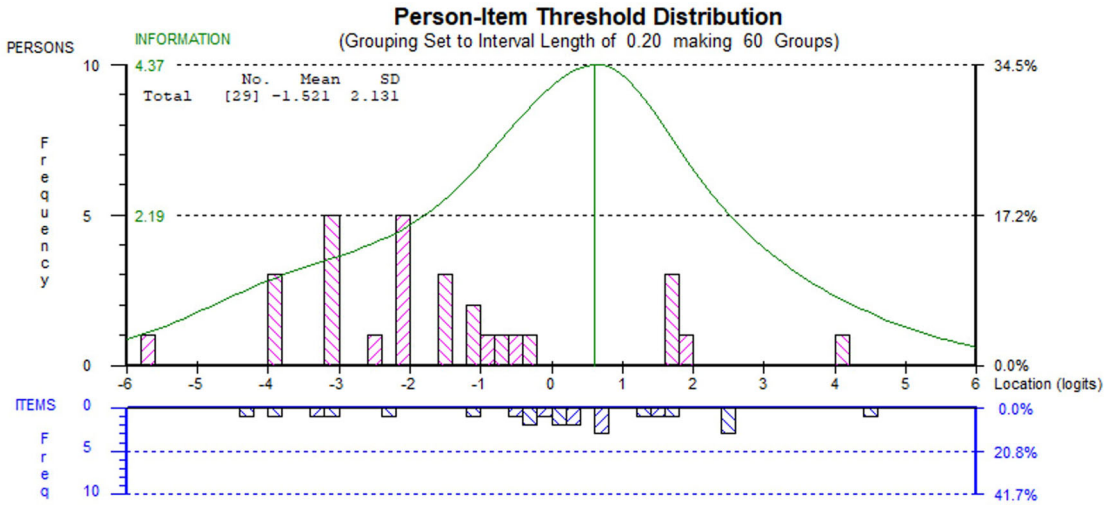
The final conceptual models and PRO scales (which together make the conceptual framework) are outlined in Fig. 1. All scales are answered using a four-point Likert scale (1—not at all, 2—a little, 3—quite a bit, 4—very much), with a recall period of the past week.

DISCUSSION

Employing mixed-methods research and utilizing the existing EORTC item library, we developed five new PRO scales aimed at measuring pain and fatigue in STS. Qualitative findings supported the items as relevant and important to patients with STS. Exploratory RMT provided further supportive evidence for the use of the newly developed scales in this COU. Our conceptual frameworks, consisting of the newly developed conceptual models and their associated PRO scales, have the potential to inform future clinical outcome assessment endpoint strategies.

The challenges of developing novel measures in rare diseases can include limited existing literature and difficult sampling and data collection due to rarity [35, 36]. Developing novel measures from comprehensive item banks, such as the EORTC, offers a pragmatic solution to some of these challenges. The EORTC has advantages in this COU over other item banks in that it was developed specifically with cancer patients in mind, as opposed to PROMIS, which was developed from a sample with a wide range of health conditions. This makes the EORTC a popular choice in oncology research. Other projects aimed at developing health-related quality of life (HRQoL) measures in sarcoma have also included the EORTC item library as part of the development protocol [14, 21]. The library has been used to develop new HRQoL measures that may supplement the QLQ-C30 in other forms of cancer, such as the EORTC QLQ-ANL27 in anal cancer [37], nuclear protein in testis (NUT) carcinoma [35], myelodysplastic

a Pain descriptors



b Pain impact

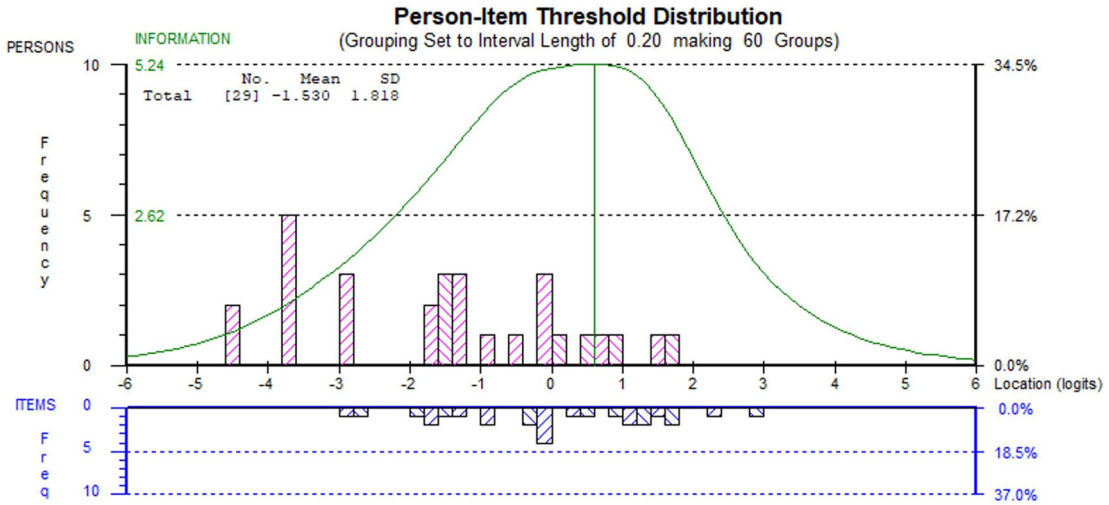
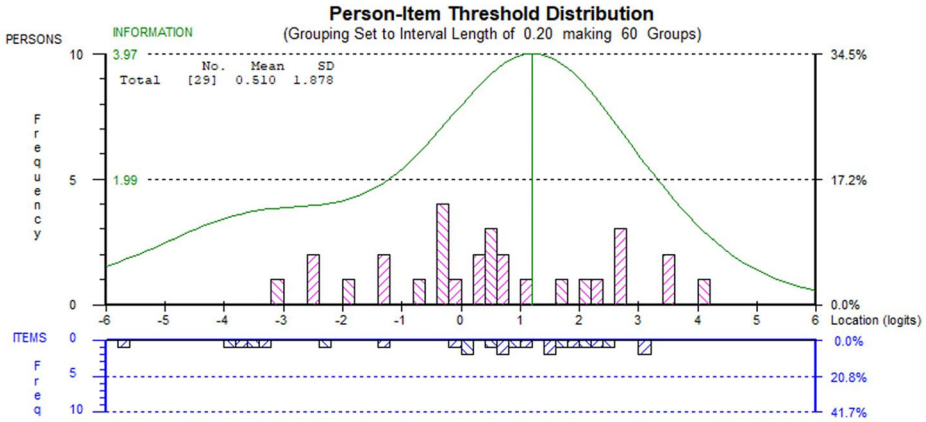


Fig. 2 Scale-to-sample targeting plots of pain descriptors (**a**) and pain impact (**b**) scales. This figure shows the distribution of person measurements (upper histogram) against the distribution of the item threshold locations (lower histogram) on the pain descriptors (**a**) and pain impact (**b**) continuum. Here, the lower histogram (blue bars) shows the distribution of item thresholds which represent the boundaries between adjacent response categories. The green curve represents an inverse function of the standard error associated with each person measurement (the peak of the curve indicating the best point of measurement). The pain scales have four response categories so there are three boundaries or thresholds for each item

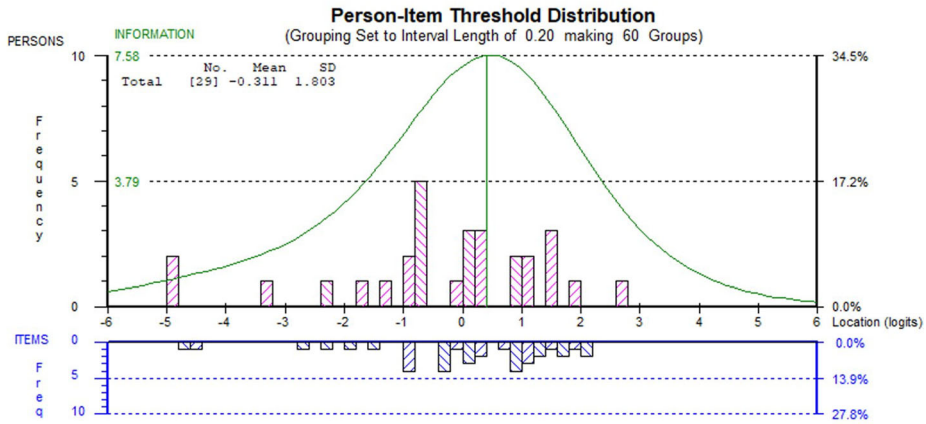
syndromes [38], and the development of four disease-specific scales in Hodgkin lymphoma [39].

The clinicians in this study reported a broad range of estimated proportions of STS patients who experience pain (30–60%) and fatigue (15–90%). These varying estimates suggest that

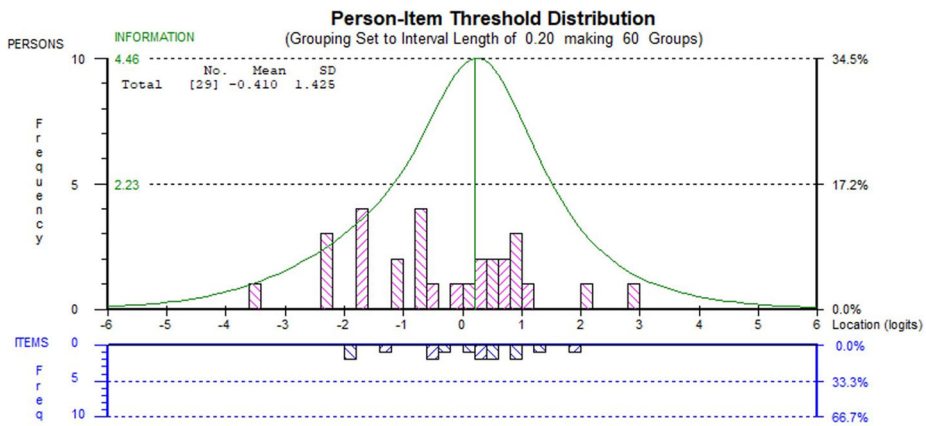
a Fatigue symptoms



b Fatigability



c Fatigue impact



◀**Fig. 3** Scale-to-sample targeting plots of fatigue symptoms (**a**), fatigability (**b**), and fatigue impact (**c**) scales. This figure shows the distribution of person measurements (upper histogram) against the distribution of the item threshold locations (lower histogram) on the fatigue symptoms (**a**), fatigability (**b**), and fatigue impact (**c**) continuum. Here, the lower histogram (blue bars) shows the distribution of item thresholds that represent the boundaries between adjacent response categories. The green curve represents an inverse function of the standard error associated with each person measurement (the peak of the curve indicating the best point of measurement). The fatigue scales have four response categories, so there are three boundaries or thresholds for each item

there are numerous factors at play but reinforce the importance of asking patients diagnosed with STS about these issues. In our interview sample, all patients were able to describe pain and fatigue experiences while living with STS. An important point raised by patients was the impact of STS treatment on the experience of pain and fatigue. It was difficult for patients to make a distinction between pain and fatigue caused by STS versus treatments such as chemotherapy or surgery. This was further supported by the clinical experts who suggested that fatigue in STS is mostly due to treatment and that some locations of reported pain may also result from treatment. Clinicians did, however, share that tumor location and bulk can affect people's experience of these concepts. The challenge of distinguishing disease-related symptoms from treatment toxicity has also been described elsewhere [40, 41].

The use of a mixed-methods approach, as described here, is integral to the development of robust and rigorous psychometrically valid scales. RMT is a particularly valuable psychometric paradigm in scale development as it allows for a more thorough examination of scale performance, for example, through the analysis of scale-to-sample targeting or ordering of response categories. Furthermore, by grounding the item reduction process in both the patient experience as well as psychometric evidence, it ensures novel PRO scales are both relevant to the patient group and fit for purpose. Including the perspectives of clinical experts in addition provides another strength. All clinicians supported the conceptual frameworks and gave insightful feedback on the EORTC items.

Although this research generated important data for consideration, there are some limitations. All health data were obtained through patient self-report, without confirmation of diagnosis; as a result, accuracy cannot be definitively confirmed. This approach is often taken in studies that do not recruit through clinical sites, and the requirement of confirmation of diagnosis could have hindered recruitment. Additionally, due to the utilization of items from an existing item library, we were unable to make changes to the wording or response categories to reflect patient or clinician suggestions. However, using this approach creates consistency across studies and more efficiency. Finally, as with all rare disease research, the sample size was small. Nevertheless, our sample covered an adequate range in terms of age, subtypes, and severity disability (performance status). Results from the exploratory quantitative analysis on $n = 29$ should be treated with caution. However, RMT has been shown to provide robust results in small samples [42, 43].

Future work should include an external validation to confirm findings and provide further in-depth examination of psychometric performance and scoring in larger, clinically defined samples. Evaluation across more than one timepoint would also enable assessment of test–retest reliability and sensitivity to change.

CONCLUSION

This mixed-methods research has generated valuable information concerning the experiences of pain and fatigue in patients diagnosed with STS. Five PRO scales to assess the pain and fatigue experience of patients with liposarcoma, undifferentiated pleiomorphic sarcoma, leiomyosarcoma, synovial sarcoma, and myxofibrosarcoma have been developed from the EORTC item library, which can be used in future clinical research in this context.

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Data Availability. The datasets generated and/or analyzed during the current study are not publicly available because they are qualitative transcripts and cannot be completely deidentified.

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