BRITISH JOURNAL OF HOSPITAL MEDICINE

REVIEW

# Outcome Measures for Sjögren Disease—Novel Developments and Further Needs

Robert Wilson[1,*], Jaiden Townsend[2], Ellie Hawkins[1], Coziana Ciurtin[1,3,*]

[1]Department of Rheumatology, University College London (UCL) Hospital Foundation Trust, London, UK
[2]University College London (UCL) Medical School, London, UK
[3]University College London (UCL) Centre for Adolescent Rheumatology, London, UK
*Correspondence: robert.wilson24@nhs.net (Robert Wilson); c.ciurtin@ucl.ac.uk (Coziana Ciurtin)

## Abstract

Sjögren disease (SjD) is a systemic autoimmune disorder affecting both children and adults, with a wide range of clinical phenotypes. It remains a challenging condition to recognise and diagnose early and manage effectively. The heterogeneous nature of the presentation, variable disease course and overlapping symptoms with other autoimmune conditions often result in delayed diagnosis. This, coupled with the lack of licensed effective therapies frequently leads to suboptimal patient outcomes. Improved outcome measures are crucial for advancing our understanding of SjD pathogenesis and developing effective treatments. They can help ensure that clinical trials are accurately capturing the impact of potential therapies on the disease and the quality of life of people with SjD. Further developments are needed in the areas of age and developmentally appropriate disease and patient-reported outcome measures, with adequate sensitivity to evaluate treatment efficacy, as well as predictor biomarkers for both treatment response and poor prognostic outcomes associated with SjD. Advancing these areas will help ensure that clinical trials adequately select the most suitable SjD cohorts to treat with a certain therapy, as well as accurately reflect the impact of a certain intervention on disease activity, progression, and quality of life, ultimately leading to better care for people with SjD.

**Key words: Sjögren disease; outcome measures; clinical trials; children; adults**

**Submitted: 4 June 2024 Revised: 29 September 2024 Accepted: 22 October 2024**

## Introduction

Sjögren disease (SjD) is a chronic autoimmune disorder typified by lymphocytic infiltration of the exocrine glands, leading to dryness, which is considered the cardinal symptom (Brito-Zerón et al, 2016a). SjD is now recognised as affecting an estimated 0.5% to 1% of the global population, with a predilection for middle-aged women (mean age at onset 45–55 years, male/female ratio of 1:9) (Beydon et al, 2024). Children are also rarely affected, although this is likely to be more common than currently recognised (Ramos-Casals et al, 2021). Extra-glandular manifestations include a variety of symptoms and organ manifestations, such as fatigue, arthralgia, myalgia, cutaneous rash, pneumonitis, glomerulonephritis, peripheral neuropathy, cognitive dysfunction, and vasculitis, in addition to a heightened risk of malignant lymphoproliferation (Brito-Zerón et al, 2016b).

**How to cite this article:**
Wilson R, Townsend J, Hawkins E, Ciurtin C. Outcome Measures for Sjögren Disease—Novel Developments and Further Needs. Br J Hosp Med. 2024. https://doi.org/10.12968/hmed.2024.0310

## Diagnosis and Classification

SjD remains challenging to recognise and diagnose early and manage effectively. The heterogeneous nature of the presentation, variable disease course and overlapping symptoms with other autoimmune conditions often result in delayed diagnosis. This, coupled with the lack of targeted therapies, frequently leads to suboptimal outcomes.

SjD is diagnosed based on a combination of symptoms, reflecting glandular and extra-glandular involvement (leading to dryness and organ-specific manifestations, respectively), in addition to specific investigations including characteristic antibodies, objective assessment of salivary and lachrymal gland hypofunction, and characteristic glandular histopathology and more recently imaging.

The most recent classification criteria, developed by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) in 2016 use a weighted composite score for SjD classification, including the evaluating of both subjective and objective disease features (Shiboski et al, 2017).

## Evolving Nomenclature

Advocacy groups have encouraged movement away from the use of the historical moniker Sjögren's Syndrome (SjS) towards SjD. This evolution in disease nomenclature has predominantly been driven by patients' preferences. Baer and Hammitt (2021b) and the Sjögren's Foundation advocated in 2021 for a change in the nomenclature due to concerns that the use of 'syndrome' (denoting a collection of symptoms) instead of 'disease' (reflecting the improved understanding of shared aetiology and pathogenesis of SjD manifestations) may contribute to the perception of the condition as less serious. Since this proposal, professional societies (ACR and British Society of Rheumatology (BSR)), as well as disease-specific charities (the Sjögren's Foundation, US, and Sjögren's UK), have already embraced this new terminology.

## Current Management and Emerging Therapies

The British Society of Rheumatology (BSR) published recently the first therapeutic guideline for SjD treatment across the life span, using a standardised methodological approach highlighting the level of evidence for the efficacy of all pharmacological and non-pharmacological interventions tested in SjD (Price et al, 2024). Particularities of SjD treatment in children and adolescents have been recently reviewed elsewhere (Ciurtin and Price, 2024).

While the current therapeutic armamentarium for SjD is mainly symptomatic (aiming to alleviate the symptoms of dryness) and has limited benefits in preventing glandular damage, advances in understanding the disease pathophysiology have opened up multiple avenues for therapies targeting both the innate and adaptive immune system. Several randomised control trials (RCTs) exploring various therapeutic approaches, including targeting pro-inflammatory cytokines (e.g., interleukin 7 (IL7) and interleukin 12 (IL12)), type I interferon system (including down-regulation of toll-like receptor (TLR)-7 or TLR-9 mediated interferon I produc-

tion or blockade of interferon I receptor), B cell activation (including anti-B cell activating factor (BAFF) antibodies, agents that target B cell receptor signalling and antibody-depleting drugs), B cell and T cell co-stimulation pathway (targeting both the CD40–CD40 and the ICOS–ICOS ligand axes) have been completed, while other targeted therapeutic approaches (such as and chimeric antigen receptor (CAR)-T cell therapy, immunoglobulin G (IgG) recycling inhibition, and nuclease therapy) are currently ongoing (Baldini et al, 2024).

### Unmet Need for Better Outcome Measures

Despite advances in understanding of SjD pathogenesis and the advent of numerous new therapeutic targets, there are no licensed targeted therapies for SjD. Some of the main explanations for the low rate of success of RCTs in SjD are the lack of correlation between symptoms burden and disease pathobiology occasionally leading to inappropriate selection of therapeutic targets; disease heterogeneity requiring biomarker enriched cohort selection for inclusion in clinical trials; need for better composite outcomes to mitigate against the high placebo response rates in SjD trials and adequate response to experimental intervention, to name only a few.

Consequently, the much-needed therapeutic success of clinical trials that will ultimately facilitate access to effective interventions for individuals with SjD requires future investment in the development, testing and validation of outcome measures able to adequately reflect and quantify the disease activity, its severity and impact on quality of life, as well as treatment response in SjD.

This paper aims to highlight the uses and limitations of existing outcome measures, with particular focus given to emerging tools with improved performance in assessing both the disease activity as well as the impact of various therapeutic interventions in SjD. Additionally, we will also explore the limitations of validated and widely used outcome measures and unmet research needs.

## Outcome Measures

The heterogeneity of SjD manifestations requires validated tools that can accurately capture both the systemic and glandular disease manifestations, as well as the disease's impact on quality of life. International collaborations have led to the development, and subsequent validation of disease-specific scores that demonstrated adequate performance in measuring both objective changes in disease activity and patients' subjective rating of symptoms' severity and impact on quality of life, namely the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) (Seror et al, 2010), the Clinical European League Against Rheumatism Sjögren's Syndrome Disease Activity Index (ClinESSDAI) (Seror et al, 2016), the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) (Seror et al, 2015), and the Profile of Fatigue and Discomfort-Sicca Symptoms Inventory-Short Form (PROFAD-SSI-SF) (Bowman et al, 2003), and the Patient Reported Outcome Measurement Information System-Short Form (PROMIS-SF) (DiRenzo et al, 2022) (Table 1). Additionally, validated outcomes measures assessing damage in SjD exist as well, but their evaluation is beyond the scope of this review.

**Table 1. Summary of domains by outcome measure.**

| ESSDAI | ClinESSDAI | ESSPRI | PROFAD-SSI-SF | PROMIS-SF |
|---|---|---|---|---|
| Cutaneous | Cutaneous | Arthritis | Somatic fatigue | Pain |
| Respiratory | Respiratory | Fatigue | Mental fatigue | Fatigue |
| Renal | Renal | Dryness | Arthralgia | Emotional distress |
| Articular | Articular | | Vascular dysfunction | Physical functioning |
| Muscular | Muscular | | Oral dryness | Social role participation |
| Peripheral nervous system | Peripheral nervous system | | Ocular dryness | |
| Central nervous system | Central nervous system | | Cutaneous dryness | |
| Haematological | Haematological | | Vaginal dryness | |
| Glandular | Glandular | | | |
| Constitutional | Constitutional | | | |
| Lymphadenopathic | Lymphadenopathic | | | |
| Biological | | | | |

ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patient Reported Index; PROFAD-SSI-SF, Profile of Fatigue and Discomfort-Sicca Symptoms Inventory-Short Form; PROMIS-SF, Patient Reported Outcome Measurement Information System-Short Form.

## Widely Validated Disease Activity Measures Used in SjD

### ESSDAI

The ESSDAI is a composite score calculated by assessing disease activity across 12 different organ and system domains, using a weighted point system based on the severity of manifestations: absent, mild, moderate, or severe, as well as type of organ involvement: e.g., significant organ involvement is rated higher than some blood test abnormalities, etc. Each domain score is generated by multiplying the domain weight by the level of activity. The domains evaluated are constitutional, lymphadenopathy and lymphoma, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral, and central nervous system, and haematological and biological domains. The total ESSDAI score is calculated as the sum of all domain scores, which can range from 0 to 123 and have well-defined cut-offs. Low, moderate, and high disease activity are defined by scores of $<5$, 5–13, and $\geq 14$, respectively. The ESSDAI score has been shown to correlate with markers of B cell activity (Pertovaara and Korpela, 2011) as well as lymphoma risk (Brito-Zerón et al, 2014). It's important to note that the ESSDAI is a clinician index, meaning it is based on objective assessments rather than patient-reported symptoms, which is relevant for its use in assessing response in interventional clinical trials (Baer et al, 2021a; Bowman et al, 2017, 2022; Dörner et al, 2019; Felten et al, 2021; Gottenberg et al, 2013; Juarez et al, 2021; Meiners et al, 2014; Price et al, 2022).

The strengths of ESSDAI are related to its validation across various SjD cohorts and wide use in clinical practice, in addition to its ability to capture relevant clinical domains and detect clinically meaningful improvement, defined as

a 3-point improvement in total ESSDAI or a one-category improvement in domain-level scores (Cooper et al, 2022).

### ClinESSDAI

The ClinESSDAI is a modified version of ESSDAI tailored specifically for use in clinical trials in SjD (Seror et al, 2016). Each of the 11 domains (excluding the biological domain) is assessed in a similar way as for ESSDAI, although the weights of some domains are slightly different. The 11 domain scores are combined to obtain the ClinESSDAI total score. The ClinESSDAI score provides an objective evaluation of disease activity, specifically excluding B-cell biomarkers, which can be useful in research to mitigate against a higher contribution of serological activity to driving the disease active score in SjD, as well as clinical practice, as it is not reliant on immunological test s availability. The ClinESSDAI has been found to perform similarly to ESSDAI in terms of validity, reliability, and sensitivity to change, as well as assessment of cases potentially suitable for inclusion in clinical trials (Dumusc et al, 2018). The main strength of ClinESSDAI is related to its ability to evaluate the clinical efficacy of a therapeutic intervention independent of its biological effect, as the assessment of changes in immunoglobulin G (IgG) and/or complement fraction levels, corresponding to the biological domain of ESSDAI, is excluded.

## Validated Patient-Reported Outcome Measures Used in SjD

### ESSPRI

The ESSPRI is scored based on three domains: dryness, limb pain, and fatigue (Seror et al, 2016). Each of the three domains is rated by the patient on a 0–10 Numerical Rating Scale. A score of 0 indicates no symptoms, and a score of 10 indicates the worst symptoms imaginable. The ESSPRI score is then calculated as the mean of the three domain scores. This means that the total score is the sum of the three domain scores divided by three. Scores $\geq$5 indicate greater symptom severity. ESSPRI also correlated well with other patient-reported outcome measures, such as the Profile of Fatigue and Discomfort (PROFAD) and Sicca Symptoms Inventory (SSI), as well as the Patient Global Assessment of Disease (Seror et al, 2011).

### PROFAD-SSI-SF

PROFAD-SSI-SF is a 19-item patient-reported outcome measure which assesses pain, fatigue and dryness derived from combining the PROFAD questionnaire (Bowman et al, 2004) with the SSI inventory (Bowman et al, 2003), and subsequently shortened from 64 to 19-items with comparable performance (Bowman et al, 2009). PROFAD-SSI-SF comprises eight domains of SjD symptoms: somatic fatigue, mental fatigue, arthralgia, vascular dysfunction, and oral, ocular, cutaneous, and vaginal dryness. Each of the eight domains is rated by the SjD patient on an eight-point (0–7) numeric rating scale. A score of 0 indicates no problem, and a score of 7 indicates the worst problem imaginable. The PROFAD-SSI-SF score is

calculated as the sum of the scores for each of the 19 items, providing a comprehensive tool to appreciate the patient's perspective of their disease, but it should not be used in isolation but in conjunction with other disease-specific assessments to fully appreciate the subjective and objective impact of SjD on patient's general health. The PROFAD-SSI-SF score has been validated and found to have good psychometric properties (Raymond et al, 2023).

### PROMIS-SF

The Patient Reported Outcome Measurement Information System (PROMIS) is a set of universal health-related quality of life (HRQOL) instruments created by a network of researchers at the National Institute of Health, which has been widely used in numerous medical conditions PROMIS-SF showed adequate reliability across various populations (Ameringer et al, 2016), and in the context of SjD provided a broader overview of HRQOL than the ESSPRI (DiRenzo et al, 2022). PROMIS-SF instruments have been used to identify the disease burden related to pain interference, fatigue, and physical function in SjD. PROMIS-SF derived pain and fatigue scores have been found to correlate highly with their respective ESSPRI domains, suggesting that PROMIS instruments can be useful in identifying relevant HRQOL patterns in patients with SjD (DiRenzo et al, 2022).

Recent research evaluated the ability of PROMS to define distinct patient groups with potential implications for patient stratification for treatment selection and found that ESSPRI can identify patient clusters with biological and clinical implications (Tarn et al, 2019). Patients with SjD have been stratified in 4 groups with unique transcriptomic and cytokine signatures, defined as High Symptom Burden (HSB) and Low Symptom Burden (LSB) groups, together with a Pain-Dominated Fatigue (PDF) and Dryness-Dominated Fatigue (DDF), groups that have been also validated in an independent cohort (Tarn et al, 2019). Re-analysis of clinical trials using ESSPRI-based patient stratification showed that the HSB group benefitted from improvement in ESSPRI following treatment with hydroxychloroquine compared to the other groups, whereas the DDF group responded to rituximab and had significant improvement in the salivary flow rate (Collins et al, 2021).

## Need for Future Research to Address the Lack of Correlation between Existing Subjective and Objective Outcome Measures

The ESSDAI and ESSPRI tools are the most widely used outcome measures in SjD. As they provide an objective versus subjective evaluation of SjD, it is not surprising that ESSDAI has been found to have a higher correlation with the Physician's Global Assessment while ESSPRI had a higher correlation with the Patient's Global Assessment. However, as both scores capture different aspects of the diseases, there was a low level of correlation between ESSDAI and ESSPRI (Seror et al, 2015). The ClinESSDAI had excellent reliability when compared to ESSDAI as most of the scoring items overlap between the two scores (Dumusc et al, 2018). The psychometric properties, disease activity categorisation, minimal clinically impor-

tant improvement threshold, and the ability to detect change over time in clinical trials were similar between ClinESSDAI and ESSDAI (Seror et al, 2016). The PROMIS Pain Interference and Fatigue scores have been found to correlate highly with their respective ESSPRI domains (DiRenzo et al, 2022).

### Limitations of Validated Outcome Measures in SjD

Despite their broad use in clinical trials and practice to assess the disease activity, guide treatment decisions, as well as assess response to treatment and the impact of the disease on QOL, the outcome measures detailed above have several limitations: e.g., ESSDAI assesses a 4-week recall period with implications on the accurate evaluation of the current disease state, while using an arbitrary item weighting method and defining items with variable complexity to score, potentially leading to inter-evaluator variability. Additionally, despite being widely used in clinical trials, ESSDAI has failed to show the benefit of many treatments, while capturing significant placebo response, suggesting that the disease activity varies over time in SjD (de Wolff et al, 2020).

ClinESSDAI is a relatively simplified version of ESSDAI, which excludes the biological domain and while this can facilitate use in routine practice, it may not fully capture all the relevant aspects of disease activity with potential implications in assessing the biological effect of treatments (Seror et al, 2016). ESSPRI, despite being very easy to calculate and reflecting the subjective experience of the disease, it does not correlate with the objective parameters of glandular function (Ture et al, 2023) and provides only a simplified disease assessment focused only on three non-specific symptoms domains, potentially influenced by many factors which may not exclusively reflect the impact of SjD.

PROFAD-SSI-SF is quite a long questionnaire and potentially burdensome to patients as well as researchers when used frequently, prompting efforts to combine all its domains into a single Visual Analogue Scales (VAS), initiative which requires further research and validation (Hammitt et al, 2017).

While PROFAD-SSI-SF has been found to have an acceptable fit of the factor structure, with adequate internal consistency, test-retest reliability, convergent validity with other patient-reported outcome measures, known-groups validity with the Patient Global Assessment score, and ability to detect change in patients with SjD, further validation studies may be needed to confirm these findings in different patient populations and settings (Raymond et al, 2023).

## Need for Improved Outcome Measures

Improved outcome measures are crucial for advancing our understanding of SjD and developing effective treatments. They can help ensure that clinical trials are accurately capturing the impact of potential therapies on the disease and the quality of life of patients. People with SjD present with a wide range of disease phenotypes, which are dependent on different underlying biological mechanisms, leading to challenges in reliably assessing treatment effects. SjD often has a long indolent course, and many patients enrolled in trials may already have irreversible disease-associated damage. This can make it difficult to measure improvement

over the course of a trial. It is increasingly clear that clinical trials in SjD will require patient stratification and relevant and sensitive outcome measures to identify successful treatment modalities. There is a need for patient-reported outcome endpoints validated specifically in SjD that can demonstrate improvement in a clearly defined patient subset. Such measures should focus on the quality-of-life aspects that are important to patients and will most likely involve gauging changes in function rather than patient-reported symptoms. Composite disease assessment tools, incorporating patient-reported outcomes and objective clinical measures to create more clinically meaningful endpoints for SjD trials could be more appropriate for a holistic disease assessment (Berry et al, 2024).

## Emerging Outcome Measures in SjD: STAR and CRESS

New outcome measures in SjD, such as the Sjögren's Tool for Assessing Response (STAR) and Composite of Relevant Endpoints for SjD (CRESS) aim to address some of the limitations of traditional measures like ESSDAI and ESSPRI by providing a multi-dimensional overview of disease impact. Both STAR and CRESS are currently undergoing additional validation (Arends et al, 2021; Seror et al, 2022) (Table 2).

**Table 2. Summary of domains STAR and CRESS.**

| | STAR | CRESS |
|---|---|---|
| Clinician assessment | ClinESSDAI | ESSDAI |
| Patient burden assessment | ESSPRI | ESSPRI |
| Measure of lacrymal gland function | OSS | Schirmer Test<br>OSS |
| Measure of salivary gland function | UWSF | UWSF<br>SGUS |
| Serological markers of disease | Not measured | RF<br>IgG |

STAR, Sjögren's Tool for Assessing Response; CRESS, Composite of Relevant Endpoints for SjD; IgG, immunoglobulin G; OSS, Ocular Staining Score; RF, Rheumatoid Factor; SGUS, Salivary Gland Ultrasound Scan; UWSF, Unstimulated Whole Salivary Flow.

### STAR

STAR is a composite score developed to assess treatment effects in SjD. It was developed using data-driven methods based on nine randomised controlled trials (RCTs) and consensus techniques involving 78 experts and 20 patients (Seror et al, 2022). The STAR includes five core domains, which are differently weighted, including systemic activity, patient symptoms, lachrymal gland function, salivary gland function, and biological parameters. The STAR also includes improvement of glandular function using simple and validated measures, such as Schirmer's test,

Ocular Staining Score (OSS), and Unstimulated Whole Salivary Flow (UWSF). STAR was designed to be used as a primary endpoint in clinical trials in SjD as it has demonstrated good sensitivity to change, as well as adequate face and content validity (Seror et al, 2022). STAR will be validated in a large international clinical trial—NEw Clinical Endpoints in primary Sjögren's Syndrome: an Interventional Trial based on Stratifying Patients (NECESSITY), which is currently underway.

### CRESS

CRESS is a novel composite endpoint developed to assess treatment efficacy in clinical trials in SjD. It was co-developed by a multidisciplinary expert team and validated using data from three independent RCTs (Arends et al, 2021). The CRESS includes five complementary items: systemic disease activity by ClinESSDAI; patient-reported symptoms by ESSPRI; lachrymal gland function by Schirmer's test and Ocular Staining Score (OSS); salivary gland function by Unstimulated Whole Salivary Flow (UWSF) and Salivary Gland Ultrasound Scan (SGUS); and serology including Rheumatoid Factor (RF) and IgG levels. Total CRESS response was defined as a response or change in at least three of the five items compared with the baseline.

## Limitations of the New Composite Scores STAR and CRESS

While STAR and CRESS represent promising advancements in outcome measures for SjD, they also have certain limitations. Both STAR and CRESS are composite indices that integrate multiple domains, including symptoms, biomarkers, and patient-reported outcomes, potentially posing challenges in terms of data collection, interpretation, and implementation in clinical practice. The need to incorporate various components and assign weights to them adds to the complexity of scoring, as well as it is more time-consuming, and may require additional training for clinicians and researchers to use these measures effectively.

Although STAR and CRESS have been developed as outcome measures for SjD, further validation studies are needed to assess their reliability, validity, responsiveness to change, and sensitivity to treatment effects. Validation studies should involve diverse patient populations, including different disease phenotypes and stages, to ensure the generalisability of these measures across the SjD spectrum.

Implementing STAR and CRESS into clinical practice may require significant resources, including time, personnel, and infrastructure, for data collection, analysis, and interpretation. The use of biomarkers and objective measures in these indices may necessitate specialised equipment and expertise, which may not be readily available in all healthcare settings.

Collecting data for STAR and CRESS may impose a burden on patients, particularly in terms of completing multiple assessments and tests during clinic visits or research evaluations. Patient-reported outcomes included in these indices may also be subject to variability and bias, depending on factors such as patient understanding, recall and reporting accuracy.

Interpreting the results of STAR and CRESS may be challenging due to the complexity of the indices and the relative weighting assigned to different components. Clinicians and researchers will need clear guidelines and thresholds for interpreting scores and determining clinically meaningful changes over time.

Addressing these limitations will be essential to optimize the utility and applicability of STAR and CRESS as outcome measures for SjD. Continued refinement, validation, and standardisation efforts are needed to enhance the reliability, validity, and accessibility of these measures for assessing disease activity, treatment response, and patient outcomes.

## Outcome Measures in Childhood-Onset Sjögren Disease

Childhood-onset Sjögren disease (cSjD) is a rare disease phenotype with onset before the age of 18 years. There are significant unmet needs in improving disease recognition, diagnosis, and classification, as well as assessing disease activity and the impact of symptoms in cSjD due to several factors (Ciurtin et al, 2021). Additionally, there is even a greater need to generate good quality evidence for effective management strategies for cSjD as there are no good quality studies in children (Doolan et al, 2022).

Because the disease presents in a different way in children compared to adults (Basiaga et al, 2021), there is a need for the development and validation of paediatric-specific outcome measures to better capture the distinct clinical features and disease progression in children and adolescents, as well as facilitate therapeutic interventions early in the disease course. These outcome measures need to reflect the distinct childhood disease phenotype, and impact of the disease on quality of life (QOL) in childhood and adolescence, in addition to being sensitive to change to reliably measure the effect of potential therapeutic interventions.

Currently, there are no validated outcome measures specifically designed for cSjD. Existing measures developed for adult SjD have been only tested in limited cohorts of children and adolescents (Iwata et al, 2020). cSjD can manifest differently in children, with variations in clinical symptoms, disease severity, and organ involvement; therefore, it is imperative to develop tools that reflect these differences (Ramos-Casals et al, 2021). In a large study, children more commonly had systemic symptoms within the constitutional, lymphadenopathy, glandular, cutaneous, and haematological domains of ESSDAI, and the lowest frequencies in the articular, pulmonary, peripheral nerve and central nervous system domains, when compared with adults with SjD (Ramos-Casals et al, 2021), while a smaller study found that ESSDAI assessment reflected disease activity assessment as per expert paediatrician opinion (Iwata et al, 2020). cSjD can significantly impact the physical, emotional, and social wellbeing of children and adolescents, affecting the quality of life and daily functioning, but despite this, patient-reported outcomes have not been tested in this population. The chronic nature of cSjD necessitates long-term monitoring to track disease progression, treatment response, and potential complications over time, as well as impact on functioning which is very relevant for young peo-

ple's long-term outcomes. However, the lack of standardised outcome measures tailored to paediatric patients hampers consistent monitoring and evaluation of disease activity and severity and should be incorporated in future research agenda.

## Conclusion

SjD is a heterogeneous chronic autoimmune disorder that can affect people across the life span. Future progress is still required to validate disease tools that can accurately capture both the objective assessment of organ and systems involvement due to chronic inflammation as well as the impact of the disease on quality of life and functioning for use in both routine clinical practice and for research purposes. New outcome measures should aim to address the limitations of traditional measures and provide a multi-dimensional overview of the disease impact as well as evaluate the most relevant disease domains. Existing and emerging outcome measures have been specifically developed for adult disease and need further testing in children and adolescents. Without good evidence that outcomes measure aspects of the disease that are relevant for improved management, clinicians face challenges in effectively assessing and managing SjD across the lifespan. Future research in SjD is focused on biomarker-driven therapeutic approaches which require highly performing outcome measures with the ability to identify distinct patient groups to guide personalised management, as well as define clinically significant responses, ultimately supporting the identification of truly effective therapies.

### Key Points

- ESSDAI and ESSPRI remain the most widely used outcome measures in SjD despite their limitations and lack of correlation between objective and subjective assessment of disease impact.
- New composite outcome measures aim to capture the disease heterogeneity as well as integrate the assessment of glandular symptoms, systemic activity, and patient-reported outcomes.
- Future research is needed to classify and define outcome measures suitable for children and adolescents with cSjD to support high-quality research in this underserved rare population.

## Availability of Data and Materials

All the data of this study are included in this article.

## Author Contributions

CC has designed the initial paper structure. RW, JT, and EH were responsible for the literature search and table design. RW wrote the first version of the paper with significant contributions from all authors. CC wrote the second version of the paper to incorporate all the reviewers' comments, which RW finalized. All authors contributed to the important editorial changes in the manuscript. All authors read

and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

## Acknowledgement

Not applicable.

## Funding

The work has been performed within the Centre for Adolescent Rheumatology Versus Arthritis at University College London (UCL), UCLH, and Great Ormond Street Hospital (GOSH) and supported by Versus Arthritis (grants 21593 and 20164), CC is funded by the National Institute of Health Research (NIHR) University College London Hospital (UCLH) Biomedical Research Centre (grants BRC4/III/CC).

## Conflict of Interest

The authors declare no conflict of interest.

## References

Ameringer S, Elswick RK, Jr, Menzies V, Robins JL, Starkweather A, Walter J, et al. Psychometric Evaluation of the Patient-Reported Outcomes Measurement Information System Fatigue-Short Form Across Diverse Populations. Nursing Research. 2016; 65: 279–289. https://doi.org/10.1097/NNR.0000000000000162

Arends S, de Wolff L, van Nimwegen JF, Verstappen GMPJ, Vehof J, Bombardieri M, et al. Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS): development and validation of a novel outcome measure. The Lancet. Rheumatology. 2021; 3: e553–e562. https://doi.org/10.1016/S2665-9913(21)00122-3

Baer AN, Gottenberg JE, St Clair EW, Sumida T, Takeuchi T, Seror R, et al. Efficacy and safety of abatacept in active primary Sjögren's syndrome: results of a phase III, randomised, placebo-controlled trial. Annals of the Rheumatic Diseases. 2021a; 80: 339–348. https://doi.org/10.1136/annrheumdis-2020-218599

Baer AN, Hammitt KM. Sjögren's Disease, Not Syndrome. Arthritis & Rheumatology. 2021b; 73: 1347–1348. https://doi.org/10.1002/art.41676

Baldini C, Fulvio G, La Rocca G, Ferro F. Update on the pathophysiology and treatment of primary Sjögren syndrome. Nature Reviews. Rheumatology. 2024; 20: 473–491. https://doi.org/10.1038/s41584-024-01135-3

Basiaga ML, Stern SM, Mehta JJ, Edens C, Randell RL, Pomorska A, et al. Childhood Sjögren syndrome: features of an international cohort and application of the 2016 ACR/EULAR classification criteria. Rheumatology. 2021; 60: 3144–3155. https://doi.org/10.1093/rheumatology/keaa757

Berry JS, Tarn J, Lendrem D, Casement J, Ng WF. P153 Exploring the relationships between objective and subjective clinical measures in Sjogren's Syndrome. Rheumatology. 2024; 63: keae163-192. https://doi.org/10.1093/rheumatology/keae163.192

Beydon M, McCoy S, Nguyen Y, Sumida T, Mariette X, Seror R. Epidemiology of Sjögren syndrome. Nature Reviews. Rheumatology. 2024; 20: 158–169. https://doi.org/10.1038/s41584-023-01057-6

Bowman SJ, Booth DA, Platts RG, Field A, Rostron J. Validation of the Sicca Symptoms Inventory for clinical studies of Sjögren's syndrome. The Journal of Rheumatology. 2003; 30: 1259–1266.

Bowman SJ, Booth DA, Platts RG, UK Sjögren's Interest Group. Measurement of fatigue and discomfort in primary Sjogren's syndrome using a new questionnaire tool. Rheumatology. 2004; 43: 758–764. https://doi.org/10.1093/rheumatology/keh170

Bowman SJ, Everett CC, O'Dwyer JL, Emery P, Pitzalis C, Ng WF, et al. Randomized Controlled Trial of Rituximab and Cost-Effectiveness Analysis in Treating Fatigue and Oral Dryness in Primary Sjögren's Syndrome. Arthritis & Rheumatology. 2017; 69: 1440–1450. https://doi.org/10.1002/art.40093

Bowman SJ, Fox R, Dörner T, Mariette X, Papas A, Grader-Beck T, et al. Safety and efficacy of subcutaneous ianalumab (VAY736) in patients with primary Sjögren's syndrome: a randomised, double-blind, placebo-controlled, phase 2b dose-finding trial. Lancet. 2022; 399: 161–171. https://doi.org/10.1016/S0140-6736(21)02251-0

Bowman SJ, Hamburger J, Richards A, Barry RJ, Rauz S. Patient-reported outcomes in primary Sjogren's syndrome: comparison of the long and short versions of the Profile of Fatigue and Discomfort–Sicca Symptoms Inventory. Rheumatology. 2009; 48: 140–143. https://doi.org/10.1093/rheumatology/ken426

Brito-Zerón P, Baldini C, Bootsma H, Bowman SJ, Jonsson R, Mariette X, et al. Sjögren syndrome. Nature Reviews. Disease Primers. 2016a; 2: 16047. https://doi.org/10.1038/nrdp.2016.47

Brito-Zerón P, Kostov B, Solans R, Fraile G, Suárez-Cuervo C, Casanovas A, et al. Systemic activity and mortality in primary Sjögren syndrome: predicting survival using the EULAR-SS Disease Activity Index (ESSDAI) in 1045 patients. Annals of the Rheumatic Diseases. 2016b; 75: 348–355. https://doi.org/10.1136/annrheumdis-2014-206418

Brito-Zerón P, Ramos-Casals M, EULAR-SS task force group. Advances in the understanding and treatment of systemic complications in Sjögren's syndrome. Current Opinion in Rheumatology. 2014; 26: 520–527. https://doi.org/10.1097/BOR.0000000000000096

Ciurtin C, Cho Y, Al-Obaidi M, Jury EC, Price EJ. Barriers to translational research in Sjögren's syndrome with childhood onset: challenges of recognising and diagnosing an orphan rheumatic disease. The Lancet. Rheumatology. 2021; 3: e138–e148. https://doi.org/10.1016/S2665-9913(20)30393-3

Ciurtin C, Price E. A Viewpoint on Therapeutic Approaches and Unmet Needs in the Management of Young People with Sjögren Disease. touchREVIEWS in RMD. 2024; 3: 31–42. https://doi.org/10.17925/rmd.2024.3.1.5

Collins A, Lendrem D, Wason J, Tarn J, Howard-Tripp N, Bodewes I, et al. Revisiting the JOQUER trial: stratification of primary Sjögren's syndrome and the clinical and interferon response to hydroxychloroquine. Rheumatology International. 2021; 41: 1593–1600. https://doi.org/10.1007/s00296-021-04927-y

Cooper C, Wratten S, Williams-Hall R, Bookman AAM, Ndife B, Hueber W, et al. Qualitative Research with Patients and Physicians to Assess Content Validity and Meaningful Change on ESSDAI and ESSPRI in Sjögren's. Rheumatology and Therapy. 2022; 9: 1499–1515. https://doi.org/10.1007/s40744-022-00487-0

de Wolff L, Arends S, van Nimwegen JF, Bootsma H. Ten years of the ESSDAI: is it fit for purpose? Clinical and Experimental Rheumatology. 2020; 38: 283–290.

DiRenzo DD, Robinson S, Bingham CO, 3rd, Baer AN, Grader-Beck T. PROMIS Provides a Broader Overview of Health-related Quality of Life Than the ESSPRI in Evaluation of Sjögren Syndrome. The Journal of Rheumatology. 2022; 49: 470–474. https://doi.org/10.3899/jrheum.210633

Doolan G, Faizal NM, Foley C, Al-Obaidi M, Jury EC, Price E, et al. Treatment strategies for Sjögren's syndrome with childhood onset: a systematic review of the literature. Rheumatology. 2022; 61: 892–912. https://doi.org/10.1093/rheumatology/keab579

Dörner T, Posch MG, Li Y, Petricoul O, Cabanski M, Milojevic JM, et al. Treatment of primary Sjögren's syndrome with ianalumab (VAY736) targeting B cells by BAFF receptor blockade coupled with enhanced, antibody-dependent cellular cytotoxicity. Annals of the Rheumatic Diseases. 2019; 78: 641–647. https://doi.org/10.1136/annrheumdis-2018-214720

Dumusc A, Ng WF, James K, Griffiths B, Price E, Pease C, et al. Comparison of ESSDAI and ClinESSDAI in potential optimisation of trial outcomes in primary Sjögren's syndrome: examination of data from the UK Primary Sjögren's Syndrome Registry. Swiss Medical Weekly. 2018; 148: w14588.

https://doi.org/10.4414/smw.2018.14588

Felten R, Devauchelle-Pensec V, Seror R, Duffau P, Saadoun D, Hachulla E, et al. Interleukin 6 receptor inhibition in primary Sjögren syndrome: a multicentre double-blind randomised placebo-controlled trial. Annals of the Rheumatic Diseases. 2021; 80: 329–338. https://doi.org/10.1136/annrheumdis-2020-218467

Gottenberg JE, Cinquetti G, Larroche C, Combe B, Hachulla E, Meyer O, et al. Efficacy of rituximab in systemic manifestations of primary Sjogren's syndrome: results in 78 patients of the AutoImmune and Rituximab registry. Annals of the Rheumatic Diseases. 2013; 72: 1026–1031. https://doi.org/10.1136/annrheumdis-2012-202293

Hammitt KM, Naegeli AN, van den Broek RWM, Birt JA. Patient burden of Sjögren's: a comprehensive literature review revealing the range and heterogeneity of measures used in assessments of severity. RMD Open. 2017; 3: e000443. https://doi.org/10.1136/rmdopen-2017-000443

Iwata N, Tomiita M, Kobayashi I, Inoue Y, Nonaka Y, Okamoto N, et al. Utility of the EULAR Sjögren syndrome disease activity index in Japanese children: a retrospective multicenter cohort study. Pediatric Rheumatology Online Journal. 2020; 18: 73. https://doi.org/10.1186/s12969-020-00458-1

Juarez M, Diaz N, Johnston GI, Nayar S, Payne A, Helmer E, et al. A phase 2 randomized, double-blind, placebo-controlled, proof-of-concept study of oral seletalisib in primary Sjögren's syndrome. Rheumatology. 2021; 60: 1364–1375. https://doi.org/10.1093/rheumatology/keaa410

Meiners PM, Vissink A, Kroese FGM, Spijkervet FKL, Smitt-Kamminga NS, Abdulahad WH, et al. Abatacept treatment reduces disease activity in early primary Sjögren's syndrome (open-label proof of concept ASAP study). Annals of the Rheumatic Diseases. 2014; 73: 1393–1396. https://doi.org/10.1136/annrheumdis-2013-204653

Pertovaara M, Korpela M. Serum $\beta 2$ microglobulin correlates with the new ESSDAI in patients with Sjögren's syndrome. Annals of the Rheumatic Diseases. 2011; 70: 2236–2237. https://doi.org/10.1136/ard.2011.153098

Price E, Bombardieri M, Kivitz A, Matzkies F, Gurtovaya O, Pechonkina A, et al. Safety and efficacy of filgotinib, lanraplenib and tirabrutinib in Sjögren's syndrome: a randomized, phase 2, double-blind, placebo-controlled study. Rheumatology. 2022; 61: 4797–4808. https://doi.org/10.1093/rheumatology/keac167

Price EJ, Benjamin S, Bombardieri M, Bowman S, Carty S, Ciurtin C, et al. British Society for Rheumatology guideline on management of adult and juvenile onset Sjögren disease. Rheumatology. 2024; keae152. https://doi.org/10.1093/rheumatology/keae152

Ramos-Casals M, Acar-Denizli N, Vissink A, Brito-Zerón P, Li X, Carubbi F, et al. Childhood-onset of primary Sjögren's syndrome: phenotypic characterization at diagnosis of 158 children. Rheumatology. 2021; 60: 4558–4567. https://doi.org/10.1093/rheumatology/keab032

Raymond K, Maher S, Saucier CD, O'Connor M, Yarlas A, Kosinski M, et al. Validation of the PROFAD-SSI-SF in Patients with Primary Sjögren's Syndrome with Organ Involvement: Results of Qualitative Interviews and Psychometric Analyses. Rheumatology and Therapy. 2023; 10: 95–115. https://doi.org/10.1007/s40744-022-00493-2

Seror R, Baron G, Camus M, Cornec D, Perrodeau E, Bowman SJ, et al. Development and preliminary validation of the Sjögren's Tool for Assessing Response (STAR): a consensual composite score for assessing treatment effect in primary Sjögren's syndrome. Annals of the Rheumatic Diseases. 2022; 81: 979–989. https://doi.org/10.1136/annrheumdis-2021-222054

Seror R, Meiners P, Baron G, Bootsma H, Bowman SJ, Vitali C, et al. Development of the ClinESSDAI: a clinical score without biological domain. A tool for biological studies. Annals of the Rheumatic Diseases. 2016; 75: 1945–1950. https://doi.org/10.1136/annrheumdis-2015-208504

Seror R, Ravaud P, Bowman SJ, Baron G, Tzioufas A, Theander E, et al. EULAR Sjogren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjogren's syndrome. Annals of the Rheumatic Diseases. 2010; 69: 1103–1109. https://doi.org/10.1136/ard.2009.110619

Seror R, Ravaud P, Mariette X, Bootsma H, Theander E, Hansen A, et al. EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI): development of a consensus patient index for primary Sjogren's syndrome. Annals of the Rheumatic Diseases. 2011; 70: 968–972. https://doi.org/10.1136/ard.2010.143743

Seror R, Theander E, Brun JG, Ramos-Casals M, Valim V, Dörner T, et al. Validation of EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient indexes (ESSPRI). Annals of the Rheumatic Diseases. 2015; 74: 859–866. https://doi.org/10.1136/annrheumdis-2013-204615

Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. Annals of the Rheumatic Diseases. 2017; 76: 9–16. https://doi.org/10.1136/annrheumdis-2016-210571

Tarn JR, Howard-Tripp N, Lendrem DW, Mariette X, Saraux A, Devauchelle-Pensec V, et al. Symptom-based stratification of patients with primary Sjögren's syndrome: multi-dimensional characterisation of international observational cohorts and reanalyses of randomised clinical trials. The Lancet. Rheumatology. 2019; 1: e85–e94. https://doi.org/10.1016/S2665-9913(19)30042-6

Ture HY, Kim NR, Nam EJ. EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI) and Other Patient-Reported Outcomes in the Assessment of Glandular Dysfunction in Primary Sjögren's Syndrome. Life. 2023; 13: 1991. https://doi.org/10.3390/life13101991