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Identification of outcome domains in primary Sjögren's disease: A scoping review by the OMERACT Sjögren disease working group

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ABSTRACT

Objectives: Sjögren's disease (SjD) is a heterogenous disease with a wide range of manifestations, ranging from symptoms of dryness, fatigue, and pain, to systemic involvement. Considerable advances have been made to evaluate systemic activity or patient-reported outcomes, but most of the instruments were not able to assess all domains of this multifaceted disease. The aim of this scoping review was to generate domains that have been assessed in randomized controlled trials, as the first phase of the Outcome Measures in Rheumatology (OMERACT) process of core domain set development.

Methods: We systematically searched Medline (Pubmed) and EMBASE between 2002 and March 2023 to identify all randomized controlled trials assessing relevant domains, using both a manual approach and an artificial intelligence software (BIBOT) that applies natural language processing to automatically identify relevant abstracts. Domains were mapped to core areas, as suggested by the OMERACT 2.1 Filter.

Results: Among the 5,420 references, we included 60 randomized controlled trials, focusing either on overall disease manifestations (53%) or on a single organ/symptom: dry eyes (17%), xerostomia (15%), fatigue (12%), or pulmonary function (3%). The most frequently assessed domains were perceived dryness (52% for overall dryness), fatigue (57%), pain (52%), systemic disease activity (45%), lacrimal gland function (47%) and salivary function (55%), B-cell activation (60%), and health-related quality of life (40%).

Conclusion: Our scoping review highlighted the heterogeneity of SjD, in the study designs and domains. This will inform the OMERACT SjD working group to select the most appropriate core domains to be used in SjD clinical trials and to guide the future agenda for outcome measure research in SjD

Introduction

Sjögren's disease (SjD) manifests itself mainly through two disease facets. The first facet is symptom burden, of which oral and ocular sicca is highly prevalent. Though non-life-threatening, these symptoms impair quality of life and are frequently associated with fatigue and pain. The second involves protean systemic manifestations including but not limited to arthritis, peripheral neuropathies, pulmonary disease, cutaneous vasculitis, and nephritis. Among these complications, lymphoma development is particularly worrisome. Approximately 5–10% of

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patients with SjD develop lymphoma, which makes SjD the autoimmune disease with the highest risk of lymphoma [1], estimated in recent studies to be 4–16-fold that in the general population [2–5].

Prior to the last decade, interventional studies determined the efficacy of drugs on sicca features (e.g., evaluating ocular or oral dryness) and/or other patient-reported outcomes (PROs) (e.g. fatigue or pain [6]) with mostly negative results even with biological therapies [7,8]. These results might be explained by the heterogeneity of SjD manifestations, leading to biologically diverse subgroups of patients [9]. However, another pragmatic explanation for the trials which did not meet their primary endpoint in SjD might be the inadequacy of the outcome measures. Since the last decade, thanks to the emergence of the EULAR (European Alliance of Associations for Rheumatology) SjD working group, international consortium consensus outcome measures have been developed: the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) for measuring systemic activity, and the EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI) for measuring patient symptoms [10,11]. However, those instruments also have limitations, and do not account for all disease facets. For example, improvement of ESSDAI does not necessarily correlate with improvement in PROs, and vice versa [12].

Thus, considering the wide spectrum of disease manifestations, choosing an outcome which reflects such heterogeneity can be difficult [13], but is of utmost importance. Nevertheless, before generating such instrument, the identification of a core domain set is necessary.

The first phase of the Outcome Measures in Rheumatology (OMERACT) process of core domain set development is called "generating", where a wide comprehensive set of potential domains are aggregated. This phase includes two initiatives: (1) a literature review to identify existing domains and (2) qualitative work, including focus groups and/or interviews of appropriate stakeholder groups to identify additional domains.

As the initial step, this scoping review aimed to identify relevant domains in SjD that have been assessed in randomized clinical trials (RCTs) to inform the development of a core set of domains.

Methods

Scoping review guidelines

As the initial step of the OMERACT core domain set generation process for outcome measure and instrument selection, our working group initiated a scoping review [14]. The protocol has been written in accordance with the OMERACT Handbook for development of core outcome sets and approved by the OMERACT Technical Advisory Group [15]. The reporting of this protocol has been done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Review Guidelines [16].

Scoping review study populations

To be included in this scoping review, the studies had to fulfill the following criteria: (1) The study population is adult human patients with SjD, defined by the 2002 American-European Consensus Group (AECG) criteria, the 2012 American College of Rheumatology (ACR) criteria, and/or the 2016 ACR/EULAR criteria [17–20]. To ensure a proper definition of SjD cases in the included studies, we only included studies after 2002, the year of the first validated SjD classification criteria [18]. (2) The study evaluated an intervention (including pharmacological, surgical, or supportive interventions); (3) the study had a comparator; (4) at least one SjD-related outcome was evaluated; and (5) the study was a randomized controlled trial. Thus, cohort studies, case control studies, case series or case reports were not included. References from systematic reviews, meta-analyses of RCTs, and review articles on outcome measures were screened to complete the search strategy, but their outcomes were not included in the data extraction. Language was restricted to English. Only articles with full text available were included, congress abstracts and posters that were not further published were excluded.

Search strategy and study selection

To identify all available literature relevant to our objectives, we searched Medline (using PubMed), and EMBASE, from 2002 through an end date of March 1st, 2023. The search strategy is described in Supplementary appendix 1. To identify studies on SjD, we used the MeSH term "Sjögren syndrome", as most literature used this terminology, until patient advocacy groups and leaders in the field recently proposed removing "syndrome" from the name [21].

First, article selection was made with the help of an artificial intelligence (AI) software called Bibliography BOT (BIBOT) [22–24]. BIBOT is an AI-powered computer software that applies natural language processing to automatically identify and interpret important words (based on MeSH terms) in abstracts published in English, and automates article selection relevant to a research question [25,26]. Its concordance with human evaluators is excellent [22]. The articles were first extracted from the two databases by the authors, and duplicates were removed. BIBOT then selected articles relevant to the research question based on the above-mentioned inclusion criteria. For concordance check, a total of 100 randomly selected studies of the extracted articles were independently evaluated for selection by blinded authors (SM and RG). As mentioned, references of meta-analyses and reviews were also screened to identify references that might have been missed by BIBOT. Thereafter, reports were individually screened, sought for retrieval, and assessed for eligibility using the inclusion criteria. Sub-studies from selected RCTs were excluded, but their results were retrieved and linked to the original RCT [27,28].

Data extraction

All data were collected by two independent authors (MB and YN). Discrepancies were discussed and eventually resolved by a third author in the absence of agreement (RS). For each RCT, extracted data included study characteristics (author, year of publication, journal), trial registration number, SjD classification criteria, restriction to inclusion criteria (age <18 years, >75 years, ESSDAI threshold, presence of anti-SSA antibodies, disease duration), name of the intervention (treatment, procedure or other), and study design (number of arms, parallel, cross over, blinding).

Studies were separated into four categories: (1) those aiming to treat overall SjD manifestations (sicca syndrome and/or systemic manifestations), and those focusing on either (2) dry eye, (3) dry mouth, (4) fatigue, or (5) other (such as pulmonary function).

Synthesis

Domains identified in their primary and secondary outcomes from the selected publications were mapped to core areas in accordance with the OMERACT 2.1 Filter [29–31]: Manifestations/Abnormalities, Life impact, Death/Lifespan, and Societal/Resource Use. The number of included publications for each reported domain was tabulated.

In each core area, each primary and secondary outcome was associated with a domain, which could otherwise be described as a measurable effect of a possible intervention. Domains were tailored to unambiguously link related outcomes to a single domain. Each domain was classified by intended benefits or harms.

Overall results were synthetized in a descriptive table, categorized by core areas, domain and intended effect or harm, along with the number of studies per domain.

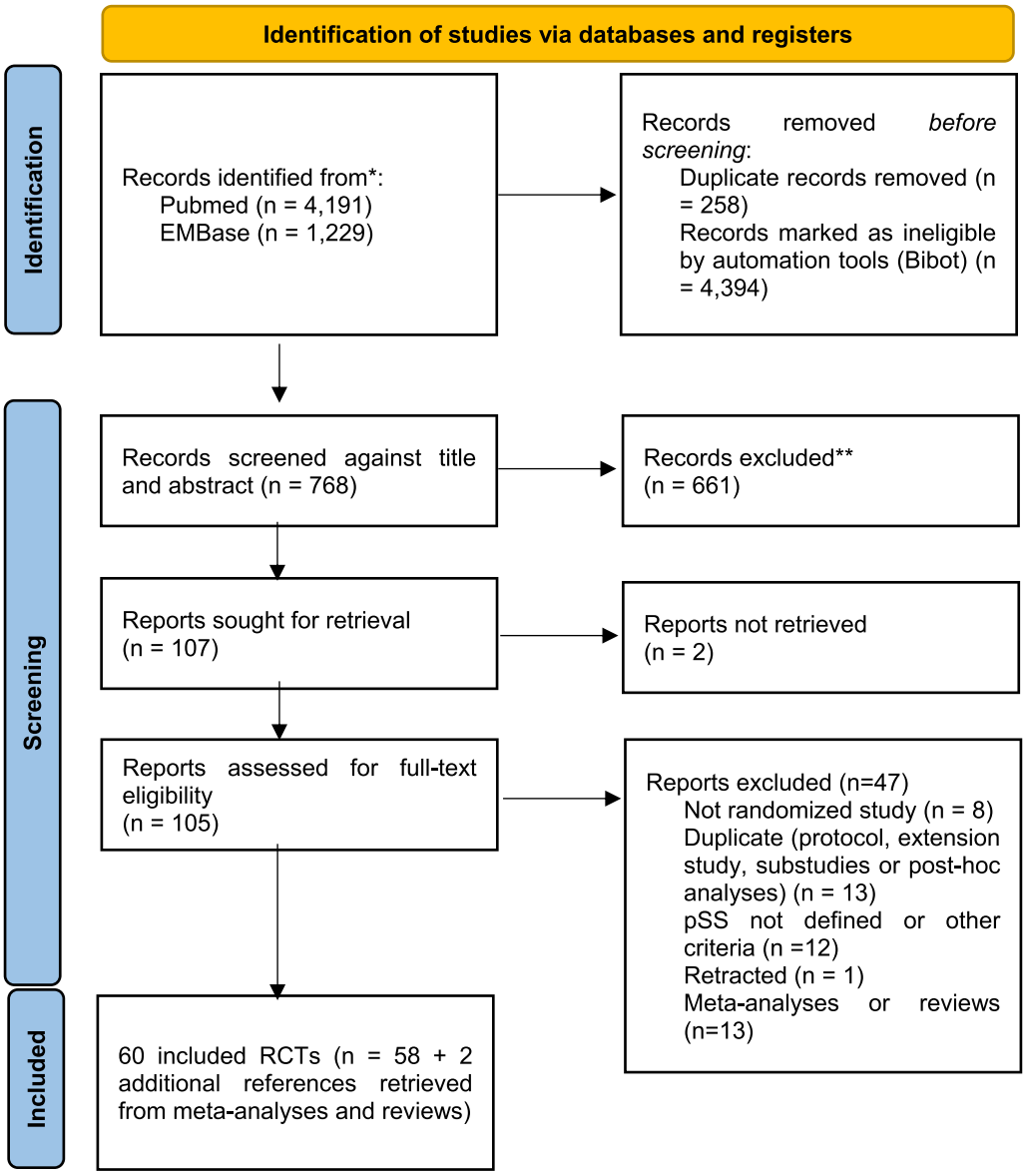

Fig. 1. PRISMA flow diagram.

Results

Search results

Our search strategy yielded 5420 references. 258 duplicate references were removed (Fig. 1). Using the artificial intelligence tool (BIBOT), 4394 references were further excluded.

In a random selection of 100 references, the blinded evaluators included 4 (4%) of the references, while BIBOT included 15 (15%). When the blinded assessment was considered as the gold standard, sensitivity, specificity, positive predictive value, and negative predictive value were 100%, 88.5%, 26.7%, and 100%, respectively. Thus, the probability of having missed studies fulfilling the inclusion criteria was low.

Of the 768 remaining titles and abstracts that were screened, 661 were excluded due to lack of relevance, and 2 could not be retrieved. Of the 105 reports assessed for full-text eligibility, 34 were excluded: 8 were not randomized; 13 studies were extension studies, protocols, or post-hoc analyses of included studies; 12 studies did not define SjD or used older criteria; 1 report was retracted; and 13 were meta-analyses of RCTs or reviews on outcome measures. Thus, 58 RCTs were included.

After screening the references from the selected meta-analyses of RCTs and reviews, two additional RCTs which were not detected by BIBOT [32,33], but were detected by the initial search strategy, were added to the final selection yielding to 60 RCTs (Fig. 1).

Characteristics of the included studies

The characteristics of the included 60 RCTs are presented in Table 1. Most studies have been published recently (53% after 2018) and the registration trial number (i.e., clinicaltrial.gov, Chinese Clinical Trial Registry, or other databases) was reported in 66%. SjD was defined by the 2002 AECG criteria for 91% studies. Thirty-two (53%) studies focused on overall disease manifestations, 10 (17%) on dry eye treatment, 9 (15%) on xerostomia, 7 (12%) on fatigue, and 2 (3%) on respiratory functional capacity. Most studies (n=49; 67%) assessed systemic medication, including oral drugs (n=20; 33%), biological therapies (n=16; 27%), or traditional Chinese medicine (n=4; 7%), 9 (15%) assessed topical medications, and 11 (18%) studies assessed procedures (as acupuncture, lid debridement, laser, irrigation, or physical activity program).

Table 1
Main characteristics of the included studies (n=60).

Characteristic	Overall, N = 60[1]	All pSS manifestations, N = 32[1]	Dry eyes, N = 10[1]	Dry mouth, N = 9[1]	Fatigue, N = 7[1]	Other, N = 2[1]
Publication year						
2002–2005	7/60 (12%)	5/32 (16%)	2/10 (20%)	0/9 (0%)	0/7 (0%)	0/2 (0%)
2006–2009	4/60 (6.7%)	1/32 (3.1%)	0/10 (0%)	1/9 (11%)	2/7 (29%)	0/2 (0%)
2010–2013	7/60 (12%)	1/32 (3.1%)	2/10 (20%)	2/9 (22%)	2/7 (29%)	0/2 (0%)
2014–2017	10/60 (17%)	6/32 (19%)	3/10 (30%)	1/9 (11%)	0/7 (0%)	0/2 (0%)
2018–2022	32/60 (53%)	19/32 (59%)	3/10 (30%)	5/9 (56%)	3/7 (43%)	2/2 (100%)
Registered RCT	40/60 (67%)	24/32 (75%)	3/10 (30%)	5/9 (56%)	6/7 (86%)	2/2 (100%)
pSS diagnosis criteria						
AECG 2002	55/60 (92%)	29/32 (91%)	8/10 (80%)	9/9 (100%)	7/7 (100%)	2/2 (100%)
ACR SICCA 2012	2/60 (3.3%)	0/32 (0%)	2/10 (20%)	0/9 (0%)	0/7 (0%)	0/2 (0%)
ACR/EULAR 2016	3/60 (5.0%)	3/32 (9.4%)	0/10 (0%)	0/9 (0%)	0/7 (0%)	0/2 (0%)
Inclusion criteria						
Only primary SjD	56/60 (93%)	30/32 (94%)	9/10 (90%)	8/9 (89%)	7/7 (100%)	2/2 (100%)
Primary and secondary Sjögren patients	4/60 (6.7%)	2/32 (6.2%)	1/10 (10%)	1/9 (11%)	0/7 (0%)	0/2 (0%)
<18 years-old included	4/60 (6.7%)	1/32 (3.1%)	2/10 (20%)	1/9 (11%)	0/7 (0%)	0/2 (0%)
>75-year-old included	27/60 (45%)	14/32 (44%)	6/10 (60%)	3/9 (33%)	2/7 (29%)	2/2 (100%)
ESSDAI threshold	14/60 (23%)	14/32 (44%)	0/10 (0%)	0/9 (0%)	0/7 (0%)	0/2 (0%)
Anti-SSA+ only	8/60 (13%)	7/32 (22%)	0/10 (0%)	0/9 (0%)	1/7 (14%)	0/2 (0%)
Anti SSA/other antibody+	5/60 (8.3%)	4/32 (12%)	0/10 (0%)	0/9 (0%)	1/7 (14%)	0/2 (0%)
Disease duration threshold	2/60 (3.3%)	2/32 (6.2%)	0/10 (0%)	0/9 (0%)	0/7 (0%)	0/2 (0%)
Intervention						
Medication	49/60 (82%)	31/32 (97%)	8/10 (80%)	5/9 (56%)	5/7 (71%)	0/2 (0%)
Procedure	11/60 (19%)	1/32 (3.1%)	2/10 (20%)	4/9 (44%)	2/7 (29%)	2/2 (100%)
Type of intervention		Abatacept (2) Baminercept (1) Cevilemine (1) Etanercept (1) Filgotinib (1) HCQ (3) Ianalumab (2) IFN alpha (1) Iguratimod (2) Infliximab (1) Iscalimab (1) Lamivudine (1) Leflunomide+HCQ (1) Doxycycline (1) Interleukin 2 (1) Pilocarpine (1) Rituximab (3) Rituximab ± Belimumab (1) Seletalisib (1) Tocilizumab (1) Traditional Chinese Medicine (4) Acupuncture (1)	Tacrolimus drops (3) Indomethacine drops (1) Clobetasone butyrate (1) Hyaluronic acid (1) Pilocarpine (2) Lid debridement scaling (1) Punctal plugs (1)	Malic acid (2) Omega 3 and vitamin E (1) Pastes (1) Xialine (1) Low laser (1) Irrigation (1) Mouthwash (1)	Anakinra (1) DHEA (2) Rituximab (1) RSLV-132 therapy (1) Physical activity program (1) Transcranial direct current stimulation (1)	Physical activity program (2)
Study design						
Number of arms						
2	51/60 (85%)	27/32 (84%)	9/10 (90%)	6/9 (67%)	7/7 (100%)	2/2 (100%)
3	5/60 (8.3%)	1/32 (3.1%)	1/10 (10%)	3/9 (33%)	0/7 (0%)	0/2 (0%
4	4/60 (6.7%)	4/32 (13%)	0/10 (0%)	0/9 (0%)	0/7 (0%)	0/2 (0%)
Design						
parallel	55/60 (92%)	31/32 (97%)	9/10 (90%)	7/9 (78%)	6/7 (86%)	2/2 (100%)
cross over	5/60 (8.3%)	1/32 (3.1%)	1/10 (10%)	2/9 (22%)	1/7 (14%)	0/2 (0%)
Blinded assessor	54/60 (90%)	30/32 (94%)	8/10 (80%)	7/9 (78%)	7/7 (100%)	2/2 (100%)
Timing of measure of primary outcome						
Early (0–12 weeks)	37/60 (62%)	18/32 (56%)	9/10 (90%)	7/9 (78%)	3/7 (43%)	0/2 (0%)

(*continued on next page*)

Table 1 (*continued*)

Characteristic	Overall, N = 60[1]	All pSS manifestations, N = 32[1]	Dry eyes, N = 10[1]	Dry mouth, N = 9[1]	Fatigue, N = 7[1]	Other, N = 2[1]
Intermediate (13–26 weeks)	20/60 (33%)	12/32 (38%)	1/10 (10%)	2/9 (22%)	4/7 (57%)	1/2 (50%)
Late (>26 weeks)	3/60 (5%)	2/32 (6%)	0/10 (0%)	0/9 (0%)	0/7 (0%)	1/2 (50%)

Domains

The reported domains for all included publications mapped into core areas, as suggested by the OMERACT Filter 2.1, are displayed in Table 4.

Manifestations and abnormalities linked to pathophysiology of the disease

This core area encompasses domains involving pathophysiology of SjD, such as clinical signs and symptoms, imaging, and biomarkers, that can be seen as manifestations of the disease. We further divided signs and symptoms into three categories: (1) patient-reported symptoms; (2) objective clinical measures; (3) global assessment of disease activity. Among patient-reported symptoms, the most described domains were overall (n=31 publications), oral (n=25) and ocular (n=21) perceived dryness, fatigue (n=34), and pain (n=31). Those domains were mostly evaluated with ESSPRI, visual, analogical, or numeric scales, and/or specific questionnaires. The most frequently reported objective clinical domains were systemic disease activity (n=27, mainly assessed by the ESSDAI), and each organ involvements. Patient (n=16) and physician (n=8) global perception of disease activity were also assessed.

Three domains were related to glandular functions: lachrymal function (n=28), ocular surface involvement (n=16) and salivary function (n=33). Regarding biological domains, systemic inflammation (n=15), B-cell activation (n=36) and hematological activity (n=27) were assessed.

Three studies reported an imaging domain, assessing salivary morphological changes (by an ultrasound evaluation) [27,34,35]. In addition, three studies reported a histological domain, assessing the salivary gland inflammation [33,36,37].

Regarding harms, 41 studies reported the adverse effects of treatments, mainly in studies evaluating overall SjD manifestations (27/32; 84%), while they were reported in only 14 (50%) of the 28 other studies.

Impact of health conditions and life impact

This core area is identified by concepts such as health perception, well-being, and the ability to function independently. Consequently, the most reported domains were health-related quality of life (n=24), depression (n=6), anxiety (n=4), sexual life (n=2) and stress (n=1).

Longevity

No study assessed the survival rate of SjD but six studies reported the number of deaths due to adverse events related to the therapy.

Societal and resource use

This core area related to the impact of SjD on society and healthcare use. Two studies assessed the frequency of use medication (artificial drops for eye dryness) and one study assessed the cost-effectiveness of a treatment with rituximab compared with placebo [38].

Discussion

This is the first scoping review that aggregates all outcome domains that have been assessed in SjD RCTs, representing the first step of the "generating" phase in the OMERACT process of developing core domain sets. This review highlights the heterogeneity of SjD manifestations.

Regarding study designs, while most RCTs aimed at treating overall SjD manifestations, almost half of the studies focused on only one aspect of SjD, such as xerostomia, xerophthalmia, fatigue, or respiratory capacity. Accordingly, the assessed domains differed depending on the RCTs' focus. In addition, among RCTs focusing on all overall SjD manifestations, some studies restricted their eligibility criteria to SjD patients with systemic manifestations, either by ESSDAI threshold or by antibody positivity. This highlights the importance of eligibility criteria and patient stratification, tailoring therapy for the domains being evaluated and targeted.

Based on the results of this scoping review, we aggregated a list of relevant domains that have been used in RCTs to generate a preliminary OMERACT Core Domain Set. The domains were mapped to core concepts of pathophysiology/manifestations, impact of health condition, longevity, and resources. Within the domains linked to pathophysiology of the disease, we further classified the domains into patient-reported symptoms, clinical measures, global assessment of disease activity, glandular function, biological parameters, imaging, and histology, to cover the different aspect of SjD pathophysiology. This separation was important, as the glandular function (i.e., lacrimal or salivary function) does not always correlate with patient perception (i.e., perceived ocular or oral dryness) [39].

In addition, many domains were included in the life impact (mainly health-related quality of life) or resource use (i.e., medication use and direct costs) categories. On the other hand, no study evaluated survival rates or mortality. This could be explained by the relatively short duration of therapeutic trials compared with the low mortality rate and life expectancy of SjD patients, making it difficult to assess in RCTs. When mortality was assessed in RCTs, it was related to severe adverse events of the evaluated medication rather that the disease itself. The low number of studies clearly reporting mortality due to the intervention can be explained by the absence of death in most RCTs. Moreover, for the same reasons and because of their rarity, no trial has evaluated the occurrence of lymphoma during follow-up.

The high number of domains highlight the need for composite outcomes assessing all aspects of the disease, that are clinically impactful. Recently, two composite outcomes to capture the full spectrum of SjD domains have been developed: the Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS), based on the reanalysis of the ASAP-III study [40], and the composite Sjögren Tool for Assessing Response (STAR) index, developed a large number of 78 experts and 20 patients within the NECESSITY consortium, and based on reanalysis of 9 previous trials [41]. Both composite indexes considered the same 5 relevant domains: systemic activity (assessed by the clinESSDAI), patient-reported outcome (assessed by ESSPRI), lacrimal gland function (assessed by Schirmer's test or ocular staining score), salivary gland function (assessed by unstimulated whole salivary flow or ultrasound), and a biological domain (assessed by IgG or rheumatoid factor levels). The STAR has been developed with rigorous methodologies akin to OMERACT process, employing consensus techniques based on a large panel and on data-driven methods from the results of nine RCTs. The selected domains used for patients and experts' vote for the definition of a core set of outcome measures were similar to the domains included in the present review. The only frequently evaluated clinical domain not assessed by the STAR was health-related quality of life, a domain usually assessed separately as a secondary outcome in previous RCTs. This new instrument is currently being prospectively validated in 5 recent RCTs, and in a dedicated RCT led by the NECESSITY consortium.

We acknowledge some limitations to our study. First, we only selected RCTs, and excluded observational studies. However, the number and variety of selected studies provide a wide coverage of SjD manifestations. In addition, we used an artificial intelligence tool

Table 2
List of selected studies and their main assessed domains (n=60).

Author, Year	Intervention	ESSDAI threshold	Antibody positivity	Main assessed domains*
Overall manifestations				
Petrone et al., 2002 [42]	Cevilemine	No	No	Perceived oral dryness
Cummins et al., 2003 [43]	IFN-alpha	No	No	Salivary function
Mariette et al., 2004 [8]	Infliximab	No	No	Perceived dryness, pain, fatigue
Sankar et al., 2004 [44]	Etanercept	No	No	Perceived dryness
Gescuk et al., 2005 [36]	Lamivudine	No	No	Salivary function
Seitsalo et al., 2007 [45]	Low dose doxycyclin	No	No	Salivary function
Meijer et al., 2010 [46]	Rituximab	No	SSA+ only	Salivary function
Devauchelle et al., 2014 [7]	Rituximab **(TEARS)**	No	SSA+, RF+, or cryoglobulin+	Perceived dryness, pain, fatigue, and patient global assessment of disease activity
Gottenberg et al., 2014 [47]	Hydroxychloroquine **(JOQUER)**	No	No	Perceived dryness, pain, fatigue
Hu et al., 2014 [48]	Traditional Chinese Medicine (ShengJinRunZaoYangXue gran)	No	No	Lacrimal function
Yoon et al., 2016 [49]	Hydroxychloroquine	No	No	Ocular surface involvement
Bowman et al., 2017 [38]	Rituximab **(TRACTISS)**	No	SSA+ only	Perceived dryness, fatigue
Li et al., 2017 [50]	Traditional Chinese Medicine (JieDuTongLuoShengJin Granules)	Yes (<5)	No	Perceived dryness, pain, fatigue
Cifuentes et al., 2018 [51]	Pilocarpine drops (5 mg)	No	No	Salivary function
St Clair et al., 2018 [52]	Baminercept	No	No	Salivary function
Dörner et al., 2019 [53]	Ianalumab	Yes (≥6)	SSA+, RF+, or ANA+	Systemic disease activity
Liu et al., 2019 [54]	Traditional Chinese Medicine (total glucosides of peony)	No	SSA+, SSB+, or RF+	Perceived dryness, pain, fatigue
Fisher et al., 2020 [55]	Iscalimab	Yes (≥6)	SSA+ or RF+ or AAN+	Adverse effects of treatment
Jiang et al., 2020 [56]	Iguratimob	Yes (≥8)	SSA+ only	Systemic disease activity
Van der Heidjen et al., 2020 [32]	Leflunomide-hydroxychloroquine **(RepurpSS-I)**	Yes (≥5)	No	Systemic disease activity
van Nimwegen et al., 2020 [57]	Abatacept **(ASAP-III)**	Yes (≥5)	No	Systemic disease activity
Baer et al., 2021 [58]	Abatacept	Yes (≥5)	SSA+ only	Systemic disease activity
Chen et al., 2021 [59]	Traditional Chinese Medicine (Gan-Lu-Yin, Jia-Wei-Xiao-Yao-San, Suan-Zao-Ren-Tang and Ye-Jiao-Teng)	No	No	Perceived dryness, pain, fatigue
Felten et al., 2021 [60]	Tocilizumab **(ETAP)**	Yes (≥5)	No	Systemic disease activity
Juarez et al., 2021 [37]	Seletalisib	Yes (≥5)	SSA+ only	Systemic disease activity
Shao et al., 2021 [61]	Iguratimod	No	No	Perceived dryness, pain, fatigue
Bowman et al., 2022 [62]	Ianalumab	Yes (≥6)	SSA+ only	Systemic disease activity
He et al., 2022 [34]	Low dose IL2	Yes (≥5)	No	Systemic disease activity
Mariette et al., 2022 [33]	Belimumab rituximab	Yes (≥5)	No	Adverse effects of treatment, systemic disease activity
Price et al., 2022 [63]	Filgotinib/lanraplenib/tirabrutinib	Yes (≥5)	SSA+ only	Perceived dryness, pain, fatigue, and patient global assessment of disease activity, systemic inflammation
Shao et al., 2022 [64]	HCQ + herbal decoction	Yes (<10)	No	Traditional Chinese Medicine Syndrome Score
Zhou et al., 2022 [35]	Acupuncture	No	No	Perceived dryness, pain, fatigue, and patient global assessment of disease activity
Ocular dryness				
Tsifetaki et al., 2003 [65]	Pilocarpine	No	No	Perceived ocular dryness
Aragona et al., 2005 [66]	0.1% indomethacine eye drop	No	No	Ocular surface involvement
Aragona et al., 2013 [67]	Clobetasone butyrate drops	No	No	Perceived ocular dryness
Moscovici et al., 2015 [68]	0.03% tacrolimus drops	No	No	Ocular surface involvement
Cagini et al., 2017 [69]	Hyaluronic acid	No	No	Ocular surface involvement
Kang et al., 2020 [70]	Topical cyclosporin A nanoemulsion	No	No	Perceived ocular dryness
Felberg et al., 2021 [71]	Pilocarpine	No	No	Perceived ocular dryness

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Table 2 (*continued*)

Author, Year	Intervention	ESSDAI threshold	Antibody positivity	Main assessed domains*
Moawad et al., 2022 [72]	Tacrolimus drops	No	No	Ocular surface involvement
Qiu et al., 2013 [73]	Punctal plugs	No	No	Ocular surface involvement
Ngo et al., 2015 [74]	Lid Debridement	No	No	Ocular surface involvement
Oral dryness				
Alpöz et al., 2008 [75]	Xialine	No	No	Perceived oral dryness
Singh et al., 2010 [76]	Omega 3 & vitamin E	No	No	Salivary function
Da Silva Marques et al., 2011 [77]	Gustatory stimulants (malic acid)	No	No	Salivary function
Peric et al., 2015 [78]	Mouth pastes	No	No	Salivary function
Da Mata et al., 2020 [79]	Malic acid mouthwash	No	No	Perceived oral dryness
Fidelix et al., 2018 [80]	Laser therapy	No	No	Perceived oral dryness
Karagozoglu et al., 2018 [81]	Sialendoscopy	No	No	Salivary function
López-Pintor et al., 2019 [82]	Xerostom	No	No	Perceived oral dryness
Du et al., 2022 [83]	Irrigation of salivary glands	No	No	Perceived oral dryness
Fatigue				
Dass et al., 2008 [84]	Rituximab	No	SSA+ or SSB+	Fatigue
Hartkamp et al., 2008 [85]	DHEA	No	No	Fatigue
Virkki et al., 2010 [86]	DHEA	No	No	Fatigue
Norheim et al., 2012 [87]	Anakinra	No	No	Fatigue
Miyamoto et al., 2019 [88]	Supervised walking	No	No	Pulmonary involvement
Posada et al., 2021 [89]	RSLV-132 therapy -Rnase Fc fusion protein)	No	SSA+ only	Systemic involvement
Pinto et al., 2021 [90]	Transcranial direct current stimulation	No	No	Fatigue
Other				
Minali et al., 2020 [91]	Physical exercise	No	No	Pulmonary involvement
Garcia et al., 2021 [92]	Physical exercise	No	No	Pulmonary involvement

Abbreviations: ESSDAI = EULAR Sjögren Syndrome Disease Activity Index. *The main assessed domain was evaluated by the primary outcome of the study.

(BIBOT) to generate the initial list of articles for our study. Even though BIBOT had been proven to have excellent reliability [22], we further estimated its accuracy with a blind assessment of a random selection of references. The negative predictive values and sensitivity of BIBOT again proved to be excellent. Nevertheless, cross checking with reviews and meta-analyses led us to include two additional studies, that were missed by BIBOT, although they were selected by the initial search strategy. Finally, limitations of this study include the use of English-only publications and the exclusions of conference abstracts, thus excluding most recent RCTs. A strength of this study is the broad inclusion of RCTs covering different aspects of SjD, including systemic activity, dry eyes and dry mouth, or fatigue. This allows a better mapping to SjD-related domains.

Finally, this scoping review exclusively identified domains that have previously been evaluated in the existing literature. However, it does not encompass any potential additional domains of interest that may have gone unnoticed. Therefore, a qualitative study is imperative, involving elements such as a qualitative literature review, focus groups, and interviews with relevant stakeholder groups, including patients. This second phase of research is currently in progress as part of the OMERACT process.

In conclusion, this scoping review provided a wide range of SjD domains covering the heterogeneity of SjD manifestations. Along with qualitative work, this will enable the selection of the most appropriate domains to assess response treatment in patients with SjD. Table 2, Table 3

CRediT authorship contribution statement

Yann Nguyen: Writing, Conceptualization, Methodology, Data curation, Data analysis; **Maxime Beydon:** Writing, Conceptualization, Methodology, Data curation, Data analysis; **Nathan Foulquier:** Methodology, Data curation, Data analysis; **Rachael Gordon:** Writing – review & editing, Methodology, Data analysis; **Coralie Bouillot:** Writing – review & editing, Data analysis; **Kathy Hammitt:** Writing – review & editing, Data analysis; **Simon J Bowman:** Writing – review & editing, Data analysis; **Xavier Mariette:** Writing – review & editing, Data analysis; **Sara S McCoy:** Writing – review & editing, Conceptualization, Methodology, Data analysis; **Divi McCoy:** Writing – review & editing, Conceptualization, Methodology, Data analysis; **Raphaele Seror:** Writing, Conceptualization, Methodology, Data analysis.

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Declaration of competing interest

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Table 3
Concepts areas and domains for outcome measures in primary Sjögren syndrome (n=60).

Concepts Areas	Pathophysiology Manifestations/ Abnormalities	Impact of health conditions Life impact	Longevity	Societal/ Resource Use
Intended effects	**Signs and symptoms** ***Patient-reported symptoms*** Perceived dryness . Overall dryness (31) . Oral dryness (25) . Ocular dryness (21) . Vaginal dryness (5) . Cutaneous dryness (4) . Tracheal dryness (1) . Ocular comfort (7) . Mouth comfort (9) Fatigue (34) Pain (31) ***Objective clinical measures*** Systemic disease activity (27) . constitutional signs (27) . lymphadenopathy (27) . glandular involvement (27) . cutaneous involvement (27) . pulmonary involvement (29) . peripheral nervous system involvement (27) . central nervous system involvement (27) . muscular involvement (27) . renal involvement (27) . articular involvement (29) **Global assessment (disease activity)** Patient global perception of disease activity (16) Physician global perception of disease activity (8) **Glandular function** Lachrymal function (28) Ocular surface involvement (16) Salivary function (33) **Biological parameters** Systemic inflammation (15) B-cell activation (36) Hematological activity (27)	**Impact of manifestations on:** Health-related quality of life (24) Sexual life (2) Sleep quality (2) Depression (6) Anxiety (4) Stress (1)	Survival (0)	Medication use (2) Direct costs (1)
	Imaging Salivary gland morphological changes (3) **Histology** Minor salivary gland inflammation (3)			
Harms	**Other manifestations:** Adverse effects of treatments (41)		Mortality (6)	

(n): number of studies with evaluated domain.

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Supplementary materials

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