

Dissertation

PATIENT RELATED OUTCOMES IN PRIMARY SJÖGREN'S SYNDROME

submitted by

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Declaration

“I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the “Standards of Good Scientific Practice and Ombud Committee at the Medical University of Graz”.”

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2 Abbreviations and definitions

EQ-5D – Euro Qol – 5 Dimensions

ESSDAI - EULAR Sjögren's Syndrome Disease Activity Index

ESSPRI - EULAR Sjögren's Syndrome Patient Reported Index

HRQL – Health Related Quality of Life

PROFAD - the Profile of Fatigue and Discomfort

PRO – Patient Reported Outcomes

PROM – Patient Reported Outcome Measure

PsA – Psoriatic Arthritis

PSAID – Psoriatic Arthritis Impact of Disease

PsAQoL – Psoriatic Arthritis Quality of Life

PSS – Primary Sjögren's Syndrome

RA – Rheumatoid Arthritis

RAQoL – Rheumatoid Arthritis Quality of Life

SCAI - Sjögren's Systemic Clinical Activity Index

SLE – Systemic Lupus Erythematosus

SSDAI - SS disease activity index

SSDDI – Sjögren's Syndrome Disease Damage Index

SSDI – Sjögren's Syndrome Damage Index

SSI - Sicca Symptoms Inventory

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5 Abstract in German

Einleitung/Ziel:

Patienten mit dem Primären Sjögren Syndrom (PSS) leiden an glandulären und extraglandulären Manifestationen, die zu einer physischen und psychischen Einschränkung der gesundheitsbezogenen Lebensqualität führen. Inwieweit die Lebensqualität jedoch bei dieser Patientengruppe beeinträchtigt ist, ist noch weitgehend unerforscht. Es wurden zwar Krankheitsaktivitätsscores entwickelt, jedoch noch kein krankheits-spezifischer Lebensqualitätsfragebogen. Das Ziel dieser Studie war es herauszufinden, welche Aspekte der Lebensqualität für PSS Patienten wichtig sind, um dadurch einen Lebensqualitätsfragebogen zu entwickeln und dessen psychometrische Eigenschaften zu testen.

Methode:

Diese Studie besteht aus zwei Teilen: (1) qualitative Interviews innerhalb von Fokusgruppen und (2) die Entwicklung und psychometrische Testung eines Lebensqualitätsfragebogens für PSS Patienten (PSS-QoL).

Im ersten Teil nahmen 20 PSS Patienten, von der Abteilung der Rheumatologie in Graz, teil, bei denen qualitative Interviews durchgeführt wurden. Insgesamt wurden sechs Fokusgruppeninterviews durchgeführt, wobei alle Interviews digital aufgenommen und wörtlich transkribiert wurden. Die „meaning condensation method“ wurde für die Analyse herangezogen.

Im zweiten Teil wurde mithilfe der Konzepte aus den Interviews von Teil eins, der PSS-QoL Fragebogen entwickelt. Der Fokus des PSS-QoL liegt auf der physischen und psychosozialen Dimension. Die erste Version des Fragebogens wurde mithilfe von Experten in semi-strukturierten Interviews evaluiert und mit diesem Feedback wurde der Fragebogen überarbeitet. Die anschließende psychometrische Testung des PSS-QoL wurde anhand von 75 PSS Patienten durchgeführt. Für die Überprüfung der internen Konsistenz wurde das Cronbach's α berechnet und die Konstruktvalidität wurde mithilfe der Korrelation des PSS-QoL mit dem ESSPRI und EQ-5D erhoben. Die Reliabilität wurde bei Patienten mit stabiler Krankheitsaktivität und Wiederholung des Fragebogens nach ein bis zwei Wochen getestet.

Ergebnisse:

Erster Teil: Pro Fokusgruppe nahmen 3-4 Patientinnen am Interview teil. Insgesamt wurden 6 Fokusgruppen durchgeführt. Die identifizierten Konzepte aus den Interviews wurden in drei Dimensionen eingeteilt: 1. physische Dimension, 2. psychologische und emotionale Herausforderungen, 3. Soziales Umfeld und tägliches Leben. Es konnte eine

Abhängigkeit zwischen den drei Dimensionen identifiziert werden. Die häufigsten Konzepte waren Schmerz, Trockenheit, und die Folgen dieser Beschwerden.

Zweiter Teil: Die interne Konsistenz des PSS-QoL zeigte ein Cronbach's α von 0,892 und eine moderate Korrelation mit dem ESSPRI (Corrcoeff=0.625) und dem EQ-5D (EQ5D-pain/discomfort; corrcoeff=0.531). Die Reliabilitätsprüfung des PSS-QoL ergab einen ICC von 0,958 (95% CI 0,926 bis 0,981), im Vergleich dazu betrug der ICC des EQ-5D 0,854 (95% CI 0,735 bis 0,933).

Schlussfolgerung:

Es konnten drei Dimensionen (1. physische Dimension, 2. psychologische und emotionale Herausforderungen, 3. Soziales Umfeld und tägliches Leben) identifiziert werden, die die Patientenperspektive in Bezug auf die gesundheitsbezogene Lebensqualität darstellen. Lebensqualität wird bei PSS Patienten nicht nur durch Trockenheit beeinflusst. Vielmehr sind die Patienten durch die psychischen und sozialen Beeinträchtigungen geprägt. In weiterer Folge wurde ein Lebensqualitätsfragebogen für PSS Patienten entwickelt und dessen psychometrischen Eigenschaften geprüft. Der PSS-QoL stellt ein Hilfsmittel für die Erhebung der Krankheitsaktivität aus Sicht der Patienten dar. Multizentrische Studien sollten für eine weitere Validierung des PSS-QoL durchgeführt werden.

6 Abstract in English

Background/objectives:

Patients with primary Sjögren's Syndrome (PSS) are affected by glandular and extraglandular manifestations leading to physical and mental impairment. How these factors affect the health-related quality of life (HRQL) of these patients is largely unexplored. Disease activity scores have been developed but there is no disease-specific HRQL questionnaire available so far. The aim of this study was 1. to investigate patients' perspectives and needs influencing HRQL and 2. to develop a questionnaire for HRQL in PSS patients and test its psychometric properties.

Methods:

This study was divided into two parts: (1) qualitative interviews within focus-groups and (2) development and testing of the psychometric properties of the HRQL questionnaire for PSS patients (PSS-QoL). In the first part, 20 consecutive PSS patients were recruited from the PSS cohort of the Medical University Graz. Six focus group sessions were performed; all interviews were audio-recorded and transcribed verbatim. A modified meaning condensation procedure was used to analyse the data.

In part two of the study, the PSS-QoL was developed based on the concepts identified in the group interviews and with focus on two main topics: physical and psychosocial dimension. The first draft of this questionnaire was evaluated by clinicians and patients using semi-structured interviews. Based on their feedback, a revised questionnaire was constructed. Subsequently, psychometric testing of the questionnaire was performed in 75 PSS patients. For testing of internal consistency Cronbach's α was used. Convergent construct validity was tested by correlating the scores with the ESSPRI and the EQ-5D. Reliability was examined by asking patients who considered themselves to be in a stable disease status to complete the questionnaire 1-2 weeks apart.

Results:

Study part one: All patients were female. The number of patients in each focus group session ranged from 3-4. The identified concepts were grouped into three dimensions: 1. physical dimension, 2. psychological & emotional challenges and 3. social life & daily living. An inter-dependency of the three dimensions was identified. The concepts most commonly reported were pain, dryness and complaints related to these symptoms which all belonged to the physical dimension.

Study part two: The PSS-QoL revealed a high internal consistency with a Cronbach's α of 0.892. A moderate correlation of the PSS-QoL with the ESSPRI (corrcoeff=0.625) and the EQ-5D (EQ5D-pain/discomfort; corrcoeff=0.531) was also found confirming convergent construct validity. Reliability testing of the PSS-QoL yielded an ICC of 0.958

(95% CI 0.926 to 0.981). In comparison, the ICC for EQ-5D in this population was 0.854 (95% CI 0.735 to 0.933).

Conclusion:

We found that three interrelated dimensions (1. physical dimension, 2. psychological & emotional challenges and 3. social life & daily living) best reflected patients' experiences and feelings concerning PSS. HRQL in PSS patients was influenced not only by dryness but also by psychological and social burden. A questionnaire to assess the HRQL in PSS patients has been developed and tested for its psychometric properties. The PSS-QoL might enable a better and more comprehensive assessment on patients' HRQL in PSS. Multicentre studies validating the new PSS-QoL are now needed.

7 Introduction

7.1 Primary Sjögren's Syndrome

Primary Sjögren's Syndrome (PSS) is one of the most common systemic autoimmune disorders affecting 0.3-0.5% of the population (1–4). PSS predominantly occurs in women (female: male ratio 9:1) and its incidence peaks in the fifth and sixth decade of life (5).

Sjögren's Syndrome (SS) is called “primary” when no (underlying) additional systemic rheumatic disease is present. It is “secondary” when the sicca-syndrome occurs in patients with another rheumatic disorder such as systemic lupus erythematosus (SLE), scleroderma or rheumatoid arthritis (RA).

The diagnosis of PSS can be delayed for several years after symptom onset, because of under-recognition of the significance of sicca symptoms by patients and health-care personnel (6).

PSS is an autoimmune epithelitis characterised by lymphocytic infiltration of exocrine glands and epithelia at multiple sites. Although the American-European consensus classification criteria have been developed to classify patients with SS for clinical studies, in clinical practice they are often applied to make a diagnosis. These criteria are based on signs and symptoms of exocrine gland dysfunction, characteristic autoantibodies and/or positive histology (see table 1) (7).

Table 1: American-European consensus classification criteria of PSS (7)

<p>I. Ocular symptoms: a positive response to at least 1 of the following questions:</p> <ul style="list-style-type: none">(1) Have you had daily, persistent, troublesome dry eyes for more than 3 months?(2) Do you have a recurrent sensation of sand or gravel in the eyes?(3) Do you use tear substitutes more than 3 times a day? <p>II. Oral symptoms: a positive response to at least 1 of the following questions:</p> <ul style="list-style-type: none">(1) Have you had a daily feeling of dry mouth for more than 3 months?(2) Have you had recurrent or persistently swollen salivary glands as an adult?(3) Do you frequently drink liquids to aid in swallowing dry foods? <p>III. Ocular signs: objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:</p> <ul style="list-style-type: none">(1) Schirmer-I test (≤ 5 mm in 5 minutes)(2) Rose bengal score (≥ 4, according to the van Bijsterveld scoring system)
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IV. Histopathologic features: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score >1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm² of glandular tissue

V. Salivary gland involvement: Objective evidence of salivary gland involvement, determined on the basis of a positive result on at least 1 of the following tests:

- (1) Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer
- (2) Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitory or destructive pattern), without evidence of obstruction in the major ducts
- (3) Unstimulated salivary flow (≤ 1.5 ml in 15 minutes)

VI. Autoantibodies: Presence of at least 1 of the following serum autoantibodies:

- (1) Antibodies to Ro/SS-A and/or La/SS-B antigens

Exclusion criteria: Pre-existing lymphoma, acquired immunodeficiency syndrome, sarcoidosis, or graft-versus-host disease, past head and neck radiation treatment, Hepatitis C infection, use of anticholinergic drugs (since a time shorter than 4-fold the half-life of the drug)

7.1.1 Clinical features of PSS

The sicca syndrome with dryness of eyes and mouth is the most common feature in PSS (8). The consequence of dry eyes can be a keratoconjunctivitis sicca with a chronic eye irritation and a destruction of the corneal and conjunctival epithelium. These patients suffer from red eyes, itching and grittiness, a burning or scratchy sensation under the eyelids and photosensitivity. The dryness of the mouth (xerostomia) leads to difficulties in chewing and swallowing dry food, difficulty in speaking and a burning sensation in the mouth. They are at increased risk of halitosis, oral thrush, periodontal disease and dental caries (6).

A chronic or episodic swelling of the major salivary glands occurs in many PSS patients, with a history of parotid involvement reported at diagnosis in 82% of patients (9). In a

retrospective study of PSS patients from the United Kingdom, 71% experienced systemic manifestations, and 28.3% developed a tumour. Non-Hodgkin lymphoma was present in 10.5% of patients, and we know that patients with a history of vasculitis, parotid swelling and lymphadenopathy are at an increased risk to develop this type of malignancy (10). Besides, up to one third of patients experience extraglandular manifestations including musculoskeletal, gastrointestinal and/or neurological symptoms (7).

Physical and mental impairment (fatigue, anxiety and depression) are common in PSS patients. These complaints are partly related to inflammation and significantly contribute to an impaired quality of life and to a limitation of activities of daily living (ADL). In addition, mood disorders cause enormous social costs due to high consumption of health care resources and work disability (4).

Until now, there is no evidence that any treatment could change the course of PSS (11). Besides, there is a need for drugs to treat symptoms and systemic manifestations of the disease. Some small, open label studies reported that some biologicals such as rituximab could improve the symptoms temporarily (12). Larger studies, however, are needed to confirm these findings. Reducing the severity of symptoms could lead to an improvement of quality of life, improved work life and a reduction of economic costs of PSS patients.

7.2 Assessment of disease activity and outcomes in PSS

Current PSS disease activity scores have either been developed using clinical databases collected by health care professionals or were agreed upon by expert groups without direct conceptual input from patients. Patient reported outcome measures (PROMs) have been “borrowed” from other diseases in clinical trials to determine the extent of fatigue or sicca symptom whereas a PSS specific tool to measure health related quality of life (HRQL) is not available thus far.

7.2.1 Physicians’ based disease activity scores

To measure disease activity of PSS patients with systemic manifestations, three composite scores are currently available: The SS disease activity index (SSDAI), the EULAR Sjögren’s Syndrome Disease Activity Index (ESSDAI) and the Sjögren’s Systemic Clinical Activity Index (SCAI). The SSDAI was the first activity index for PSS and includes 11 clinical items within 8 domains and was developed by statistical means using clinical data from a large PSS cohort (13). The SCAI is an ordinal transition scale similar to the BILAG scoring system in SLE (14). This index reflects the change of disease activity in the

past 4-weeks compared to the preceding 4-week period. The SCAI includes 42 items in 8 domains (constitutional, musculoskeletal, skin/vasculitis, respiratory, neurological, renal, salivary gland and haematological), which each can be scored as absent, improving, same or worse (15). The ESSDAI was developed by consensus of a group of experts. It was designed to measure disease activity in patients with glandular and extraglandular manifestations focussing on constitutional symptoms, lymphadenopathy, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral nervous system, central nervous system and haematological abnormalities. The activity within each domain is rated by a 3- or 4-levels scale (16).

Two indices are available to evaluate disease damage: The SS disease damage index (SSDDI) and the SS damage index (SSDI). The SSDDI was developed in the same cohort with similar methods as the SSDAI and includes 6 domains and 15 items (13).

The SSDI is a modified version of the SLICC, a damage index for SLE. This index was developed by an expert panel and is composed of 29 items. In comparison to the SLICC, the SSDI focuses on ocular and oral parameters in addition to systemic domains (17).

7.2.2 Patient based indices

Three disease-specific patients' questionnaires are available in PSS: the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), the Profile of Fatigue and Discomfort (PROFAD) and the Sicca Symptoms Inventory (SSI). These questionnaires were developed in large cohort studies corroborating patients' symptoms and complaints but did not involve patients directly to develop the questionnaires. The SSI was the first PSS-specific patient questionnaire available addressing the extent of ocular, oral, vaginal and cutaneous dryness (18). The PROFAD consists of 9 items gathered into 4 domains: somatic fatigue, mental fatigue, arthralgias and Raynaud's phenomenon (19). The ESSPRI – domains were developed based on data from SSI and PROFAD cohorts identifying 3 important domains: dryness, fatigue and pain. All items are measured with a numerical scale ranging from 0 to 10 (20,21).

In addition, a brief cognitive symptoms index was developed for PSS patients to measure cognitive symptomatology in patients (22).

Although all these questionnaires may be useful to assess patients' symptoms and activity, they are of only limited value to investigate patients' HRQL. Besides, these scores do not directly reflect the perspective of patients (23,24).

There is a need for an outcome measure that is developed on concepts and parameters important to patients, is specific for PSS, focuses HRQL and fulfils all psychometric properties to be used in clinical practice and in future trials (25).

7.3 Health related quality of life (HRQL)

According to a WHO-definition (World Health Organization), quality of life can be defined as *“individuals’ perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”* (26). In the context of a chronic disease such as PSS, health related quality of life (HRQL) may be understood as the overall burden of disease and therapy on patients’ daily individual and social life (27). HRQL refers to the components of quality of life (physical, mental and social factors) that are in relation to an individual’s health (28). The most important dimensions of HRQL include overall physical and social function, burden of symptoms and emotional status and general life satisfaction (29).

HRQL measurement is patient centred, subjective and has a multidimensional structure comprising physical (individuals’ perception of their physical state), psychological (individuals’ perception of their cognitive and affective state) and social factors (individuals’ perception of the interpersonal relationships and social roles in their life) contributing to daily living. In contrast, disease activity and disease damage scores (as described above) are based on disease specific clinical tests, laboratory results and patients’ global assessments. These factors only represent a few facets of the disease and not necessarily reflect the most relevant ones to patients (27). Besides, the possible burden of therapeutic interventions is not addressed by disease activity scores.

In patients with SLE, it was observed that self-reported physical and mental status were more important than clinical status variables in understanding patients’ satisfaction with medical care (30). In RA, it was reported that patients and physicians rated physical and mental function differently. Besides, the grading of the value of the Health Assessment Questionnaire (HAQ) items by patients and physicians showed a slight to fair agreement only. The HAQ is a questionnaire designed to measure the disability of patients with arthritis (31,32).

In summary, HRQL assessment provides an accurate summary of the impact of the disease and its consequences from a the perspective of patients (33).

7.4 Importance of HRQL in rheumatology

HRQL has gathered increasing importance as an outcome parameter in rheumatology (and in medicine in general) (34). Pharmaceutical industries, regulatory authorities and health politicians have envisioned the improvement of patients' HRQL as a central part of their policy (35). Besides, new anti-rheumatic drug treatments are licenced under the premise that they do not only reduce patients' signs and symptoms but also improve HRQL (35). Clinical practice guidelines developers specifically focus on patients' values and preferences aimed at the improvement of HRQL (36).

The accurate measurement of HRQL in rheumatology, however, is challenging because of its multidimensional nature taking into account not only peoples physical, mental and social function but also their perception of well-being concerning their physical, mental and social aspects of daily life (37).

The assessment of HRQL thus provides a comprehensive summary of the impact of the disease from the patients' perspective. The content of HRQL instruments should be generated with methods that directly involve patients. This ensures that the content of the final instrument is relevant to the target population.

7.5 Measurement of HRQL in rheumatology

A few disease-specific HRQL assessment tools are available in rheumatology: In psoriatic arthritis, the psoriatic arthritis quality of life questionnaire (PsAQoL) and the Psoriatic Arthritis Impact of Disease (PsAID) have been proposed, for ankylosing spondylitis, the ankylosing spondylitis quality of life questionnaire (ASQoL) has been developed and for RA, the rheumatoid arthritis quality of life questionnaire (RAQoL) and the Rheumatoid Arthritis Impact of Disease are available (33,38–41). These scores were developed by a qualitative research approach and have been intended to be used in clinical trials and routine practice (33,38). In contrast to the HAQ focussing on functional deficits (42), the PsAQoL, ASQoL and RAQoL include social, physical and emotional dimensions of HRQL, as well (33,38,39).

The involvement of patients in developing HRQL measurements is essential, because these instruments are intended to reflect outcomes that are important to patients. Besides, tools developed in cooperation with patients have a greater face validity than instruments proposed by expert groups involving physicians only (43).

7.6 HRQL in PSS

Several factors may contribute to the impairment of HRQL in PSS: Dryness, chronic pain, physical and mental fatigue, neuropsychiatric symptoms as well as other glandular and extraglandular manifestations may all negatively affect patients' well-being (23,44–46).

Sicca symptoms are known to severely impair patients' HRQL, and lead to depression and fatigue regardless of objective test results of salivary/lacrimal gland function (47). In addition, oral dryness has been correlated with pain, psychological distress, poor sleep and vascular risk factors (48). Sexuality is an integral part of HRQL and patients with PSS may suffer from gynaecological problems (such as vaginal dryness) which lead to impaired sexual activity (49,50). Depression, unemployment with disability compensation and a number of other life events as well as burden of treatment and/or the absence of effective therapies may additionally impair HRQL of PSS patients (4,51,52).

A disease-specific instrument for the evaluation of HRQL of PSS patients has not been developed so far. In clinical studies, generic tools or instruments “borrowed” from other diseases such as the 36-item short form health survey (SF-36), various Visual Analogue Scales (VAS), EuroQoL-5 dimension (EQ-5D) and different fatigue and depression scales have been applied (53,54). The SF-36 is a HRQL questionnaire used in different diseases and populations, and consists of 36 questions about functional, physical and mental health (55). Different VAS scores for fatigue (somatic and mental), sicca symptoms and pain have been tested in previous studies assuming that they are critical features of patients' HRQL (44,56). The EQ-5D is a generic instrument to assess HRQL within five domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) (57). The Profile of Fatigue and Discomfort (PROFAD) has frequently been used to assess the extent of fatigue, and the Hospital Anxiety and Depression Scale (HADS) has been applied to grade patients' affection by depression (58).

Although generic HRQL instruments are advantageous regarding their compatibility with different disease groups, their most important disadvantage is a low sensitivity to detect disease specific factors impairing HRQL (59). The US Food and Drug Administration has therefore recommended to apply disease specific measures instead of generic tools to assess HRQL wherever possible (60).

A recently published study conducted in a large PSS cohort (n=120) associated the HRQL (measured with the SF-36) with the ESSPRI and the ESSDAI. They demonstrated that symptoms of PSS like dryness, pain and fatigue, were stronger predictors of HRQL impairment than systemic manifestations. They proposed to use the cardinal symptoms of PSS as endpoints in therapeutic trials rather than focusing on systemic manifestations (25).

7.7 The qualitative research approach

Qualitative research can be defined as *“The investigation of phenomena, typically in an in-depth and holistic fashion, through the collection of rich narrative materials using a flexible research design”* (61). Qualitative research can be characterized by their priority to obtain and analyse textual data out of observations or interviews. These textual data can include transcripts of interviews, free text comments on a questionnaire, observation notes, case histories or medical records.

Qualitative research enables a deeper insight into individuals’ experiences and perspectives of a disease. The interaction with the study participants as individuals or in groups is the most important factor of qualitative research. The aim is to explore peoples’ feelings and experiences as well as their values and preferences in relation to a specific topic. The typical methods used for this purpose are observations and semi-structured interviews (62).

Analysis of qualitative research involves interpretative forms where the perspective and experiences of patients are in the focus of the study. The results of qualitative studies are a representation of reality that makes this methodology preferable for further development of questionnaires or patient-based indices. The better understanding of a phenomenon with the perspective of patients can help to recognize further symptoms or sights of a disease that may have been unknown before. These methods provide more detailed descriptions and a better understanding of concepts (63).

7.8 Qualitative research in rheumatology

In rheumatology, qualitative research projects have been conducted to develop HRQL tools for PsA and RA as described above. Another study incorporated the perspectives of rheumatology patients and healthy people to develop an occupational questionnaire. Eight concepts of occupational balance were identified including challenging and relaxing activities, impact of health on activities, satisfaction with rest and sleep, acknowledgement at work, stress, engagement adaption of activities and activities intended to care (64). Besides, focus group interviews have been performed in patients with systemic lupus erythematosus and systemic sclerosis (65,66). Qualitative research studies were also conducted to assess patients’ thinking about treatment success and satisfaction with therapy, as well as about the factors contributing to patients’ treatment decisions (67). We

are not aware of any qualitative research studies in PSS so far; only a small interview study was performed in SS patients with focus on oral health (68).

7.9 Study rationale

The importance to assess patients' HRQL is increasing in rheumatology. In PSS, no disease-specific tool to measure HRQL exists and therefore, physician-based disease activity measures, PROMs addressing a few clinical aspects of the disease as well as generic HRQL questionnaires have been applied in clinical trials and daily practice so far (21,69).

It is uncertain whether these tools adequately reflect HRQL of PSS patients. For example, it has been shown that social factors correlate with pain and depression (70) and we know that pain, fatigue, depression and cognitive symptoms are all related to work disability and contribute to HRQL. The impact of sicca symptoms (as determined by the SSI) or items included in physician based disease scores on HRQL has not determined so far (71,72).

The qualitative research approach in this study facilitated the exploration of the perspective of patients in a biopsychosocial way (73). Based on the concepts obtained by patients' interviews, we constructed a patient centred assessment tool to specifically addresses PSS related HRQL.

7.10 Objectives

To reach the overall goal of this study, namely to establish a new disease-specific PROM to determine HRQL in PSS, this project was divided into two parts, each with a distinct objective and methods.

The aim of part one was to identify the perspective of PSS patients concerning HRQL using qualitative, focus-group interviews.

The aim of part two was the development and psychometric testing of a new HRQL questionnaire for PSS patients.

Part one of the project has been published in peer-reviewed SCI-listed journal PlosOne (in press) (74).

8 Methods, study design

The following steps are recommended to for the development of a HRQL questionnaire (75):

1. Identification of concepts
2. Instrument criterion
3. Assessment of instrument properties
4. Possible instrument modification

Steps 1-3 were performed within this study using a mixed methods research approach: qualitative study for part 1, qualitative and quantitative methods for part 2. Focus groups were conducted in the first part of the study to identify concerns and expectations of PSS patients related to HRQL. In the second part of the study, concepts identified by patients' interviews were used to generate items for a preliminary questionnaire, the quality of life in Primary Sjögren's Syndrome Questionnaire (PSS-QoL). The preliminary questionnaire was piloted in a small group of patients (n=6) and physicians (n=4) and revised based on experts' feedback. Subsequently, the psychometric properties of the questionnaire were tested (quantitatively) in a larger group (n=75) of PSS patients (see figure 1).

The mixed-methods approach has previously been used to develop HRQL questionnaires in rheumatology and was for example applied to develop the occupational-balance questionnaire in rheumatology (64), the RAQoL(38) and the PsAID (40). The advantage of the mixed-methods approach is that hypotheses resulting from (qualitative) interviews can be tested by quantitative means including tests for psychometric properties (63). This project was approved by the institutional review board of the Medical University Graz and written informed consent was obtained (EK Nr. 26-273 ex 13/14).

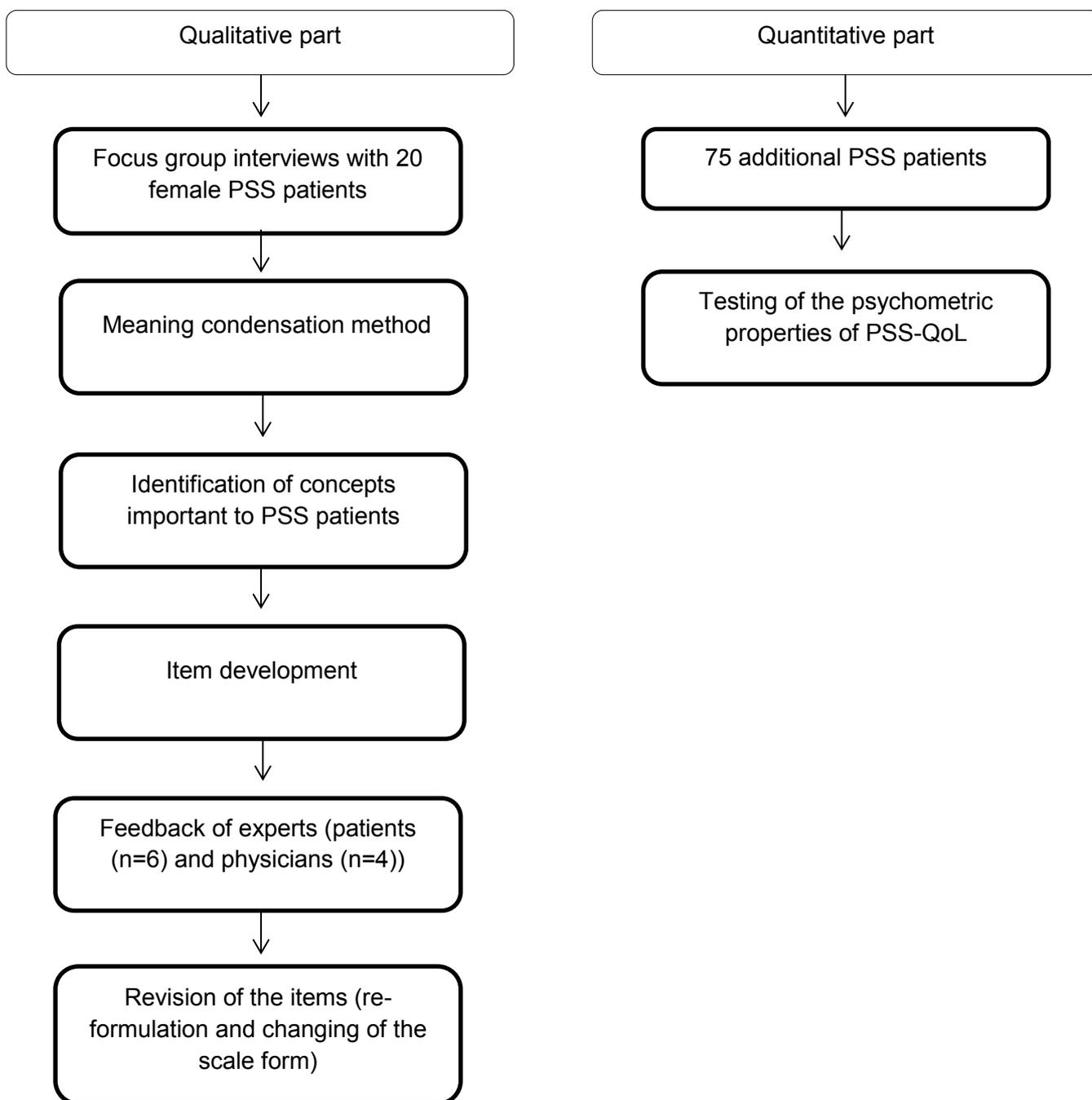


Figure 1: Method of the development of the HRQL questionnaire

8.1 Methods of part 1 – Exploration of HRQL concepts relevant to PSS patients

We used focus group interviews for this part of the study. Qualitative methodology provides the possibility to explore patients' views, experiences and attitudes (76). We conducted focus groups rather than individual interviews because we expected that exploration of views and opinions through group discussion will provide more information and concepts than individual questioning (73).

8.1.1 Participants

PSS patients from the rheumatology outpatient clinic of the Medical University of Graz with a diagnosis fulfilling the American-European consensus classification criteria (7) were asked by phone for participation in this study (74).

In qualitative studies are typically used small sample sizes with a diverse range of participants to obtain the required level of rich and meaningful data. The individual experience of the participants can be highlighted, which can be expressed in variations of a present phenomenon and potentially raise new and unexpected issues. This is more important than numbers and frequencies (62). The purposeful sampling of participants followed the maximum-variation strategy based on the two criteria, disease duration and age group. The criteria ensure that patients with a broad range in disease duration and age were included to provide a comprehensive description of experiences with PSS (74,77). Data saturation was determined as the point when no further concepts could be identified and adequate information about the study aim was obtained (74).

Inclusion Criteria

1. Patients with a diagnosis of PSS based on the American-European consensus classification criteria
2. Male or female patients between 18 and 90 years of age
3. Written informed consent
4. Sufficient language skills to be able to participate the group discussion in German (investigator's judgement, no formal test applied)

Exclusion Criteria

1. Patients with neoplastic disorders and chronic infections
2. Patients with acute severe medical illness requiring hospitalisation

8.1.2 Focus group interviews

All focus groups were chaired by the same moderator (AL) aided by one assistant responsible for observing the group and recording the data. Interviews were conducted in German language (74).

A discussion guide was developed with an opening question and four main open-ended questions based on the three (i.e. the physical, mental and social) dimensions of HRQL (21) and a further literature review (see table 2 for topic guide) (74).

Table 2: Topic guide used to maintain focus group discussions (74)

Opening question: Could you introduce yourself and describe the way of your disease?

Open-ended questions:

1. Which PSS-related problems do you experience and which parts of the body are involved? (e.g. Dryness of eyes, mouth, nose, vagina, skin, side-effects of medication, limitation through treatment?)
 2. Do you experience any limitations in mental health? (e.g. depression, fatigue)
 3. Do you experience any difficulties in your activities of daily living? (e.g. which kind of work, sick leave, household, hobbies and leisure activities)
 4. Do you experience any limitations in your social environment? (e.g. impairment of social contacts, support from family/friends)
-

The moderator declared the interview process and the aim of the study at the beginning of the focus group session. The discussion was started with the opening question. The supposed duration of the focus-group interview was about one hour, like in other qualitative studies (78,79).

All interviews were digitally recorded and transcribed verbatim and the patients' data were anonymised. For transcription of interview, software F4 transcripts (80) was used (74).

8.1.3 Data analysis

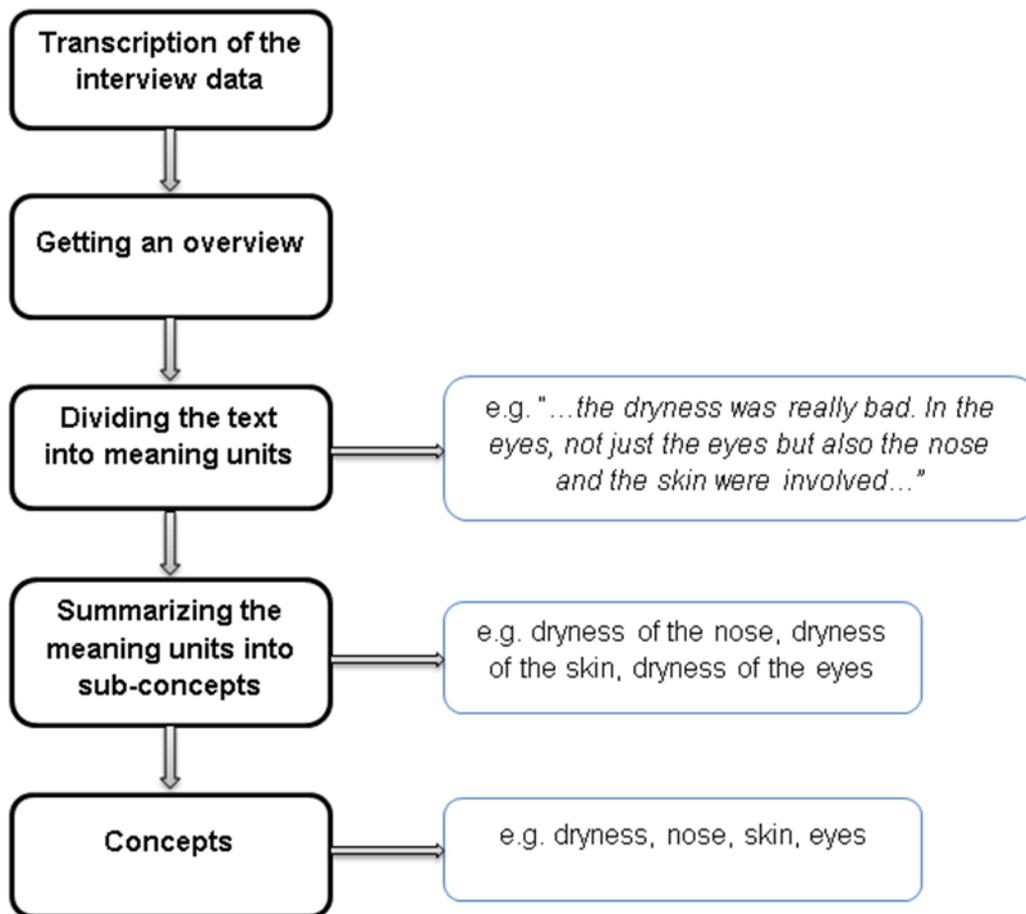
For data analysis of the focus group session a modified meaning condensation procedure was performed (figure 2) (62,74). This method makes it possible to reduce the transcribed text stepwise into short formulations reflecting interviewees' meanings:

The first step was to read through the transcribed focus group interviews to get an insight of the data material. At the second step, the data material was classified into 'meaning units', which referred to a specific unit of text with a phrase or a few words or a few sentences with a common meaning important to the aim of the study. Within the third step, sub-concepts were determined among the meaning units which best reflected the meaning units, while a meaning unit could contain more than one sub-concept. The fourth step contained a grouping of the identified sub-concepts into more comprehensive concepts (62,74).

For the management of interview data and handling of the concepts, the software Atlas.Ti (81) was used. The analysis was evaluated by three interviewed patients by checking and verifying the resulted concepts. According to the aim of the study, namely to explore the aspects of HRQL, the identified concepts were attributed to the most appropriate main dimension of HRQL (29,74).

For description of demographic data, the statistical program SPSS Version 22.0 was used (74).

Figure 2: „Meaning condensation method“- steps of data analysis (74)



8.2 Methods of part 2 – Development and testing of the questionnaire

8.2.1 Development of PSS-QoL

An item pool was developed based on the concepts and subconcepts identified in part 1. Items of PSS-QoL Version 1 are shown with their concepts in table 3. One investigator (AL) phrased the items with the concepts of the interviews for the first draft questionnaire using as much as possible the wording of patients as retrieved during the focus groups. This approach ensured that the final instrument was relevant and understandable to the target population (43). The items can be scored by a 5-point- Likert scale and by marking the symptoms and by a VAS Scale (0-100mm) (39,82). Subsequently, the first draft of the PSS-QoL was constructed (for detail see appendix A for PSS-QoL Version 1).

Table 3: Items of PSS-QoL version 1 with their concepts

Items (=I), PSS_QoL version 1	concept/subconcept
I 1	⇒ joint pain
I 2	⇒ wandering pain
I 3	⇒ obstipation
I 4	⇒ stomach pain
I 5	⇒ dryness of mouth
I 5a	⇒ burning in the mouth
I 5b	⇒ speaking
I 5c	⇒ loss of teeth
I 5d	⇒ reduced sense of taste
I 5e	⇒ inability to eat and chew, limitation in nutrition, eating disturbances
I 5f	⇒ sleeping disturbances due to dryness of mouth
I 6	⇒ dryness of eyes
I 6a	⇒ inflammation of the eyes
I 6b	⇒ pain
I 6c	⇒ gritty eye sensation
I 6d	⇒ inflammation of the eyes
I 6e	⇒ worsening of vision
I 6f	⇒ inability to shed tears
I 6g	⇒ difficulties at work, household activities, hobby
I 7	⇒ dryness of skin
I 7a	⇒ redness of skin

I 7b	⇒	tightening of skin
I 8	⇒	dryness of nose
I 8a	⇒	reduced sense of smell
I 8b	⇒	nose bleeding
I 9	⇒	vaginal dryness
I 9a	⇒	pain due to dryness
I 9b	⇒	itching
I 9c	⇒	pain during sexual intercourse
I 10	⇒	loneliness, prostration
I 11	⇒	complaints were dismissed
I 12	⇒	psychological stress
I 13	⇒	decreased performance
I 14	⇒	lack of understanding of complaints
I 15	⇒	social contacts
I 16	⇒	loneliness
I 17	⇒	fear of side-effect, side effects
I 18	⇒	worries about the future
I 19	⇒	living with a chronic disease
I 20	⇒	impaired self-confidence
I 21	⇒	household activities, sports, difficulties at work, standard of living, hobby
I 22	⇒	fatigue
I 23	⇒	standard of living
I 24	⇒	physical therapy, complementary therapy, financial dependency, financial stress
I 25	⇒	Overall question about HRQL

Further revisions of the draft were done after conduction of semi-structured interviews with a small sample of PSS experts (6 patients and 4 physicians) (changed questions are marked in appendix A). Interviewees were asked to complete the questionnaire and to comment on its applicability, comprehensibility, relevance and comprehensiveness. The first draft of the questionnaire was amended in accordance to experts' feedback (83,84). In the first draft of the questionnaire, questions 1-4 were rated on a VAS scale ranging from 0-100 mm. Experts felt that checkboxes with yes or no can be handled easier and the question of pain intensity can be scored from 0 to 10 by checking a box. Some questions were revised and a question about global pain was added. Examples for

changes are: the scales were changed from a VAS line from 0 to 100mm to a VAS scale from 0 to 10. One question about sleeping problems was added (Question 6) as well as two questions from dimension of psychosocial were deleted (Question 13 and 19 from Version 1). Answer options “none” in dryness category of version 1 were deleted as well.

The final version for testing of the PSS-QoL consisted of 25 questions. The version delivered to patients did not contain scoring points or the number of questions to avoid that patients are influenced by the numbers at scoring (see appendix B for details). For testing of the psychometric properties of the final questionnaire, we included 75 PSS patients (study period February to July 2016) which is slightly below the recommended 5-10 subjects per item of a questionnaire undergoing psychometric testing (84). Given that the PSS cohort of the Medical University Graz is not big enough to comply with these recommendations, we plan a multi-centre study to (re-)test the psychometric properties of the PSS-QoL in a sufficiently large cohort.

8.2.2 Calculation of the PSS-QoL

The PSS-QoL was divided into a physical and psychosocial dimension. The physical dimension focuses on pain and dryness. Global pain of the last four weeks can be scored on a numeric scale ranging from 0 to 10. All questions related to dryness of organs/areas are enlisted (according to the interviews and experts' feedback) and can be answered by using checkboxes (if checkbox is marked, means “yes”). Each “yes” adds 1 point to the score. One question related to vaginal dryness is intended to be answered by women only. The dimension of overall quality of life (psychosocial) contains 14 questions/statement with the following possible answers: never, rarely, sometimes, often and always. These questions can be scored 0 (=never) to 4 (=always). This section also contains two inverse questions (Question 15 and 20). A total score of 96 (for women) and 92 (for men) (excluding vaginal dryness with a maximum of 4 points) can be calculated. For further details of sum score see questionnaire in appendix B.

8.2.3 Psychometric testing of PSS-QoL

For psychometric testing of the PSS-QoL in this study, we included 75 consecutive PSS patients from the Medical University of Graz fulfilling the same inclusion and exclusion criteria as described in part 1). Patients involved in focus group interviews (part 1) were not considered for this part of the study.

Descriptive statistics as well as tests of psychometric properties were conducted using SPSS Version 22.0.

The following psychometric tests were performed:

- Feasibility: the percentage of missing data for all questions
- Validity: face and construct validity
- Reliability and internal consistency

8.2.3.1 Assessment of validity

Face validity was tested by semi-structured interviews with patients and physicians as described above and feasibility was assessed using the percentage of missing data for each of the questions.

Construct validity was tested by comparing PSS-QoL with other disease activity or HRQL instruments: EQ-5D, ESSDAI, ESSPRI, sicca score and eye sicca score. Construct validity was determined by using Spearman's correlation between PSS-QoL and the mentioned questionnaires and scores.

Therefore, we asked all patients to complete the EuroQuol-5D (EQ-5D) questionnaire, which is a generic instrument to assess HRQL. This questionnaire contains five questions with three possibilities to answer: none, some and extreme problems, and a VAS scale (0=very bad; 100=very good) for today's health state. The questions of the EQ-5D are related to mobility, self-care, pain/discomfort, usual activities and anxiety/depression (57). Additionally, the ESSDAI and ESSPRI were assessed. Moreover, a global sicca and an eye sicca score were calculated: The sicca score consists of ten questions, where each question is rated by patients on a VAS scale from 0 to 100 mm. The score is determined by calculating the mean of all (global sicca score) questions or questions 1-6 (eye sicca score). This score has been developed by our department and is used in clinical routine although it has not been formally validated yet.

8.2.3.2 Assessment of reliability

Determination of reliability is essential to demonstrate that the questionnaire produces consistent results. Assessing the stability of an instrument involves the evaluation of the test-retest reliability (84). A change of health status was determined by questioning patients directly, whether they felt that their condition was stable, better or worse compared to the previous visit. For this purpose, we administered the same questionnaire twice to a proportion of PSS patients (n=21) with clinically stable disease (as determined by the patient) 1-2 weeks apart. Results of both PSS-QoL assessments were compared

and the reliability (reproducibility) was calculated using the intraclass correlation coefficient (ICC) with a 95% CI (84).

Internal consistency reliability assesses the correlation among items in a section of an instrument. We therefore calculated the Crohnbach's alpha, to estimate the extent to which different subparts of an instrument are reliably measuring the critical attribute (29,61,83). A Crohnbach's alpha equal or higher 0.70 indicates a high consistency (85).

9 Results

9.1 Results of part 1: Exploration of aspects of HRQL in PSS patients

9.1.1 Participants

While sixty-two patients were invited by phone to participate in the focus group study, twenty patients (32.3%) finally participated. Six focus group sessions were conducted (three (4 focus groups) or four (2 focus groups) participants each group) (74). The focus groups were smaller than originally planned (four to six participants per group) (62) because of non-attendance of patients. Patients' characteristics are summarized in table 4. Each focus group session lasted in the average 58 (SD \pm 13) minutes (74).

Table 4: Patient characteristics (n=20) (74)

<i>Characteristic</i>	<i>Value</i>
<i>Age, mean \pm SD years</i>	62 \pm 8
<i>Disease duration \pm SD years</i>	5 \pm 2
<i>Treatment no. (%)</i>	
<i>None</i>	11 (55)
<i>Pilocarpine</i>	2 (10)
<i>Pilocarpine+Chloroquine</i>	3 (15)
<i>Pilocarpine+Hydroxychloroquine</i>	1 (5)
<i>Chloroquin</i>	1 (5)
<i>Hydroxychloroquine</i>	1 (5)
<i>Corticosteroids</i>	1 (5)

9.1.2 Concepts and sub-concepts identified by the qualitative analysis

Overall, from analysis we could identify 484 meaning units, which were reduced to 254 sub-concepts and subsequently grouped into 86 concepts (table 5). The concepts were classified to three dimensions: 1. physical, 2. psychological & emotional as well as 3. social life & daily living (figure 3) (29). These three dimensions mirrored the various aspects of HRQL in PSS patients (74).

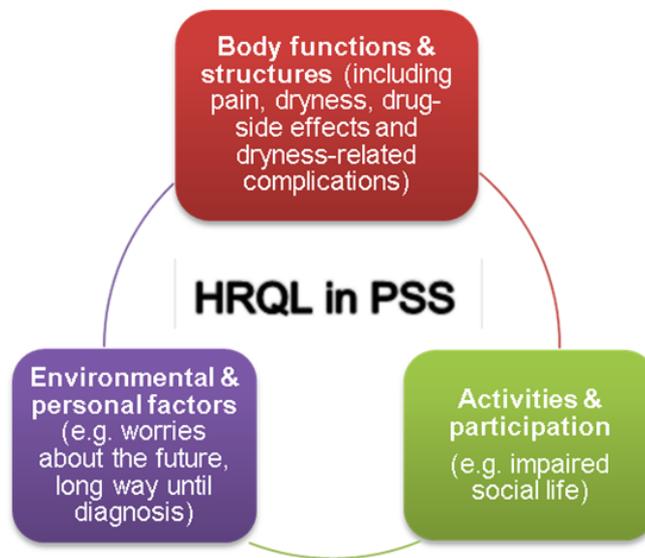


Figure 3: Three main themes of HRQL in PSS patient with their influence among each other (74)

Table 5: Identified concepts of HRQL in PSS patients (74)

Concepts		
Physical dimension	Psychological & emotional challenges	Social life and daily living
Pain <ul style="list-style-type: none"> - Joints (swelling & stiffness) - back/spine - extremities - stomach - wandering pain - pain due to dryness 	<ul style="list-style-type: none"> - fear of physician - fear of side effects - feeling of being an encumbrance for relatives - Loneliness - Hobby - Prostration - worries about the future - living with a chronic disease - long way until diagnosis - standard of living - decreased performance - Complaints were dismissed by health professionals - psychological stress (chronic dryness and getting dismissed) - Worsening of complaints while stress - suicidal ideation - excessive demands - Getting dismissed - impaired self-confidence - dissatisfaction with treatment - lack of understanding for complaints - impossibility to shed tears - additional stress with family 	<ul style="list-style-type: none"> - Impaired social life - Family is considerate of patient - dependency on relatives in daily life - Difficulties at work (computer, speaking, fatigue) - working despite feeling sick - fear of unemployment - different specialists - difficulties at driving a car - Sports - household activities - limitation in nutrition - Eating disturbances - financial dependency - financial stress - hobby - walking - disease education - Dissatisfaction with the look - aids for dryness - complaints depend on season - Inability to paint one's face - Hospitalization - drug efficacy - physical therapy - complementary medicine
Dryness <ul style="list-style-type: none"> - eyes - mouth - skin - nose - ears - vagina 		
Additional physical complaints <ul style="list-style-type: none"> - sensitive to coldness - lymphoma - arthrosis - shortness of breath - loss of muscle power - swelling of lymph nodes - fatigue - Raynaud syndrome - photophobia - Obstipation - Depression 		
Dryness-induced complaints <ul style="list-style-type: none"> - burning in the mouth - inflammation of eyes & ears - reduced sense of smell - reduced sense of taste 		

<ul style="list-style-type: none"> - loss of weight - Inability to shed tears - gritty eye sensation - worsening of vision - speaking - Loss of teeth - sleeping disturbances due to dryness of mouth and eyes - inability to eat and chew - drinking compulsion at night 		
<p>Side effects</p> <ul style="list-style-type: none"> - hair loss - excessive sweating - sight disorder 		

Although some of the concepts could have been assigned to more than one dimension, most common concepts were classified into the physical dimension:

pain, dryness and dryness-induced complaints such as for example burning sensation in the mouth, reduced sense of smell and taste, inability to shed tears, drinking compulsion at night and the inability to eat and chew. Furthermore, patients reported about joint pain, shortness of breath, fatigue und obstipation. Further concepts of the physical dimension were categorized into group of side effects (e.g. excessive sweating) and additional physical complaints (e.g. arthrosis, loss of muscle power) (74).

Dryness-induced complaints were not only limited to the physical dimension. It was shown that all dimensions had an impact among each other: For example, patients reported that dryness of the oral mucosa resulted in a burning sensation in the mouth, loss of senses of smell and taste, loss of weight, inability to eat and chew food as well as speaking difficulties (74). Subsequently, these symptoms led to psychological & emotional challenges because of a perceived lack of understanding by relatives as well as difficulties at work, limitation of nutrition and impaired social life (74). Additionally, dry eyes caused not only photophobia, inflammation of the eyes, gritty eye sensation, impaired sight, impossibility to drive a car or work on the computer and financial burden due to expensive eye drops (74). Patients reported about their inability to shed tears, that they can't handle emotional happenings accordingly, with an additional social aspect, that people judged them as being insensitive.

The three dimensions are discussed below, with examples and supporting quotes (G=Group, I=Interviewee) (74).

9.1.3 Physical dimension

The physical dimension revealed most concepts (n=38), while five major subcategories of this dimension could be identified: pain, dryness, drug-side effects, dryness-induced complaints and additional complaints (74).

Patients reported pain of joints, wandering muscle pain and pain due to dryness, as expressed by the following statements (74):

G4, I4: 'Every week I have pain somewhere else. I mean, the whole spine, feet, the knee. Sometimes I think I'm going crazy. Every week it hurts somewhere else. And I don't know why.'

G4, I3: 'Yes, when it doesn't hurt in the morning, I'm thinking that I'm not alive.'

G4, I2: 'Every week it hurts somewhere else and you think that can't be real. The limbs, everything hurts.'

As stated above, dryness caused several secondary complaints. One female patient expressed problems with eating as follows (G4, I4) (74):

'The whole time I have a bottle of water with me. But, I can't eat some dry food. You can't swallow it. You have the feeling that you are suffocating.'

The dryness of mouth also caused sleeping disturbances (G1, I3) (74):

'Sleeping was just possible, when I was sitting in bed. As soon as I turned around, I had a feeling of suffocation. So I was sleeping in a sitting position for one and a half year.'

Excessive sweating after intake of pilocarpine was the main reason why patients stopped this medication, while this was the most commonly reported drug side-effect (74).

As an example of additional physical complaints, patients experienced obstipation, photophobia, depression and loss of muscle power (74).

9.1.4 Psychological & emotional challenges

Many patients reported about their experiences from onset of symptoms of the disease, when the diagnosis was not yet established. Most of the patients had to handle with the symptoms several years before they were finally referred to a rheumatologist. As no final diagnosis was found because of variety of symptoms, patients reported that physicians frequently suspected them as having a mental/psychiatric disorder or simply ignored their complaints (74).

One patient described her experience (G3, I1) (74):

'I had problems with my stomach and digestion, felt pain in my joints. The physician did not find a reason for that. After a while, I also had dry eyes with burning and pain. I went to my general practitioner but he did not take me seriously. Then I recognised that my mouth became dry. I was afraid to go to a doctor because they looked at me, as being crazy myself. They wanted to send me to a psychologist. Then, after 5 years of symptoms and unsatisfying visits at different doctors, one doctor was on the right way and I finally got the diagnosis of Sjögren's. I really felt relieved.'

Patients reported that they had fear of physicians until their diagnosis was established and beyond. They had to learn to live with a chronic disease and tried to ignore their worries about the future. The psychological stress during way of establishment of diagnosis led to a decreased performance and impaired self-confidence (74).

One patient reported how the inability to shed tears emotionally challenged her (G2, I4) (74):

'I'm starting to cry tears, which I don't have. In former times, when I had problems, I was able to shed tears and the problems were easier to handle. Now, I want to shed tears, because I have this disease and pain but I don't have tears, and the feeling of shedding tears is going by. I just want to shed tears.'

Through the inability to shed tears patients had the feeling that they can't cope with their feelings. This dimension contained concepts like the feeling of being an encumbrance for family, excessive demand due to complaints and worries about the future. Most patients reported that their complaints worsened while additional stress with family and/or job (74).

9.1.5 Social life & daily living

Most patients were not able to drive a car due to dryness of eyes or perform household activities without help because of pain – they felt a dependency on relatives in daily life. Dryness of eyes and mouth caused challenges at work especially in case of computer work and conversations with costumers. Patients were afraid to lose their job and worked despite feeling sick (74).

Fatigue was a common reason for impairment of social life as expressed by the following statements (74):

(G2, I2) 'Yes I can say that I'm often really tired, when friends are calling me; they want to go out after work. But I don't have enough energy. I don't want. Then I'm done. Honestly, I'm just happy when I can lay down. I do not have any energy anymore.'

(G5, I2) 'My husband has adjusted to this situation. But when you are never able to do anything together and you are not fit enough (...) You have to take care. You have to take care because otherwise you will be alone. And the others are living their lives. It is like that. And in the family (...) that hurts.'

(G5, I2) ' (...) But now everything is so painful. I can't go out in the evening. I miss that. I mean, my life is really impaired. Really impaired. And the others can't understand that. They go riding a bike and you can't go with them. Yes, then you are alone.'

Besides, dimension of social life and daily living contained impaired social life, difficulties with family and work also maintained concepts related to therapy. These included relevance, efficacy and costs of complementary medicine, conventional drugs, physical therapy and aids for symptoms of dryness, which were particularly emphasized by patients causing a financial burden (74).

9.2 Results of part 2: Development and testing of the psychometric properties of PSS-QoL

A first draft questionnaire (detailed in Appendix A) was generated based on the identified concepts from focus group interviews. Upon review and feedback from experts, the questionnaire was revised; the final version was subsequently proceeded to psychometric testing as detailed in the Methods section.

The final, german version of PSS-QoL is shown in figure 4. Questions refer to the average status in the preceding 4 weeks. The total score of the PSS-QoL ranges from 0 to 96 in women and from 0 to 92 in men (one question on vaginal dryness is not intended to be answered by men). Patients needed about 4 minutes to complete the PSS-QoL. In our cohort, the mean PSS-QoL was 34.4 with a range of 3 to 76 points.

In total, 75 PSS patients participated in the psychometric evaluation of the PSS-QoL. Demographic data as well as results of questionnaires are presented in table 6. The vast majority of patients were female (90.7%) with an average disease duration of 4.8 years.

The following scores and variables of the new PSS-QoL were calculated (table 6):

- Totalscore PSS-QoL (Sum of all questions)
- Physical PSS_QoL: Sum of question 1 to 11c
 - Pain_PSS_QoL: Sum of question 1 to 6
 - Dryness_PSS_QoL: Sum of question 7 to 11c
- Psychosocial_PSS_QoL: Sum of question 12-25

These scores were calculated at baseline (n=75) and after two weeks (n=23). The total score at baseline is comparable with score after two weeks (34.4 vs. 37.7). The mean global health state according to the EQ-5D was 66, with possible scores ranging from 0 (worst) to 100 (best).

Fragebogen zur Einschätzung der Lebensqualität bei PatientInnen mit dem primären Sjögren Syndrom

Die nachfolgenden Fragen beziehen sich auf Ihre Beschwerden innerhalb der letzten vier Wochen.

Wie stark waren Ihre Schmerzen?

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

Keine Schmerzen

unerträgliche Schmerzen

Ich hatte Schmerzen in den Gelenken

Nein Ja

Ich hatte immer wiederkehrende, wandernde Schmerzen

Nein Ja

Ich hatte Verdauungsprobleme

Verstopfung: Nein Ja

Magen/Bauchschmerzen: Nein Ja

Ich hatte Probleme beim Schlafen

Nein Ja

Spüren Sie eine Trockenheit im Mund?

Nein Ja

Wenn ja: Hatten Sie folgende zusätzliche Beschwerden? (Mehrfachantworten möglich)

- Brennen im Mund
- Schwierigkeiten beim Sprechen
- Zahnprobleme
- Veränderter Geschmacksinn
- Schwierigkeiten beim Essen trockener Speisen
- Zwang, in der Nacht etwas trinken zu müssen

Spüren Sie eine Trockenheit in den Augen?

Nein Ja

Wenn ja: Hatten Sie folgende zusätzliche Beschwerden? (Mehrfachantworten möglich)

- Wiederkehrende Entzündungen
- Schmerzen
- Sandkorngefühl
- Verklebte Augen
- Verschlechterte Sehkraft
- Keine Tränenflüssigkeit (weinen ist nicht möglich)
- Alltagsaktivitäten wie Autofahren, lesen und fernsehen sind eingeschränkt bis gar nicht möglich

Spüren Sie eine Trockenheit Ihrer Haut?

Nein Ja

Wenn ja: Hatten Sie folgende zusätzliche Beschwerden? (Mehrfachantworten möglich)

- Rötungen der Haut
- Die Haut spannt

Spüren Sie eine Trockenheit im Nasenbereich?

Nein Ja

Wenn ja: Hatten Sie folgende zusätzliche Beschwerden? (Mehrfachantworten möglich)

- Veränderung des Geruchsinns
- Nasenbluten

Folgende Frage ist nur von Frauen zu beantworten:

Spüren Sie, dass Ihre Scheide trocken ist?

Nein Ja

Wenn ja: Hatten Sie folgende zusätzliche Beschwerden? (Mehrfachantworten möglich)

- Allgemeine Schmerzen
- Juckreiz
- Schmerzen beim Geschlechtsverkehr

Bitte kreuzen Sie an, inwieweit folgende Aussagen auf Sie zutreffen:

	Nie	Selten	Manchmal	Oft	immer
<u>Ich habe das Gefühl, dass</u>					
- ich die einzige mit diesen Beschwerden bin	<input type="checkbox"/>				
- meine Beschwerden nicht ernst genommen werden	<input type="checkbox"/>				
- ich mit meinen Beschwerden überfordert bin	<input type="checkbox"/>				
- meine Familie/Freunde Verständnis für mich zeigen	<input type="checkbox"/>				
Ich bin zu müde um Verabredungen mit der Familie/Freunden einzuhalten	<input type="checkbox"/>				
Ich ziehe mich zurück	<input type="checkbox"/>				
Ich habe Angst vor Nebenwirkungen	<input type="checkbox"/>				
Ich habe Angst vor dem weiteren Verlauf meiner Erkrankung	<input type="checkbox"/>				
Ich fühle mich wohl in meinem Körper	<input type="checkbox"/>				
Ich schaffe in meinem Alltag weniger, als vor Krankheitsbeginn	<input type="checkbox"/>				
Ich werde schnell müde	<input type="checkbox"/>				
Alltagsaktivitäten, wie Autofahren, Arbeiten, Haushalt, sportliche Aktivität sind eine Herausforderung	<input type="checkbox"/>				
Hilfsmittel, wie Augentropfen, Cremes und Physiotherapie stellen für mich eine finanzielle Belastung dar	<input type="checkbox"/>				
Meine Lebensqualität ist durch die Erkrankung eingeschränkt	<input type="checkbox"/>				

Figure 4: German version of PSS-QoL

Table 6: Demographic data of PSS cohort (n=75)

		Count (%)	Mean±SD	Maximum	Minimum
Sex	Female	68 (90.7)			
	male	7 (9.3)			
<i>Totalscore_PSS-QoL</i>			34.4±15.9	76.0	3.0
<i>Disease duration</i>			4.8±4.1	16.0	0.0
<i>age</i>			58.51±12.5	84.0	23.0
<i>eye_SICCA</i>			20.9±24.1	86.0	0.0
<i>SICCA</i>			25.3±26.7	89.3	0.0
<i>ESSDAI</i>			2.2±2.3	9.0	0.0
<i>ESSPRI</i>			4.1±2.1	8.3	1.0
<i>physical_PSS-QoL</i>			16.1±7.5	34.0	0.0
<i>pain_PSS-QoL</i>			5.4±3.4	14.0	0.0
<i>dryness_PSS-QoL</i>			10.7±5.1	22.0	0.0
<i>Psychosocial_PSS-QoL</i>			18.3±9.9	48.0	0.0
<i>Pain NRS</i>			4±3	10	0

ESSDAI= EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI=EULAR Sjögren's Syndrome Patient Reported Index; Eye-Sicca=Eye Sicca Score; Pain NRS= Pain Numeric Rating Scale; PSS= Primary Sjögren's Syndrome; PSS-QoL= Quality of Life in Primary Sjögren's Syndrome; SICCA= Sicca Score.

9.2.1 Results of PSS-QoL

As mentioned before, the PSS-QoL questionnaire can be divided into a physical (dryness and pain) and a psychosocial part. The mean of the total score was 34.3 points, of the physical score 16.1 and of the psychosocial score 18.3 points. Mean of global pain score was 4 (on a numeric rating scale from 0-10).

9.2.1.1 Physical dimension of PSS-QoL

As shown in figure 5, dryness of the mouth (91%), eyes (89%) and skin (85%) were reported by the vast majority of patients. Sixty-two percent of (female) patients experienced vaginal dryness. Joint pain (72%), sleeping problems (55%) and wandering pain (52%) were also among the most common complaints of patients.

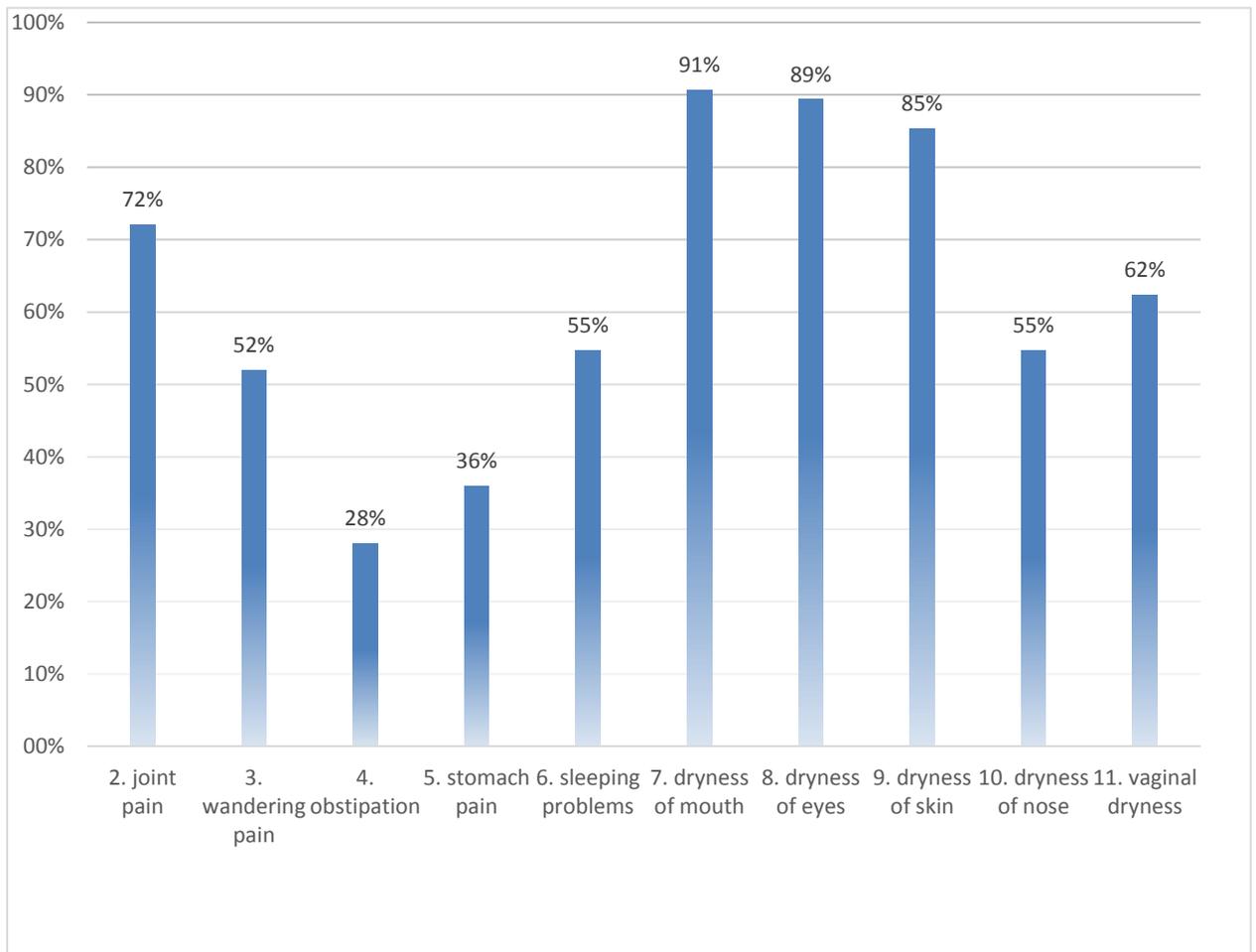


Figure 5: Prevalence of the PSS-QoL: physical dimension

Results of the EQ-5D demonstrated that 75% of patients reported at least some level of pain (figure 6). Difficulties were also related to daily activities (30.6%) or fear/depression (33.3%). Only about 9% had difficulties with self-care, and 25% had problems with mobility. The mean (\pm SD) of EQ-5D health state was 66.0 \pm 22.

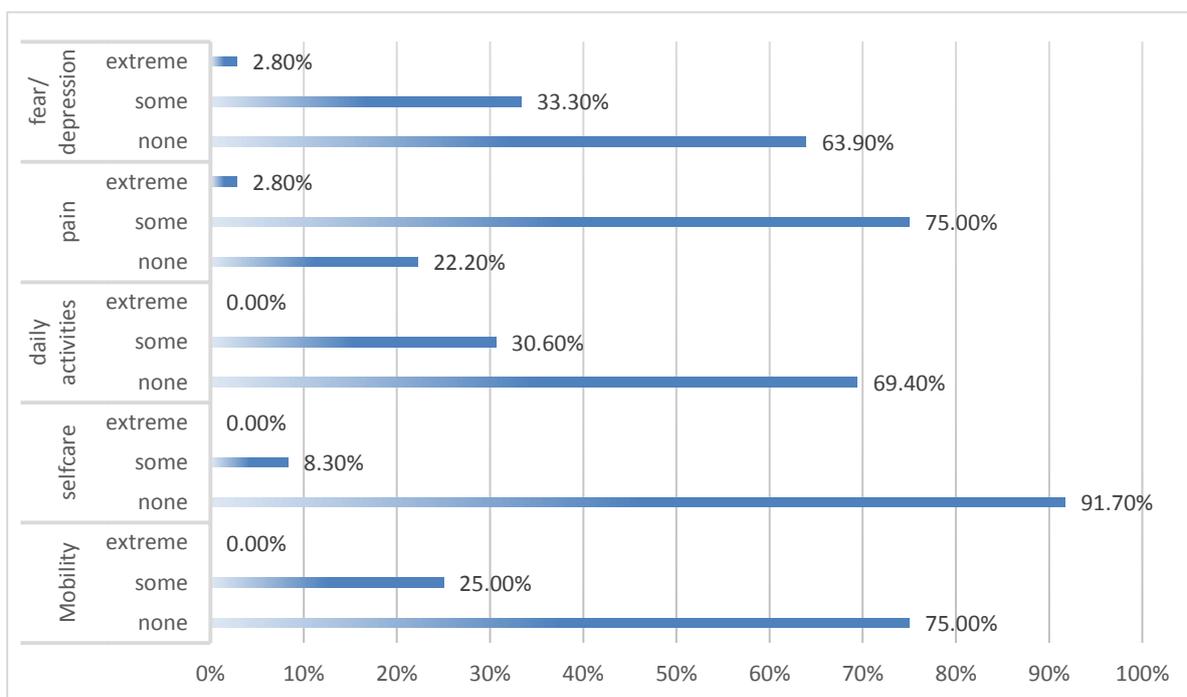


Figure 6: HRQL in EQ-5D

The frequencies of the occurrence of dryness and functional complaints caused by dryness, are demonstrated in figure 7. Patients most commonly reported drinking compulsion at night (53%), difficulties with eating dry food (59%), speaking difficulties (27%) and problems with teeth (33%) because of oral dryness. Gritty eye sensation occurred in 71% of patients with dry eyes, and about 49% of patients with dry skin reported a tightening of the skin. Twenty-five percent of patients with vaginal dryness complained about pain during sex and itching of the vagina.

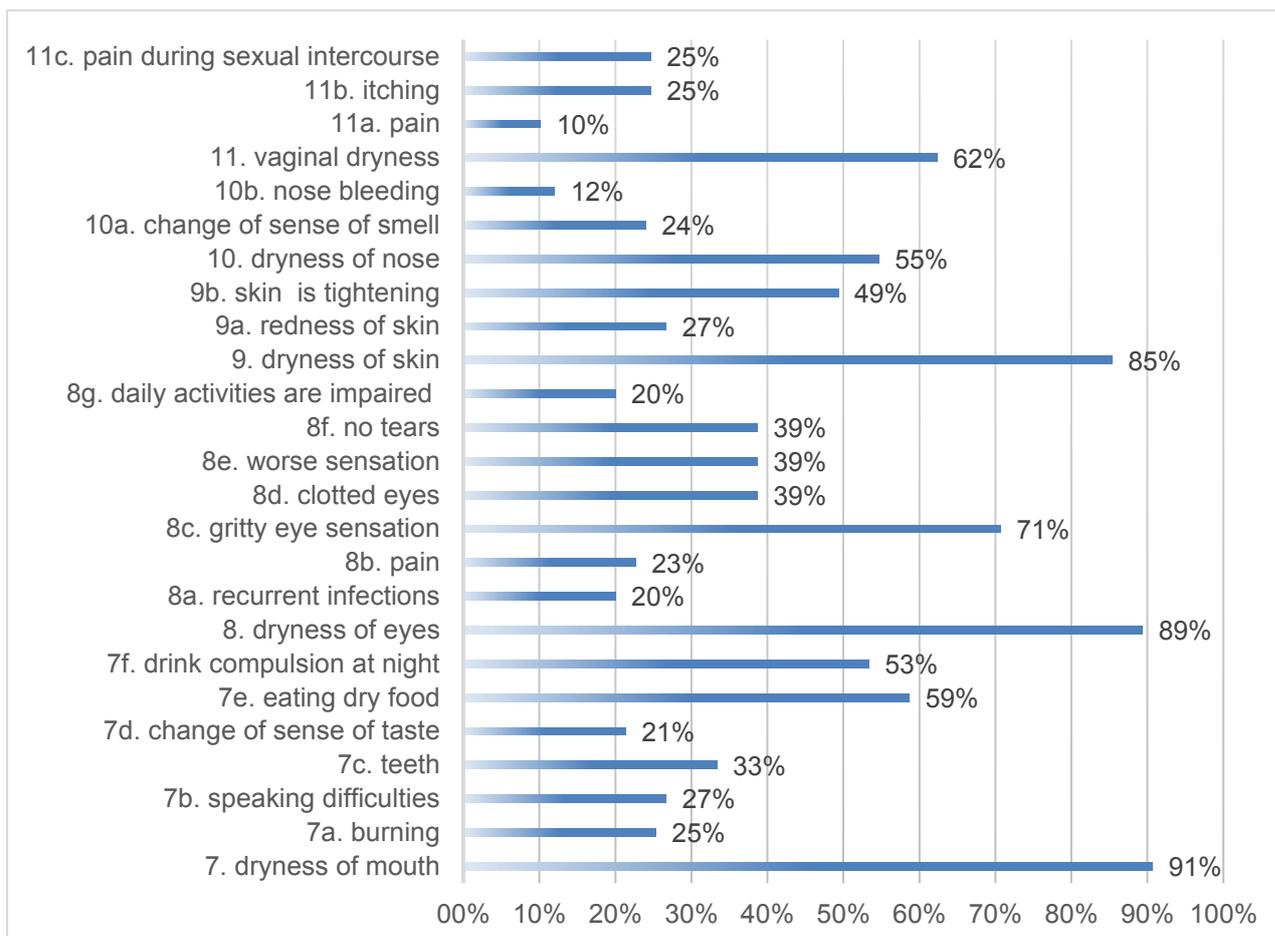


Figure 7: Dryness and dryness-induced complaints – PSS-QoL

9.2.1.2 Psychosocial dimension

The results related to the psychosocial dimension of the PSS-QoL are detailed in table 7. The majority of PSS patients (78.7%) felt that their HRQL was impaired. Sixty-four percent of PSS patients reported that they were too tired to pursue appointments with friends/family, 89.3% fatigued easily. Interestingly, 72% of PSS patients felt comfortable with their own body.

Almost half of patients (49.3%) felt that their complaints were undervalued by the society and by their physicians; 52% reported that they were overburdened by their disease. Many patients (78.7%) also reported that their ability to follow daily activities was lower than it was before the disease had started, and for the majority of cases (73.3%) daily activities were a challenge.

Table 7: Psychosocial dimension of PSS-QoL

	Never (%)	Rarely (%)	Some- times (%)	Often (%)	Always (%)
12. I feel that I'm the only one with this complaints	68.0	6.7	16.0	8.0	1.3
13. I feel that my complaints get dismissed	50.7	17.3	17.3	12.0	2.7
14. I feel that I'm overextended with my complaints	48.0	16.0	26.7	6.7	2.7
15. I feel that my family/friends show understanding for me	4.0	4.0	8.0	60.0	24.0
16. I'm too tired to maintain appointments with friends/family	36.0	20.0	32.0	9.3	2.7
17. I withdraw myself	42.7	25.3	20.0	8.0	4.0
18. I'm scared of side-effects	28.0	18.7	37.3	8.0	8.0
19. I'm scared of the course of the disease	21.3	16.0	38.7	17.3	6.7
20. I feel comfortable in my body	4.0	9.3	21.3	37.3	28.0
21. I can do less in daily practice than before start of disease	21.3	14.7	29.3	22.7	12.0
22. I feel tired, quickly	10.7	18.7	26.7	32.0	12.0
23. daily activities like driving a car, working, household, sports are a challenge	26.7	26.7	28.0	14.7	4.0
24. Aids like eye-drops, lotions or physical therapy are a financial burden	45.3	24.0	14.7	8.0	8.0
25. My quality of life is limited due to disease	21.3	20.0	34.7	20.0	4.0

9.2.2 Psychometric properties

9.2.2.1 Feasibility

Feasibility of the PSS-QoL was excellent, the percentage of missing data was 0.

9.2.2.2 Validity

PSS-QoL scores moderately correlated with the ESSPRI and the EQ-5D (see table 8). All sub-scores of the PSS-QoL (total score, physical, pain, dryness, psychosocial) correlated with patients' global assessment and pain/discomfort of the EQ-5D as well as with the ESSPRI. Interestingly, the psychosocial dimension of the PSS-QoL revealed a moderate correlation with the ESSPRI ($r=0.604$).

The component "dryness" of the PSS-QoL demonstrated a significant correlation with EQ-5D pain/discomfort ($r=0.279$) and the global health state of EQ-5D ($r=-0.420$). But with the other components of EQ-5D was found no significant correlation with "dryness" PSS-QoL. There were no significant correlations between scores of PSS-QoL with ESSDAI.

Table 8: Correlations of PSS-QoL and EQ-5D

	Totalscore PSS_QoL	Physical PSS_QoL	Pain PSS_QoL	Dryness PSS_QoL	Psychosocial PSS_QoL
EQ-5D_Mobility	0.427**	0.359**	0.519**	n.s.	0.408**
EQ-5D_usual activities	0.387**	0.318**	0.438**	n.s.	0.376**
EQ- 5D_pain/discomfort	0.531**	0.461**	0.592**	0.279*	0.498**
EQ-5D_ anxiety/depression	0.346**	n.s.	0.301*	n.s.	0.381**
EQ-5D_PGA	-0.559**	-0.501**	-0.471**	-0.420**	-0.509**
Eye_SICCA	0.294*	0.320**	n.s.	0.343**	n.s.
SICCA	n.s.	0.255*	n.s.	0.299**	n.s.
ESSPRI	0.625**	0.536**	0.715**	0.328**	0.604**

EQ-5D= EuroQoL-5 dimension; ESSPRI=EULAR Sjögren's Syndrome Patient Reported Index; Eye-Sicca=Eye Sicca Score; PSS-QoL = Quality of Life in Primary Sjögren's Syndrome; SICCA= Sicca Score.

9.2.2.3 Reliability

Testing of internal consistency reliability of the PSS-QoL revealed a Cronbach's α of 0.892.

Twenty-three patients had a second assessment for reliability after 1 to 2 weeks, 21 (91.3%) of them (1 male, 20 female) considered themselves to be in a stable disease state. Reliability of the PSS-QoL in these 21 patients was high yielding an ICC of 0.958 (95% CI 0.926 to 0.981). In comparison, the ICC for EQ-5D in this population was 0.854 (95% CI 0.735 to 0.933).

Results of the PSS-QoL and its subscores at baseline and at follow up are depicted in table 9. The mean of PSS-QoL totalscore (37.7 vs. 37.7), psychosocial PSS-QoL (20.3 vs. 19.5) and physical PSS-QoL (17.4 vs 17.3) were comparable at baseline and follow-up

mean \pm SD (range)	Baseline	Follow-up
Totalscore_PSS_QoL	37.7 \pm 17.8 (7.0-76.0)	37.74 \pm 19.03 (9.0-67.0)
Physical_PSS_QoL	17.34 \pm 8.89 (4.0-34.0)	19.5 \pm 12.2 (1.0-42.0)
Psychosocial_PSS_QoL	20.3 \pm 10.9 (0-48.0)	17.3 \pm 7.8 (2.0-28.0)

visit.

Table 9: Comparison of PSS-QoL at baseline and after 2 weeks

10 Discussion

Concepts of HRQL important to PSS patients were identified within focus-group interviews, whereas concepts were classified into three dimensions: physical dimension, psychological & emotional challenges, social life & daily living (74). Furthermore, a HRQL questionnaire was developed and tested for its psychometric properties – the PSS-QoL. The questionnaire was divided into a physical and psychosocial category.

Through the open questions in the interviews, patients could talk about what's important to them while living with this disease. PSS patients reported about the complaints caused by dryness of mouth, eyes, nose, ears, vagina and skin. Problems secondary to dryness symptoms, however, seemed to have an even higher impact on HRQL. Xerostomia for example not only led to discomfort and pain of the mouth, but also caused sleep disturbances because of nightly drinking compulsion which subsequently led to fatigue and tiredness the next day. Additionally, patients were unable to eat certain (particularly dry) foods or needed long time to eat because of difficulties to chew and swallow. One patient reported that she often felt ashamed when she went out for dinner with family or friends, because she needed a long time to eat and everyone else had to wait for her. Consequently, she chose not to go out anymore and she has been withdrawing herself from friends and family. Nearly all patients reported similar stories stressing the fact that not only the physical component but also psychological and social factors contribute to the HRQL of PSS patients.

Within the focus groups, patients most commonly raised the concepts of pain, dryness and the consequences of dryness (inflammation of eyes and ears, loss of sense of smell and taste etc.) (66). These factors could be classified in addition to the physical dimension as well as to the psychological/emotional dimension and patients' social life: Several study participants suffered from "psychological stress" because of chronic dryness and getting dismissed and were "worried about the future" of their disease (dimension of psychological & emotional challenges) (74). They were "working despite feeling sick", had "fear of unemployment" and felt an "impaired social life" (dimension of social life & daily living) (74). Additionally, the symptoms of the disease caused "dependency on relatives in daily life", "difficulties at work" and "financial burden" (social life & daily living). Physicians may currently not pay enough attention to (or even ignore) these aspects of disease in daily practice because of time constraints and/or lack of awareness (74). However, these factors appeared to be equally important to patients than physical complaints and should thus be assessed in a frequently and routine manner (74). Furthermore the discrepancy

between patients' and physicians' disease perception in chronic diseases is well known (86,87).

The observation that the majority of the concepts raised by patients belonged to the physical dimension has also been reported in qualitative studies of other rheumatic conditions including Psoriatic Arthritis, Systemic Sclerosis, RA, SLE and Hand Osteoarthritis (88). Impairment of HRQL of PSS in general is comparable to that of patients with SLE, RA and Fibromyalgia, as measured by the generic Short Form-36 questionnaire (89,90).

The long time from symptom to diagnosis caused an emotional burden to PSS patients. They experienced that they not being taken serious during the pre-diagnostic phase by their family practitioners and other physicians (68,74). After diagnosis of PSS, many patients felt relieved to have an explanation for their complaints – even if a causative or at least effective symptomatic therapy is not available yet (74). The awareness of PSS should be increased among general practitioners, ophthalmologists, dentists and other specialists with the help from educational programs. As a result such kind of programs could help to support an early recognition of the disease and reduce the emotional stress for PSS patients in the pre-diagnostic phase (74).

In qualitative studies of SLE (66) and Systemic Sclerosis (65) were also identified the concepts of “a long way until diagnosis” and not “being taken serious”. . An explanation for this observation could be the fact that this kind of diseases has a wide range of unspecific symptoms and family physicians may have less experience with rheumatic diseases (74). Moreover, misunderstandings and disagreements between physicians and patients about the relevance of dryness symptoms, pain, fatigue and other symptoms are often caused by a disagreement between subjective impairments and objective tests (24).

An interesting observation was the different perception of PSS patients of the importance and necessity of medical visits. Most of patients required to be treated for symptom relief, at least in the early phase of the disease (59,74).

Because of the low to moderate efficacy of current therapies (91), most patients have designed their own strategies to better sustain and live with the disease. Some patients asked about the need of clinical visits, because “nothing is getting better, so why should we go to the doctor?” (74) Nevertheless, most of patients were worried about the course of disease with possible resulting complication and therefore still preferred a regular medical control (92).

Patients reported that they had “the feeling to go crazy” because they had changing pain areas every day/week. For example, one patient reported that when nothing is hurting, she thinks that she does not function properly anymore. In PSS, different types of pain

can be present at different localisations and these can be caused by different mechanics (articular pain, neuropathic pain and widespread pain). Articular pain can be assigned to a usually light synovitis of the peripheral joints but the mechanisms of neuropathic and widespread pain are still largely unknown (93).

About 33% of our patients reported in EQ-5D about depressive and anxiety feelings. Only one patient talked about her suicide attempts in the qualitative interview. Psychological stress and depression are well known in PSS (47,94), but therapy with anti-depressants is particularly difficult, because of their intrinsic anti-cholinergic effect, that may increase the sicca symptoms (93).

Patients are limited in daily practice with household activities or car driving. These observations are comparable to those made in other rheumatic diseases like SLE or RA (66,88). An impaired self-confidence is present in PSS patients and they feel unable to cope with their disease (95).

Few patient-derived outcome measures have been developed for the assessment of dryness, fatigue and pain so far, and although these tools have already been used in PSS patients (23,96), a dedicated tool for the assessment of PSS related HRQL has been lacking. We used the same strategy to develop a disease specific HRQL measure in PSS as suggested earlier for RA (41) or Psoriatic Arthritis (40). Although certain aspects of dryness and pain are already covered by other PROs (23), the PSS-QoL corroborates symptoms of dryness important to patients as well as aspects of their social life, which are impaired due to the disease. While sicca symptoms are the most important burden to PSS patients (8), the first part of the PSS-QoL questionnaire consists of items related dryness of eyes, mouth, skin, nose and vagina. The psychosocial part includes concepts like self-confidence, fatigue, emotional burden and an overall HRQL question. Fatigue was present in nearly 90% of patients and was closely related to the perception of pain. In the PSS-QoL, fatigue was not integrated into the physical dimension because patients expressed in interviews that fatigue often prevented social contacts. Therefore it was considered to better fit into the psychosocial dimension (46).

Testing of the reliability of PSS-QoL (Cronbach's α 0.892) was comparable to other HRQL instruments: PSAID (Cronbach's α 0.93), (40) and the RA-QoL (Cronbach's α 0.79) (38).

We know, that there is only a limited correlation between PROs and physician's assessment of disease activity in PSS (96). Furthermore, there was no significant correlation between PSS-QoL and ESSDAI. In addition to the physician-based evaluation of the disease activity using composite scores like the ESSDAI, the ESSPRI is often applied in clinical trials to capture the patients' perspective of disease activity (23). The

new developed PSS-QoL is intended to reflect HRQL additionally the area of dryness, the psychological and social aspects of HRQL. For evaluation of HRQL, generic instruments like SF-36 were used, leading to prolonged time requirements, while patients needed about four minutes for completion of PSS-QoL. Using our HRQL questionnaire should make it easier to assess the impact of PSS and choose the most appropriate therapy in a multiprofessional team for an individual patient. In clinical trials, PSS-QoL could measure HRQL in PSS patients effectively.

10.1 Limitations

An important limitation of this study is the sample selection given that patients were included only from a single region in Austria. We stratified the patients according to different age groups and professional backgrounds, however, we only included female patients because none of our (few) males wanted to participate (5,74). A limitation of the focus groups is a potential self-consciousness of participants to talk about sensitive topics in front of other unknown people. Therefore, it cannot be excluded that full data enrichment has not been achieved (74).

An important limitation of the psychometric testing of the questionnaire is the small sample size of 75 PSS patients. It is recommended that 5-10 patients per item of a questionnaire should be studied, and therefore at least 125 patients would have been need for the PSS-QoL. Given the relative rarity of PSS, it is almost impossible to recruit a sufficient number of patients within a single centre. A prospective multicentre study is now needed in order to re-evaluate the psychometric properties of the PSS-QoL in a large cohort of PSS patients.

Another limitation is the fact that we were unable to test the sensitivity to change of the questionnaire. Only 2 out of the 23 patients who completed the questionnaire twice reported that their disease status had changed. Ideally, the sensitivity to change had been investigated in a sample of severely impaired patients undergoing an effective therapy. In such a setting, a significant improvement of the disease status might be expected and the PSS-QoL could have demonstrated whether it was sensitive to detect this change.

10.2 Conclusions

In summary, the PSS-QoL was developed as an aid for the evaluation of HRQL of PSS patients in clinical practice and treatment trials. Pain, dryness and complaints induced by these symptoms are important to patients with PSS, which affect the physical, psychological and social life components of HRQL. It was demonstrated that PSS is more

than just dryness and fatigue. Patients are suffering from a wide range of symptoms affecting their physical, emotional and social well-being (74).

Further research is necessary to further validate and confirm the good psychometric properties of the PSS-QoL. A future multicentre study including outpatient clinics from various countries with translation of this questionnaire into other languages would be desirable in order to promote the introduction of the PSS-QoL in clinical routine and future clinical trials.

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12 Appendix

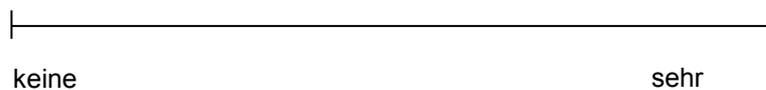
12.1 Appendix A

Fragebogen zur Einschätzung der Lebensqualität bei PatientInnen mit dem primären Sjögren Syndrom

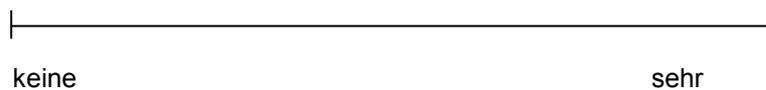
Die nachfolgenden Fragen beziehen sich auf Ihre Beschwerden innerhalb der letzten **vier Wochen**:

Bitte geben Sie auf den nachfolgenden Skalen mit einem senkrechten Strich auf der Linie den durchschnittlichen Schweregrad Ihrer Beschwerden an (von keine bis sehr starke Beschwerden)

- Ich hatte Schmerzen in den Gelenken



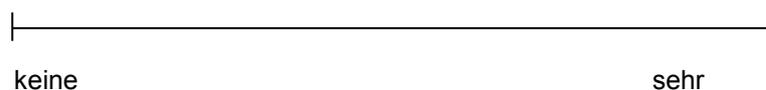
- Ich leide unter immer wiederkommenden, wandernden Schmerzen



- Ich hatte Verdauungsprobleme



- Ich hatte Magenschmerzen



- Spüren Sie eine Trockenheit im Mund?

Nein Ja

Wenn ja: Hatten Sie folgende zusätzliche Beschwerden? (Mehrfachantworten möglich)

- 5a. Brennen im Mund
- 5b. Schwierigkeiten beim Sprechen
- 5c. Zahnprobleme
- 5d. Veränderter Geschmacksinn
- 5e. Schwierigkeiten beim Essen trockener Speisen
- 5f. Zwang, in der Nacht etwas trinken zu müssen
- 5g. Schlafstörungen
- 5h. Keine

- Spüren Sie eine Trockenheit in den Augen?

Nein Ja

Wenn ja: Hatten Sie folgende zusätzliche Beschwerden? (Mehrfachantworten möglich)

- 6a. Wiederkehrende Entzündungen
- 6b. Schmerzen
- 6c. Sandkorngefühl
- 6d. Verklebte Augen
- 6e. Verschlechterte Sehkraft
- 6f. Keine Tränenflüssigkeit (weinen ist nicht möglich)
- 6g. Alltagsaktivitäten wie Autofahren, lesen und fernsehen sind eingeschränkt bis gar nicht möglich
- 6h. Keine

- Spüren Sie eine Trockenheit Ihrer Haut?

Nein Ja

Wenn ja: Hatten Sie folgende zusätzliche Beschwerden? (Mehrfachantworten möglich)

- 7a. Rötungen der Haut
- 7b. Die Haut spannt
- 7c. Keine

- Spüren Sie eine Trockenheit im Nasenbereich?

Nein Ja

Wenn ja: Hatten Sie folgende zusätzliche Beschwerden? (Mehrfachantworten möglich)

- 8a. Veränderung des Geruchsinns
- 8b. Nasenbluten
- 8c. Keine

- Spüren Sie, dass Ihre Scheide trocken ist?

Nein Ja

Wenn ja: Hatten Sie folgende Beschwerden? (Mehrfachantworten möglich)

- 9a. Allgemeine Schmerzen
- 9b. Juckreiz
- 9c. Schmerzen beim Geschlechtsverkehr
- 9d. Keine

Bitte kreuzen Sie an, inwieweit folgende Aussagen auf Sie zutreffen:

	Nie	Selten	Manchmal	Oft	immer
<u>Ich habe das Gefühl, dass</u>					
- ich die einzige mit diesen Beschwerden bin	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>
- meine Beschwerden nicht ernst genommen werden	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>
- ich mit meinen Beschwerden überfordert bin	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>
- <u>mir alles zu viel wird</u>					
- meine Familie/Freunde	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>
Verständnis für mich zeigen	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>
- Ich bin zu müde um Verabredungen mit der Familie/Freunden einzuhalten	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>
- Ich ziehe mich zurück	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>
- Ich habe Angst vor Nebenwirkungen	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>
- Ich habe Angst vor dem weiteren Verlauf meiner Erkrankung	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>
- <u>Ich habe gelernt mit meiner chronischen Erkrankung umzugehen</u>	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>
- Ich fühle mich <u>nicht wohl</u> in meinem Körper	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>
- Ich schaffe in meinem Alltag weniger, als vor Krankheitsbeginn	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>
- Ich werde schnell müde	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>
- Alltagsaktivitäten, wie Autofahren, Arbeiten, Haushalt, sportliche Aktivität sind eine Herausforderung	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>
- Hilfsmittel, wie Augentropfen, Cremes und Physiotherapie stellen für mich eine finanzielle Belastung dar	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>
- Meine Lebensqualität ist durch die Erkrankung eingeschränkt	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>

12.2 Appendix B

Fragebogen zur Einschätzung der Lebensqualität bei PatientInnen mit dem primären Sjögren's Syndrom (pSS-QoL)

Die nachfolgenden Fragen beziehen sich auf Ihre Beschwerden innerhalb der letzten vier Wochen.

1 **Wie stark waren Ihre Schmerzen?** 0-10

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

Keine Schmerzen

unerträgliche Schmerzen

2 **Ich hatte Schmerzen in den Gelenken** 0/1

Nein Ja

3 **Ich hatte immer wiederkehrende, wandernde Schmerzen** 0/1

Nein Ja

Ich hatte Verdauungsprobleme

4 Verstopfung: Nein Ja 0/1

5 Magen/Bauchschmerzen: Nein Ja 0/1

Ich hatte Probleme beim Schlafen 0/1

6 Nein Ja

Spüren Sie eine Trockenheit im Mund? 0/1

7 Nein Ja

Wenn ja: Hatten Sie folgende zusätzliche Beschwerden? (Mehrfachantworten möglich)

- 7a Brennen im Mund 0/1
- 7b Schwierigkeiten beim Sprechen 0/1
- 7c Zahnprobleme 0/1
- 7d Veränderter Geschmacksinn 0/1
- 7e Schwierigkeiten beim Essen trockener Speisen 0/1
- 7f Zwang, in der Nacht etwas trinken zu müssen 0/1

8 Spüren Sie eine Trockenheit in den Augen? 0/1

Nein Ja

Wenn ja: Hatten Sie folgende zusätzliche Beschwerden? (Mehrfachantworten möglich)

- | | | |
|----|---|-----|
| 8a | <input type="radio"/> Wiederkehrende Entzündungen | 0/1 |
| 8b | <input type="radio"/> Schmerzen | 0/1 |
| 8c | <input type="radio"/> Sandkorngefühl | 0/1 |
| 8d | <input type="radio"/> Verklebte Augen | 0/1 |
| 8e | <input type="radio"/> Verschlechterte Sehkraft | 0/1 |
| 8f | <input type="radio"/> Keine Tränenflüssigkeit (weinen ist nicht möglich) | 0/1 |
| 8g | <input type="radio"/> Alltagsaktivitäten wie Autofahren, lesen und fernsehen sind eingeschränkt bis gar nicht möglich | 0/1 |

9 Spüren Sie eine Trockenheit Ihrer Haut? 0/1

Nein Ja

Wenn ja: Hatten Sie folgende zusätzliche Beschwerden? (Mehrfachantworten möglich)

- | | | |
|----|---|-----|
| 9a | <input type="radio"/> Rötungen der Haut | 0/1 |
| 9b | <input type="radio"/> Die Haut spannt | 0/1 |

Spüren Sie eine Trockenheit im Nasenbereich? 0/1

10 Nein Ja

Wenn ja: Hatten Sie folgende zusätzliche Beschwerden? (Mehrfachantworten möglich)

- | | | |
|-----|---|-----|
| 10a | <input type="radio"/> Veränderung des Geruchsinns | 0/1 |
| 10b | <input type="radio"/> Nasenbluten | 0/1 |

Folgende Frage ist nur von Frauen zu beantworten:

Spüren Sie, dass Ihre Scheide trocken ist?

11 Nein Ja 0/1

Wenn ja: Hatten Sie folgende zusätzliche Beschwerden? (Mehrfachantworten möglich)

- | | | |
|-----|---|-----|
| 11a | <input type="radio"/> Allgemeine Schmerzen | 0/1 |
| 11b | <input type="radio"/> Juckreiz | 0/1 |
| 11c | <input type="radio"/> Schmerzen beim Geschlechtsverkehr | 0/1 |

Bitte kreuzen Sie an, inwieweit folgende Aussagen auf Sie zutreffen:

	Nie	Selten	Manchmal	Oft	immer
12	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>
13	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>
14	0 <input type="checkbox"/>	1 <input type="checkbox"/>	2 <input type="checkbox"/>	3 <input type="checkbox"/>	4 <input type="checkbox"/>
15 Invers	4 <input type="checkbox"/>	3 <input type="checkbox"/>	2 <input type="checkbox"/>	1 <input type="checkbox"/>	0 <input type="checkbox"/>
16	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
17	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
18	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
19	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
20 Invers	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1	<input type="checkbox"/> 0
21	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
22	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
23	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
24	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
25	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4