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A systematic literature review on patient-reported outcome domains and measures in nonsurgical efficacy trials related to chronic pain associated with endometriosis: an urgent call to action

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Abstract

Endometriosis, a common cause for chronic pelvic pain, significantly affects quality of life, fertility, and overall productivity of those affected. Therapeutic options remain limited, and collating evidence on treatment efficacy is complicated. One reason could be the heterogeneity of assessed outcomes in nonsurgical clinical trials, impeding meaningful result comparisons. This systematic literature review examines outcome domains and patient-reported outcome measures (PROMs) used in clinical trials. Through comprehensive search of Embase, MEDLINE, and CENTRAL up until July 2022, we screened 1286 records, of which 191 were included in our analyses. Methodological quality (GRADE criteria), information about publication, patient population, and intervention were assessed, and domains as well as PROMs were extracted and analyzed. In accordance with IMMPACT domain framework, the domain *pain* was assessed in almost all studies (98.4%), followed by *adverse events* (73.8%). By contrast, assessment of *physical functioning* (29.8%), *improvement and satisfaction* (14.1%), and *emotional functioning* (6.8%) occurred less frequently. Studies of a better methodological quality tended to use more different domains. Nevertheless, combinations of more than 2 domains were rare, failing to comprehensively capture the bio–psycho–social aspects of endometriosis-associated pain. The PROMs used showed an even broader heterogeneity across all studies. Our findings underscore the large heterogeneity of assessed domains and PROMs in clinical pain-related endometriosis trials. This highlights the urgent need for a standardized approach to both, assessed domains and high-quality PROMs ideally realized through development and implementation of a core outcome set, encompassing the most pivotal domains and PROMs for both, stakeholders and patients.

Keywords: Chronic pelvic pain, PROMs, Systematic literature research, Endometriosis, Core outcome set

1. Introduction

Endometriosis, affecting approximately 10% of women of reproductive age worldwide, is a chronic inflammatory disease of uncertain etiology and a common cause of chronic pelvic pain (CPP).[105,180,235] The prevalence may be underestimated because symptoms are very heterogeneous and complex, and surgical confirmation is necessary for definitive diagnosis with severity of symptoms not being related to the extent or location of disease found at surgery.[54,210] Hence, patients often face diagnostic delays of up to 7 to 9 years.[151,168,235] Typical symptoms, such as chronic noncyclical pelvic pain, dysmenorrhea, dyspareunia, and many other associations (including infertility), drastically affect physical and mental function, quality of life, as well as social and sexual well-being in the affected women.[151,185,235] Treatment options, both medical and surgical, are often insufficient or even fail in up to 50% of patients.[22,168] Ineffective treatment of chronic pain contributes to the burden of suffering for those affected.

When studying the efficacy of interventions for pain in general, the assessment of pain-related symptoms is crucial. Particularly

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chronic pain is inherently a bio–psycho–social disease.[164] Consequently, a variety of pain-related outcomes for trials have been recommended several years ago already as a minimum to be assessed,[67] and a very recent update can be found here.[33] However, in most pain-related studies, the domain *pain* (particularly the subdomain *pain intensity*) is the primary focus, whereas other domains are much less considered.[30,50] As a result, outcomes chosen to assess treatment response are often difficult to compare across trials. The outcomes often fail to encompass important aspects related to chronic pain, and their significance might be of less relevance to caregivers and patients themselves.

For a study to be beneficial and transferable to clinical practice, it is essential to identify the domains (and based on the domains, the corresponding patient-reported outcome measures [PROMs]) that are the most relevant (for all stakeholders, including the patients), the most suitable (based on psychometric properties and comprehensiveness), and the most feasible. However, this is often lacking in pain research, particularly in endometriosis-related studies, despite its multiple and complex symptoms.[149,235] The definition and implementation of a minimum standard set of domains and PROMs to be assessed in clinical studies on endometriosis, a Core Outcome Set (COS), could address these problems.[223] Previous work focusing on outcome measures used in surgical trials (plus or minus adjunctive medical therapies)[106] has recommended a COS on this basis.[66] However, the recommended COS focusses on fertility-related outcomes and much less on pain domains, particularly those recommended by IMMPACT for chronic pain trials.[67]

The main objective of this review was the investigation of domains and PROMs assessed in clinical trials evaluating the efficacy of nonsurgical pain-related interventions in patients with endometriosis. This work aimed to lay the groundwork for a more targeted assessment of pain-related outcomes in endometriosis-related pain trials and clinical practice by developing a COS of domains (followed by corresponding PROMs) specific to endometriosis.

2. Methods

This systematic literature review (SLR) was conducted as part of the Innovative Medicines Initiative (IMI) Pain Care Project (Improving the care of patients suffering from acute or chronic pain, Grant Agreement NR. 777500), following the Cochrane's methodology (Participants, Intervention, Comparator, Outcome, Study design) and in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA) 2009 guidelines.

This SLR was pre-registered at the International Prospective Register of Systematic Reviews (PROSPERO) (Registration Number 147765, 12/2019, update 05/2021).

2.1. Inclusion and exclusion criteria

The inclusion and exclusion criteria were defined following the PICOS criteria (P, population; I, intervention; C, comparison; O, outcome; S, study design[137]). Only peer-reviewed, randomized controlled trials evaluating the effectiveness of pharmacological and nonpharmacological pain management for chronic pelvic pain associated with endometriosis were included. When screening studies for inclusion, particular attention was given to ensure that participants had experienced symptomatic pain related to endometriosis for a minimum duration of ≥3 months. Trials investigating primary surgery as an intervention were not considered because differentiation between diagnostic and treatment studies is difficult. Eligible interventions were systemic (oral and intravenous) or topical (eg, subcutaneous and cutaneous) medication, additionally, nonpharmacological treatments, such as acupuncture, physiotherapy, or psychotherapy were included if pain was a primary target of the intervention. All interventions were eligible if they either had a duration of ≥2 weeks or, for single administrations of drugs with long-term efficacy (such as hormonal depot application), if the follow-up was ≥2 weeks.

According to the current International Association for the Study of Pain (IASP) and ICD-11 definition, chronic pelvic pain was defined as pain with a duration of 3 months or longer.[206] Only studies in English, French, or German language were included.

Studies investigating less than 20 patients, patients younger than 18 years, or conditions other than chronic pelvic pain related to endometriosis without subgroup analysis were excluded. Ongoing studies, retrospective studies, and studies that were only published as abstracts were also excluded.

The inclusion and exclusion criteria are summarized in **Table 1**.

2.2. Search strategy

The MEDLINE, CENTRAL, and Embase electronic databases were electronically searched from the inception date of the respective database to July 2022. The database-specific search strings are shown in the supplemental digital content. Additional records were identified by an additional citation searching from the reference lists of included articles ("hand/citation search").

2.3. Screening of studies

All identified possibly eligible studies were screened after exclusion of duplicates, using titles and abstracts by 5 independent reviewers (I.S., D.R., E.M., K.S., and F.F.) in a double-blinded manner by use of the RAYYAN program (https://rayyan.qcri.org/). Thereby, every abstract was evaluated by at least 2 reviewers. Then, full-text screening, data extraction and grading of study quality was conducted by the same 4 reviewers with an overlap of ≥20% of studies extracted by more than one reviewer (differences in extraction were discussed and resulted in refinement of extraction criteria applied by all reviewers on all extractions). In case of disagreement during the process that could not be resolved by discussion, the principal investigator of this study (E.P.Z.) was involved for a final decision.

2.4. Data collection

The following data were gathered from the included studies: (1) study characteristics (first author, publication year, pharmaceutical funding, country of study conduction, study design, number of investigated patients, and a description of study population including mean disease duration, mean pain duration, and age), (2) information on interventions and comparators used (investigated treatment, comparators, methods, and duration of administration), and (3) all outcome parameters. A detailed list of extracted data is given in supplemental digital content (see Table 1, http://links.lww.com/PAIN/C69).

All domains assessed with specific PROMs and the PROMs used (eg, completely used, short form, incompletely used, modified, self-constructed, description and reference article, and time points of assessment) were extracted. Patient-reported outcome measures were categorized and aggregated under their domains as recommended by the Core Outcome Measures in Effectiveness Trials (COMET) initiative (an initiative that fosters methodological research in this area[222]) and, more recently, by Young et al.[228] Content wise, the domains recommended by IMMPACT for chronic pain (including *pain, physical functioning*,

Table 1

Inclusion and exclusion criteria.

Category	Inclusion	Exclusion
Formal	Article written in English, German, or French Abstract and full text available Completed study (peer-reviewed)	Foreign language (other than English, German, and French) No abstract or full text available Ongoing study Duplicate
Population (P)	Chronic pelvic pain of ≥3 mo duration, related to endometriosis (including disease duration with painful symptoms ≥3 mo) No. of patients ≥20 Age ≥18 y	Not chronic pain (<3 mo duration) Diseases other than endometriosis Children, animals
Intervention (I)	Topic or systemic drugs, or nonpharmacological treatment Treatment duration ≥2 wk or follow-up ≥2 wk in case of drugs with long-term efficacy	Treatment duration <2 wk No pain management
Comparison (C)	Not applicable	No limitations
Outcome (O)	Patient-reported outcome measures (PROMs) used	Proxy-/clinician-reported outcomes, objective measures Pain not assessed
Study design (S)	Randomized-controlled trial Original article	Observational study/retrospective analysis Review article

mo, months; wk, weeks; y, years

emotional functioning, participant ratings of improvement and satisfaction with treatment (short: improvement and satisfaction), and *adverse events*) were considered a major guide for subgrouping PROMs.[67] However, potential other domains were considered as well. The domain *participant disposition*[67] was addressed by extracting general information about the included studies (eg, recruitment and patients lost to follow-up) and evaluating this information in the context of risk of bias grading.

To cover the different aspects of the domain *pain*, PROMs within this domain were further divided in the subdomains *pain intensity scales*, *pain intensity other* (ie, questionnaires rating p*ain intensity* by other measures, such as *daily activity* or *analgesic intake*) and *other aspects of pain*. Accordingly, the domain *physical functioning* was subdivided into *daily activity*, *sleep*, and *generic measures of health-related quality of life* (HRQOL). Measures for health-related quality of life addressing *physical functioning* and *emotional functioning* specifically were assigned in these categories. Patient-reported outcome measures covering other aspects were also extracted, as well as questionnaires or scales to assess other symptoms, adverse events, and rescue medication.

The risk of bias was evaluated for each study according to the GRADE guidelines[95,113] and rated as "fulfilled" (no limitation), "not fulfilled" (crucial limitation), and "not clear" (some limitation) for the criteria lack of allocation concealment, lack of blinding, incomplete accounting of patients and outcome events, selective outcome reporting bias, stopping early for benefit, use of nonvalidated outcome measures, and the carryover effect in cross over trials. The criteria for rating each item were defined precisely to guarantee that all reviewers graded as similarly as feasible (supplemental digital content, Table 2, http://links.lww.com/PAIN/C69). The quality of each study was then classified in 3 categories, "high," "moderate," and "low". High quality was defined as a low risk of bias for all GRADE criteria. Moderate quality allows for either one crucial limitation for one criterion and/or some limitations for ≥ one criterion. Low quality was defined as a crucial limitation for more than one criterion or a crucial limitation for one criterion and some limitation for multiple criteria.

Finally, to evaluate the quality of endometriosis-specific PROMs, the development process of PROMs used in around 10% of the trials or more was assessed according to the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) initiative recommendation risk of bias checklist, box 1.[162,204] The checklist consists of 35 items, which were assessed by 2 independent raters (DCR and EPZ) for the Biberoglu and Behrman scale (used in ~30% of all trials) and the Endometriosis Health Profile Questionnaire (EHP-30, used in ~10% trials) by using the respective inauguration/development articles.[29,117]

2.5. Data analysis

Data analysis was primarily descriptive as the aim of this SLR was to identify domains and PROMs used in clinical trials on chronic pelvic pain associated with endometriosis. First, all PROMs were listed within the appropriate domain. Second, for each study, the number of domains and PROMs per domain were listed. Third, PROMs and number of domains were compared for different study groups based on study quality and publication year (before or after publication of the IMMPACT recommendations for chronic pain trials).[67]

Statistical analysis was performed using IBM SPSS statistics for Windows (version 23.0, NY).

3. Results

The PRISMA flowchart of the literature search is shown in **Figure 1**. In total, 1315 potentially eligible records were identified through database searching (MEDLINE, Embase, and CENTRAL). In addition, 57 articles were identified by hand/citation search. After removing all duplicates, 1286 abstracts were screened according to the predefined inclusion and exclusion criteria. After resolving all disagreements, 310 full-text articles were assessed for eligibility. Finally, 189 publications met the inclusion criteria and were included in the SLR. Two articles, comprising results of more than one study, were considered and extracted as 2 separate studies each. Thus, the final number of analyzed studies was 191.

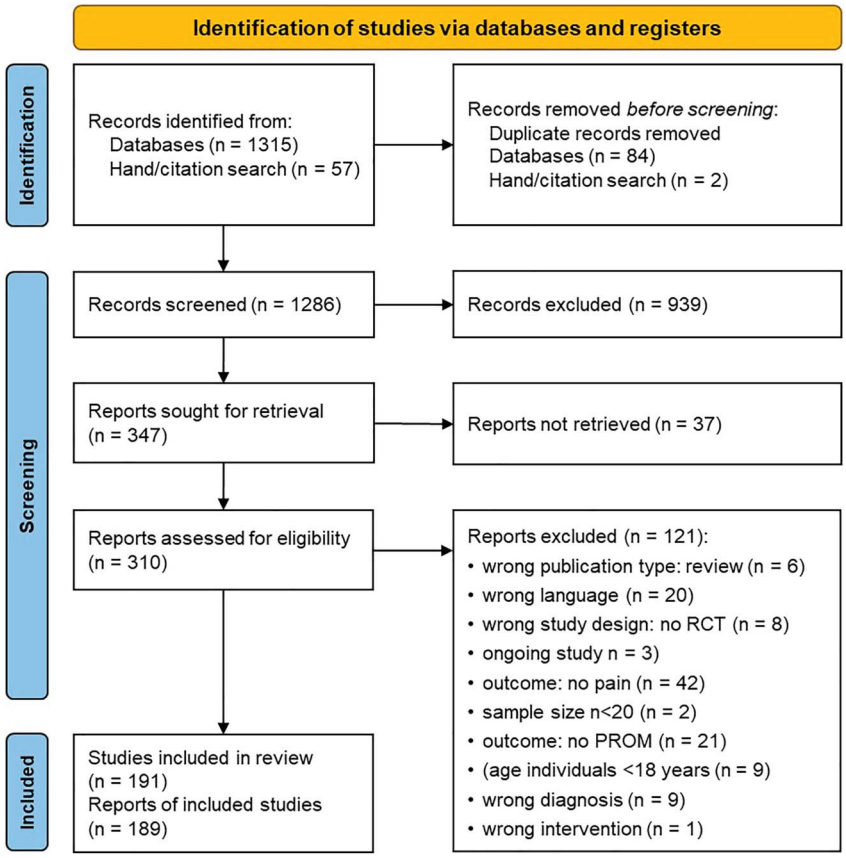

Figure 1. PRISMA Flowchart of included studies.

3.1. Descriptive analysis of study characteristics

A total of 191 studies were included in the analysis. Approximately half of these studies (101, 52.9%) were double-blinded RCTs with a parallel-group design. 83 studies (43.5%) had an open-label phase after randomization or single-blind (8, 4.6%) phase, mostly due to the form of intervention (eg, injections vs oral medication), whereas only 2 studies had a cross-over design and 4 studies had a different or not clearly defined study design. Almost half of the studies (78, 40.8%) were sponsored or initiated by a pharmacological company, and in 64 studies (33.5%), no conflict of interest was stated, whereas in 49 studies (25.7%), this information was missing. In 49 studies (25.7%), pain assessment was defined as the only primary outcome, further 20 studies (10.5%) defined it as one of the primary outcomes, while 27 studies (14.1%) assessed it as a secondary outcome. In 91 studies (47.6%), the primary outcome was not defined, and 4 studies (2.1%) defined primary and secondary outcomes, but pain assessment was not a part of it.

Included patients were exclusively female and most frequently in the age group of 30 to 40 years (102, 53.4%), followed by 18 to 29 years (20, 10.5%). In 32 studies (16.8%), the intervention groups differed in age. Most of the patients included in the studies had previously undergone diagnostic (102, 53.4%) or therapeutic surgery (48, 25.1%) to confirm the diagnosis (endometriosis). 25 studies (13.1%) specifically defined chronic pelvic pain ≥3 months and 29 studies (15.2%) described the pain as "chronic" or "recurrent" for inclusion. In all other studies (137, 71.7%) for the included patients, a disease duration ≥3 months (including painful symptoms) was given.

Most interventions studied in the trials were hormonal treatments, including GnRH receptor antagonists (162, 84.8%). Only 6 studies (3.1%) used analgesics, 10 (5.2%) used other drugs, and 21 (11.0%) used nonpharmacological treatments. Of 22 studies combining interventions, 20 were combined with hormonal treatment. In total, 69 studies (36.1%) were placebo-controlled, while 123 studies (64.4%) used a hormonal treatment or other pharmacological (2, 1.0%) or nonpharmacological comparators (8, 4.2). 42 studies (22.0%) had more than one comparator arm.

A detailed list of study characteristics is given in supplemental digital content (see table 3, http://links.lww.com/PAIN/C69).

3.2. Quality-dependent analysis

All included studies were graded according to the risk of bias GRADE criteria[95,113] (supplemental digital content, Table 2, http://links.lww.com/PAIN/C69). More than half of the studies (113, 59.2%) were of a moderate-to-high methodological quality, while the rest (78, 40.8%) were of low methodological quality. GRADE for each study is shown in supplemental digital content (see Table 4, http://links.lww.com/PAIN/C69).

3.3. Analysis of domains and patient-reported outcome measures

The outcome assessment items (ie, PROMs) used within the included studies were sorted according to the IMMPACT domains *pain* (including the subdomains *pain intensity [scales]*, *pain intensity other, pain relief, pain other aspects*, and *rescue medication*), *emotional functioning*, *physical functioning*

Table 2

IMMPACT—Core DOMAINs (Pain, Emotional Functioning, Physical Functioning, Satisfaction, and Adverse events) and subdomains assesses by each study included in this SLR

Studies				Pain				Physical functioning						
Ref	First author	year of publication	Grading: Quality	Pain intensity	Pain other items	Rescue medication	Emotional functioning	General measures HRQOL	Sleep	Daily activity	Other aspects	Satisfaction	Adverse events
103	Healy, D. (ZOLADEX)	1996	Low	●									●
70	Elstein, M. (NEET)	1992	Low	●		●							●
1	Abdou, A	2018	High	●									●
2	Abokhrais, I	2020	High	●	●	●	●	●		●	●		●
3	Acién, P	2003	High	●									
4	Acién, P	2021	High	●		●							●
5	Àcs, N	2015	High	●	●	●		●					●
6	Adamson, G	1994	High	●									
8	Agarwal, S	2015	Low	●	●	●		●			●		●
9	Agarwal, S	1997	High	●		●							●
10	Alborzi, S	2007	Low	●	●								
11	Alborzi, S	2011	Low	●									
12	Alborzi, S	2019	High	●									
13	Alkatout, I	2013	Low		●								
14	Almassinokiani, F	2013	High	●									●
15	Amirsalari, S	2021	High	●									
18	Audebert, A	1998	Low		●								●
19	Audebert, A	1997	Low		●	●							●
20	Badawy, A	2012	Low		●								●
21	Bayoglu Tekin, Y	2011	Low	●	●							●	●
23	Beissner, F	2018	Low	●		●	●	●					
26	Bergqvist, A	1997	High	●		●							●
25	Bergqvist, A	1998	High	●	●	●							●
24	Bergqvist, A	2000	Low	●		●							●
27	Bergqvist, A	2001	Low		●	●	●	●	●		●		●

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Table 2 (*continued*)

Studies			Grading: Quality	Pain			Emotional functioning	Physical functioning				Satisfaction	Adverse events
Ref	First author	year of publication		Pain intensity	Pain other items	Rescue medication		General measures HRQOL	Sleep	Daily activity	Other aspects		
28	Bianchi, S	1999	Low		●								●
35	Bromham, D. (b)	1995	High	●									●
34	Bromham, D. (a)	1995	High	●									●
36	Burry, K	1989	Low		●								●
37	Busacca, M	2001	Low	●	●								●
39	Carpenter, S	1995	Low		●								●
40	Carr, B	2014	High	●	●	●		●					●
41	Carr, B	2013	High		●	●		●				●	●
42	Caruso, S	2022	High	●				●			●		●
43	Carvalho, N	2018	High	●		●		●					●
44	Ceccaroni, M	2021	High	●									●
47	Cheewadhanaraks, S	2009	High	●	●							●	●
46	Cheewadhanaraks, S	2012	High	●	●							●	●
45	Cheewadhanaraks, S	2013	High	●									
48	Chen, Y	2017	High	●		●							●
49	Cheng, M	2005	Low	●									●
51	Cirkel, U	1995	Low		●								●
53	Cobellis, L	2004	High	●		●						●	●
52	Cobellis, L	2011	High	●	●								●
55	Cosson, M	2002	Low	●									●
57	Crosignani, P	2006	Low		●			●		●		●	●
56	Crosignani, P	1996	Low		●								●
58	da Mendes Silva, D	2017	High	●		●							●
60	Diamond, M	2014	High	●	●	●		●				●	●
61	Dlugi, A	1990	Low		●	●							●

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Table 2 (*continued*)

Studies			Grading: Quality	Pain			Emotional functioning	Physical functioning				Satisfaction	Adverse events
Ref	First author	year of publication		Pain intensity	Pain other items	Rescue medication		General measures HRQOL	Sleep	Daily activity	Other aspects		
62	Dmowski, W	1989	Low	●									●
64	Donnez, J	2004	Low		●								●
65	Donnez, J	2020	High	●	●	●		●		●		●	●
68	Edelstam, G	2012	Low	●									
69	El Taha, L	2021	High	●	●	●		●					●
72	Fedele, L	1989	Low		●								●
75	Fedele, L	1989	Low		●								●
73	Fedele, L	1993	Low		●								●
74	Fedele, L	1999	Low		●								●
76	Fernandez, H	2004	High		●	●							●
77	Ferreira, R	2010	High	●									
78	Ferrero, S	2011	Low	●	●	●						●	●
79	Flower, A	2011	High	●		●		●			●		●
80	Fraser, I	1991	High	●		●							●
81	Freundl, G	1998	Low	●									●
83	Gerlinger, C	2010	High	●		●						●	
85	Ghahiri, A	2012	Low	●									
88	Giannini, A	2015	High	●									●
89	Gomes, M	2007	High	●									
90	Gonçalves, A	2016	High	●				●					
91	Gong, L	2015	High	●									●
92	Granese, R	2015	High	●				●					●
94	Gregoriou. G	1997	Low	●									●
96	Guzick, D	2011	High	●	●		●				●		●
97	Halbe, H	1995	Low		●	●							●
100	Harada, T	2008	High	●	●								●
99	Harada, T	2009	High	●		●		●					●

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Table 2 (*continued*)

Studies			Grading: Quality	Pain			Emotional functioning	Physical functioning				Satisfaction	Adverse events
Ref	First author	year of publication		Pain intensity	Pain other items	Rescue medication		General measures HRQOL	Sleep	Daily activity	Other aspects		
98	Harada, T	2017	High	●		●			●	●		●	●
101	Harada, T	2022	Low	●	●	●		●		●			●
102	Harrison, R	2000	High			●							●
104	Henzl, M	1988	High	●									●
110	Hornstein, M	1995	High		●								
109	Hornstein, M	1998	High		●								●
108	Hornstein, M	1997	Low		●								
112	Howell, R	1995	Low		●								●
114	Huang, C	2018	Low	●									●
115	Itoh, H	2011	High	●	●								●
118	Kamencic, H	2008	Low		●	●							●
119	Kennedy, S	1990	High	●									●
120	Khodaverdi, S	2019	High	●		●							
121	Kiilholma, P	1995	High	●									
123	Köhler, G	2010	Low		●	●							●
124	Koninckx, P	2008	High	●	●	●							●
145	Mukhopadhyay, P	2018	Low	●									●
125	Lalchandani, S	2005	Low	●									
126	Lang, J	2017	High	●	●	●		●				●	●
127	Leyland, N	2019	High		●	●		●					●
128	Ling, F	1999	High	●	●	●	●		●				●
129	Loverro, G	2008	Low		●								
130	Low, R	1984	High	●									●
132	Mäkäräinen, L	1996	High	●									●
134	Margatho, D	2018	High	●									
133	Margatho, D	2020	High	●									
135		2021	High	●		●		●					●

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Table 2 (*continued*)

Studies			Grading: Quality	Pain			Emotional functioning	Physical functioning				Satisfaction	Adverse events
Ref	First author	year of publication		Pain intensity	Pain other items	Rescue medication		General measures HRQOL	Sleep	Daily activity	Other aspects		
	Mehdizadeh Kashi, A												
136	Meissner, K	2016	High	●		●	●	●			●		
138	Mettler, L	2014	Low		●								
139	Miller, J	2000	High	●				●					●
140	Mira, T	2015	High	●	●			●					
141	Mira, T	2020	Low	●		●		●			●		●
142	Moghissi, K	1998	High	●									●
143	Moreira, M	2022	Low	●	●	●	●	●					●
144	Morgante, G	1999	Low	●									●
147	Muzii, L	2000	Low	●									
146	Muzii, L	2011	High	●								●	●
148	Niakan, G	2021	High	●				●					●
150	Nieto, A	1996	Low	●									●
152	Odukoya, O	1995	Low		●								
153	Osuga, Y (a)	2021	High	●	●	●		●					●
154	Osuga, Y (b)	2021	High	●	●	●		●					●
155	Overton, C	1994	High	●		●							●
157	Parazzini, F	1994	Low	●	●	●							
156	Parazzini, F	2000	Low	●	●	●							
158	Parker, J	2006	Low	●									
159	Petta, C	2005	High	●			●						●
160	Pokrzywinski, R	2020	High		●	●		●		●			
161	Pokrzywinski, R	2020	High	●	●	●						●	
165	Razzi, S	2007	Low	●									●
166	Regidor, P	2001	Low		●								●
167	Rock, J	1993	Low	●									●
169	Roghaei, M	2010	Low	●									●

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Table 2 (*continued*)

Studies			Grading: Quality	Pain			Emotional functioning	Physical functioning				Satisfaction	Adverse events
Ref	First author	year of publication		Pain intensity	Pain other items	Rescue medication		General measures HRQOL	Sleep	Daily activity	Other aspects		
171	Rotondi, M	2002	Low	●				●					●
172	Rubi-Klein, K	2010	High	●		●		●					
173	Rukhliada, N	2020	Low	●				●					
59	Del Salinas-Asensio, M	2022	Low	●	●		●	●	●		●		
175	Santanam, N	2013	Low	●				●					
176	Schlaff, W	2006	Low		●			●		●		●	●
177	Schwertner, A	2013	High	●		●	●	●	●				●
178	Seracchioli, R	2010	High	●									
179	Sesti, F	2007	High	●				●					●
182	Shaw, R	1990	High		●								●
183	Shaw R	1992	Low	●									●
181	Shaw, R	2001	High	●									●
184	Shokeir, T	2015	High	●								●	●
186	Soysal, S	2004	High		●								●
187	Stratton, P	2008	High	●	●			●					●
189	Strowitzki, T	2010	High	●	●	●		●					●
188	Strowitzki, T	2010	High	●	●	●		●				●	●
190	Strowitzki, T	2012	High	●	●			●					●
192	Surrey E	1992	Low	●									●
191	Surrey, E	2002	High		●								
193	Surrey, E	2019	High	●		●					●		●
194	Takaesu, Y	2016	Low	●	●								●
195	Takenaka, M	2015	Low	●									
196	Tang, H	2017	Low		●								●
197	Tanmahasamut, P	2012	High	●		●		●				●	●
198	Tanmahasamut, P	2017	High	●		●						●	●

(*continued on next page*)

Table 2 (*continued*)

Studies			Grading: Quality	Pain			Emotional functioning	Physical functioning				Satisfaction	Adverse events
Ref	First author	year of publication		Pain intensity	Pain other items	Rescue medication		General measures HRQOL	Sleep	Daily activity	Other aspects		
199	Taskin, O	1997	High	●									●
200	Taylor, H	2017	High	●	●	●		●				●	●
200	Taylor, H	2017	High	●	●	●		●				●	●
201	Teixeira, M	2017	High	●		●	●	●					●
202	Telimaa, S	1987	High	●	●								●
203	Telimaa, S	1987	High	●									●
205	Thabet, A	2018	Low	●	●			●					
208	Trummer, D	2017	High	●	●	●						●	●
209	Vercellini, P	1999	Low		●								
212	Vercellini, P	2002	High	●	●		●	●			●	●	●
211	Vercellini, P	2003	High	●	●							●	●
216	Vercellini, P	1994	Low	●	●								●
213	Vercellini, P	1996	High	●	●								●
217	Vercellini, P	1996	High	●	●							●	●
214	Vercellini, P	2005	High	●	●	●						●	●
215	Vercellini, P	1993	High	●	●								●
218	Walch, K	2009	High	●		●						●	●
219	Wheeler, J	1992	Low		●	●							
220	Wickström, K	2012	High	●	●	●							●
221	Wickström, K	2013	High	●		●		●					●
224	Wong, A	2004	High		●								●
225	Wong, A	2010	High		●								●
226	Xue, H	2016	Low	●									●
227	Ylänen, K	2003	High	●									●
232	Zhao, S	1999	Low		●			●					●
231	Zhao, R	2013	High					●					●
229	Zhao, L	2012	High				●	●					●

(*continued on next page*)

Table 2 (*continued*)

Studies			Grading: Quality	Pain			Emotional functioning	Physical functioning				Satisfaction	Adverse events
Ref	First author	year of publication		Pain intensity	Pain other items	Rescue medication		General measures HRQOL	Sleep	Daily activity	Other aspects		
230	Zhao, R	2013	Low		●								●
233	Zhao, Yi	2021	High	●									●
234	Zhu, S	2014	High	●									●
236	Zupi, E	2004	Low	●				●					●
38	Carbonell, J	2016	High	●		●		●					●
122	Kitawaki, J	2008	Low	●									●
170	Rolland, R	1990	Low		●								●

● Domain was assessed.

(including *generic measures of HRQOL, daily activity, sleep,* and *physical functioning other aspects*), *improvement and satisfaction*, and *adverse events*.[67] **Table 2** summarizes the assessed domains for each individual study included in the analysis. The following section will focus first on domains across all included studies, followed by the PROMs used to assess the domains.

3.4. Domains

The domain *pain* was assessed in almost every study (188, 98.4%) and the domain *adverse events* (and side effects) in almost 3/4 of the studies (144 studies, 73.8%). By contrast, other domains were assessed much less frequently (**Figure 2A**, **Table 2**): *physical functioning* in only 57 studies (29.8%), *improvement and satisfaction* in only 27 studies (14.1%), and *emotional functioning* in only 13 studies (6.8%) (**Figure 2A**, **Table 2**).

Comparing the studies with high/moderate methodological quality to those with low quality, we found some differences related to domains assessed. Overall, an average (±SD) of 2.3 ± 0.9 domains were assessed, but the number of domains assessed was slightly higher (2.5 ± 0.9 domains) for studies of moderate-to-high methodological quality as compared with studies of low quality (2.0 ± 0.8 domains). Sixteen studies of high/moderate quality, but only 4 of low quality, investigated 4 or 5 domains. Similarly, of those studies using 3 domains or more (65 studies [34.0%]), 51 studies (45.1%) were of high/moderate quality and 14 (17.9%) of low quality (**Figure 2A** and supplemental digital content, Fig. 1, http://links.lww.com/PAIN/C69). The subdomain *pain intensity* was used more frequently in studies of high quality than in studies of low quality (87.6% vs 57.7%). *Physical functioning* was used in 38.9% of all high/moderate-quality studies, but only in 16.7% of all low-quality studies. *Emotional functioning* was assessed in slightly more studies of high/moderate quality (8.0% vs 5.1%). For the subdomains *sleep, daily activity*, *and other aspects*, there were only slight differences as both were hardly used at all. *Improvement and satisfaction* was examined more frequently in high/moderate-quality studies compared with low-quality studies (20.4% vs 5.1%). Regarding *adverse events*, there was only a slight difference between high/moderate-quality and low-quality studies (80.5% vs 71.8%).

Combinations of used domains varied widely between studies. The most frequent combinations were *pain* and *adverse events* (77.0% of all studies, 80.5% of high/moderate quality, and 71.8% of low methodological quality), followed by *pain* and *physical functioning* (29.8% of all studies, 38.9% of high/moderate quality, and 16.7% of low methodological quality; see **Figure 2B**). The most frequent combinations of 3 domains assessed together were *pain*, *adverse events*, and *physical functioning* (47 studies, 24.6%, 33.6% of high/moderate quality, 11.5% of low methodological quality), as well as *pain*, *adverse events*, and *improvement and satisfaction* (25 studies, 13.1%, 18.6% of high/moderate quality, 5.1% of low methodological quality), followed by *pain* with *emotional* and *physical functioning* (12 studies, 6.3%, 7.1% of high/moderate quality, 5.1% of low methodological quality) and *pain, improvement and satisfaction*, and *physical functioning* (12 studies, 6.3%, 8.9% of high/moderate quality, 2.6% of low methodological quality) (Fig. 2B). Combination of 4 domains was rare. *Pain, improvement and satisfaction, physical functioning*, and *adverse events* were assessed in 12 studies together (6.3%, 8.9% of high/moderate quality, 2.6% of low methodological quality), followed by *pain*, *emotional* and *physical functioning*, and *adverse events* in 9 studies (4.7%, 6.9% of high/moderate quality, 2.6% of low methodological quality). Only 2 studies assessed all 5 domains

(1 study of high/moderate quality and 1 of low methodological quality). A detailed overview of the distribution of the domains is summarized in **Table 2** and combination of used domains over all studies is summarized in **Table 3**.

3.5. Patient-reported outcome measure related to the 5 IMMPACT domains

Patient-reported outcome measures used to assess the above-mentioned domains are summarized in **Table 4**. Results will be presented for each domain separately here.

For the domain *pain* (n = 188, 98.4%, **Table 4**), a variety of different PROMs were used (**Table 4**). To assess *pain*, in general, 129 studies (67.5%) used one PROM, 46 studies (24.1%) used 2 PROMs, 12 studies (6.3%) used 3 PROMs, and 2 studies (1.0%) used 4 PROMs. Most of these studies assessed *pain* through instruments, which can be categorized into the subdomain *pain intensity* (144, 75.4%). The most frequently used PROMs for *pain intensity* were visual analog scales (VAS; 98 studies, 51.3%), followed by verbal rating scales (VRS; 35 studies, 18.3%) and numeric rating scales (NRS; 16 studies, 8.4%). For *pain intensity*, 12 studies (6.3%) used 2 PROMs and 2 studies (1.0%) used 3

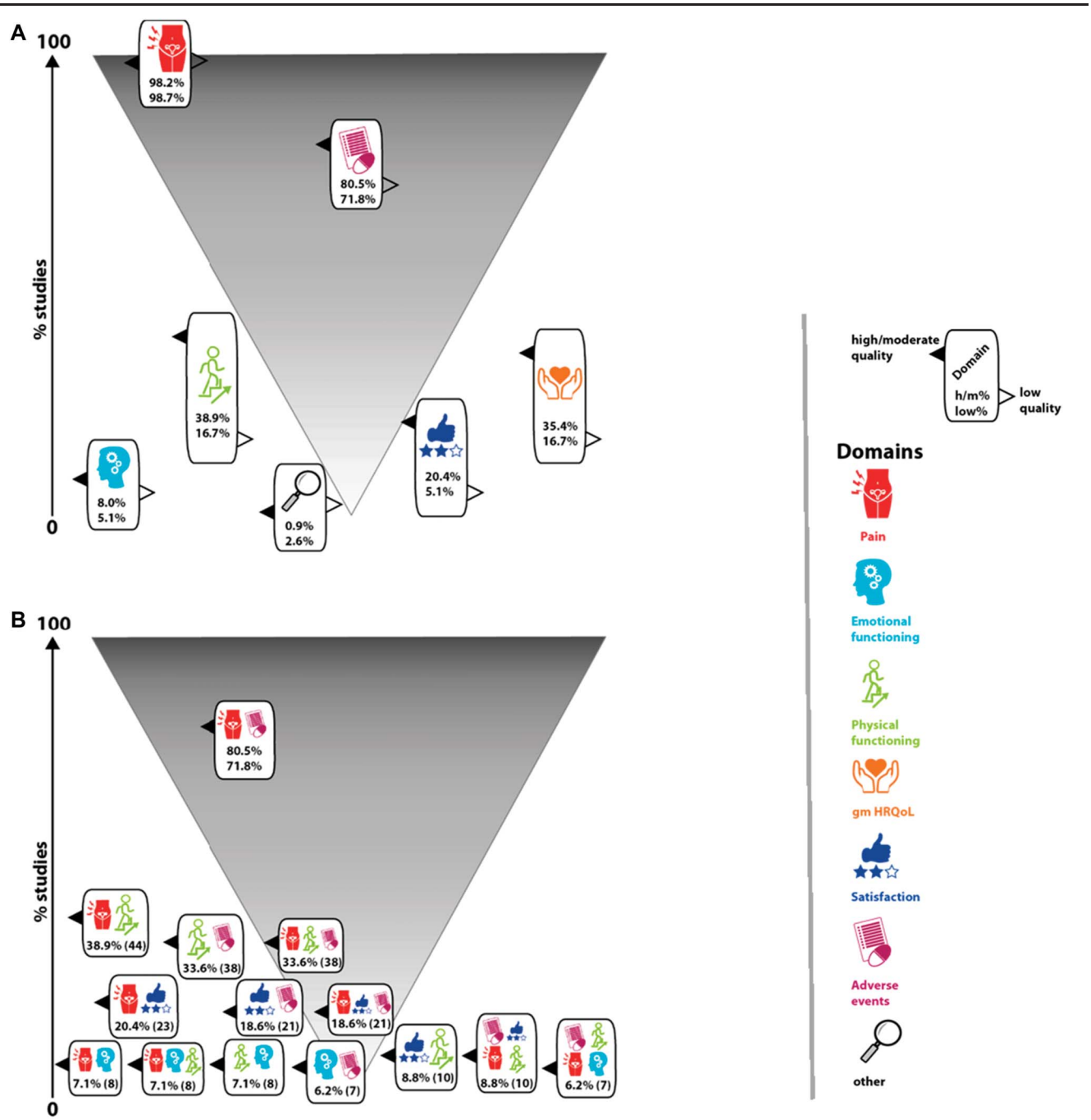

Figure 2. (A) Occurrence of domains assessed in studies on management of endometriosis-related pain (n = 191) (% of studies, see indicator on the left side of the boxes [black triangle, upper number] for studies of moderate to high methodological quality [h/m] and indicator on the right side [empty triangle, lower number] for studies of low methodological quality [low]); (B) combinations of domains in these studies (% of studies [and total numbers]). For better readability, only studies of moderate to high methodological quality and combinations that were used more than once are included in graph (B). If a combination of three domains is congruent with a combination of four domains, only the combination of four domains is shown. For more details see Table 3. gmHRQoL, general measures of health related quality of life.

Table 3

Combination of domains assessed within the same studies (n [%]).

	Used as PROM		
	All studies (n = 191)	Studies of high/moderate quality (n = 113)	Studies of low quality (n = 78)
Combination of 2 domains			
Pain and			
Emotional functioning	12 (6.3)	8 (7.1)	4 (5.1)
Physical functioning	57 (29.8)	44 (38.9)	13 (16.7)
Improvement and satisfaction	27 (14.1)	23 (20.4)	4 (5.1)
Adverse events	147 (77.0)	91 (80.5)	56 (71.8)
Emotional functioning and			
Physical functioning	12 (6.3)	8 (7.1)	4 (5.1)
Improvement and satisfaction	1 (0.5)	1 (0.9)	0
Adverse events	9 (4.7)	7 (6.2)	2 (2.6)
Physical functioning and			
Improvement and satisfaction	12 (6.3)	10 (8.8)	2 (2.6)
Adverse events	47 (24.6)	38 (33.6)	9 (11.5)
Improvement and satisfaction and			
Adverse events	25 (13.1)	21 (18.6)	4 (5.1)
Combinations of 3 domains			
Pain, emotional functioning, and			
Physical functioning	12 (6.3)	8 (7.1)	4 (5.1)
Improvement and satisfaction	1 (0.5)	1 (0.9)	0
Adverse events	9 (4.7)	7 (6.2)	2 (2.6)
Pain, physical functioning, and			
Improvement and satisfaction	12 (6.3)	10 (8.8)	2 (2.6)
Adverse events	47 (24.6)	38 (33.6)	9 (11.5)
Pain, improvement and satisfaction, and adverse events	25 (13.1)	21 (18.6)	4 (5.1)
Combination of 4 or more domains			
Pain, emotional functioning, physical functioning, and adverse events	9 (4.7)	7 (6.2)	2 (2.6)
Pain, physical functioning, improvement and satisfaction, and adverse events	12 (6.3)	10 (8.8)	2 (2.6)
Pain, emotional functioning, improvement and satisfaction, and adverse events	1 (0.5)	1 (0.9)	0
Pain, emotional functioning, physical functioning, and improvement and satisfaction	1 (0.5)	1 (0.9)	0
Pain, emotional functioning, physical functioning, improvement and satisfaction, and adverse events	1 (0.5)	1 (0.9)	0

PROMs. Other PROMs that assessed *pain intensity* by using a scale that evaluates pain intensity through surrogate parameters were summarized as *pain intensity other*. These were used in 67 studies (35.1%; 10 studies [5.2%] used 2 PROMs). A prominent example of such composite measures specific for endometriosis is the Biberoglu and Behrman Scale (compare below, *endometriosis-specific PROMs*). Similarly, PROMs assessing several aspects of pain not falling under the *pain* subdomain *pain intensity* (eg, composite measures) were categorized under *pain-specific PROMs*, *other aspects*. This was, however, rarely the case. For example, the painDETECT questionnaire was used by one study (0.5%) and the McGill Pain Questionnaire by 2 studies (1.0%). Seventeen studies (9.9%) used other PROMs for assessing *pain*, which were not specified (eg, "(symptom) diary" and "valid questionnaire"), 4 studies (2.1%) used self-constructed questionnaires, and 3 studies (1.6%) asked for "pain relief," using a 4-point VRS scale.

Rescue pain medication, allowed additionally to the investigated treatment, was assessed in 68 studies (35.6%), mostly using diaries (25 studies, 13.1%). Two studies used the Endometriosis Daily Impact Diary, while 35 studies (18.3%) did not indicate the used measure at all.

PROMs for the assessment of *emotional functioning* were used in 13 studies (6.8%); 4 studies (2.1%) used 1 PROM, 8 studies (4.2%) used 2, and 1 study (0.5%) used 4 PROMs for this domain. The most frequently used PROMs for *emotional functioning* were the Hospital Anxiety and Depression Scale (used in 5 studies [2.6%]; 1 incompletely) and the State-Trait Anxiety Inventory (4 studies, 2.1%). Two studies used *author-indicated* PROMs for the assessment of *emotional functioning*, that is, the PROMs were used differently than intended (Woman Health Questionnaire, incompletely used, and Psychological general wellbeing questionnaire).

Physical functioning was assessed in 57 studies (29.8%) by using different PROMs. 12 studies (6.3%) used 2, 3 studies (1.6%) used 3 PROMs, 1 study (0.5%) used 4, and 2 studies (1.0%) used 5 PROMs. Most studies assessed *physical functioning* through the subdomain *generic measures of HRQOL* (53 studies, 27.7%; 5 studies [2.6%] used 2 PROMs) (**Table 4**). For *generic measures of HRQOL*, the SF-36 (22 studies, 11.5%; 4 studies [2.1%] used the short form SF-12 and 2 [1.0%] used it incompletely), followed by the Endometriosis Health Profile Questionnaire (EHP-30) were used (19 studies, 9.9%; 6 [3.1%] used the short form EHP-5 and 9 used it incompletely). The subdomain *daily activity* was assessed in 8 studies (4.2%) and

Table 4

Frequencies of PROMs that were used in the included studies according to the IMMPACT domains (n [%]).

	Used as PROM		
	All studies (n = 191)	Studies of high/moderate quality (n = 113)	Studies of low quality (n = 78)
Domain "*pain*"			
Pain (all)	**188 (98.4)**	**111 (98.2)**	**77 (98.7)**
Studies using 1 PROM	129 (67.5)	67 (59.3)	62 (79.5)
Studies using 2 PROMs	46 (24.1)	33 (29.2)	13 (16.7)
Studies using 3 PROMs	12 (6.3)	9 (8.0)	3 (3.8)
Studies using 4 PROMs	2 (1.0)	2 (1.8)	0
Pain intensity	**144 (75.4)**	**99 (87.6)**	**45 (57.7)**
Studies using 1 PROM	130 (68.1)	88 (77.9)	42 (53.8)
Studies using 2 PROMs	12 (6.3)	9 (8.0)	3 (3.8)
Studies using 3 PROMs	2 (1.0)	2 (1.8)	0
Numerical rating scale (NRS)	18 (9.4)	9 (8.0)	9 (11.5)
Visual analog scale (VAS)	98 (51.3)	74 (65.5)	24 (30.8)
Verbal rating scale (VRS)	35 (18.3)	27 (23.9)	8 (10.3)
Other*	10 (5.2)	1 (0.9)	9 (11.5)
Pain intensity other	**67 (35.1)**	**40 (35.4)**	**27 (34.6)**
Studies using 1 PROM	57 (29.8)	33 (29.2)	24 (30.8)
Studies using 2 PROMs	10 (5.2)	7 (6.2)	3 (3.8)
Biberoglu and Behrman scale	56 (29.3)	34 (30.1)	22 (28.2)
Incompletely used	25 (13.1)	17 (15.0)	8 (10.3)
Modified	16 (8.4)	11 (9.7)	5 (6.4)
Andersch and Milsom score (all modified)	7 (3.7)	4 (3.5)	3 (3.8)
Other†	14 (7.3)	11 (9.7)	3 (3.8)
Pain-specific PROMs, other aspects	**3 (1.6)**	**2 (1.8)**	**1 (1.3)**
PainDETECT	1 (0.5)	1 (0.9)	0
McGill questionnaire	2 (1.0)	1 (0.9)	1 (1.3)
World Health Organization QOL-BREF ("pain and discomfort")‡	1 (0.5)	1 (0.9)	
SF-36 (2 items)‡	1 (0.5)	1 (0.9)	
Pain relief (4-point VRS)	**3 (1.6)**	**2 (1.8)**	**1 (1.3)**
Self-constructed scales (pain all)	**4 (2.1)**	**1 (0.9)**	**4 (5.1)**
Others (not further defined)	**16 (8.4)**	**3 (2.7)**	**13 (16.7)**
Studies using 1 PROM	16 (8.4)	3 (2.7)	13 (16.7)
Rescue medication	**68 (35.6)**	**51 (45.1)**	**17 (21.8)**
Diary	25 (13.1)	20 (17.7)	5 (6.4)
Not indicated	35 (18.3)	28 (24.8)	7 (9.0)
Other*	8 (4.2)	3 (2.7)	5 (6.4)
Domain "*emotional functioning*"			
Emotional functioning	**13 (6.8)**	**9 (8.0)**	**4 (5.1)**
Studies using 1 PROM	4 (2.1)	4 (3.5)	0
Studies using 2 PROMs	8 (4.2)	4 (3.5)	4 (5.1)
Studies using 3 PROMs	0	0	0
Studies using 4 PROMs	1 (0.5)	1 (0.9)	0
Beck depression inventory (BDI)	2 (1.0)	2 (1.8)	0
Hospital anxiety and depression scale (HADS)	5 (2.6)	3 (2.7)	2 (2.6)
1 incompletely used		1 (0.9)	0
Beck anxiety inventory	1 (0.5)	1 (0.9)	0
GHQ 12 (shortform)	2 (1.0)	1 (0.9)	1 (1.3)
Hamilton depression scale	1 (0.5)	1 (0.9)	0
State trait anxiety inventory	4 (2.1)	3 (2.7)	1 (1.3)
Pain catastrophizing questionnaire	3 (1.6)	2 (1.8)	1
Woman health questionnaire (incompletely used, author-indicated)	1 (0.5)	0	1 (1.3)
Psychological general well-being questionnaire (author-indicated)	1 (0.5)	1 (0.9)	0
WHO-five	1 (0.5)	1 (0.9)	0
Perceived stress scale	1 (0.5)	0	1 (1.3)
Five facets of mindfulness questionnaire	1 (0.5)	0	1 (1.3)
Others: "Diary"	**1 (0.5)**	**1 (0.9)**	**0**
Self-constructed instruments	**0**	**0**	**0**

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Table 4 (*continued*)

	Used as PROM		
	All studies (n = 191)	**Studies of high/moderate quality (n = 113)**	**Studies of low quality (n = 78)**
Domain "physical functioning and generic measures of HRQOL"			
Physical functioning	**57 (29.8)**	**44 (38.9)**	**13 (16.7)**
Studies using 1 PROM	39 (20.4)	33 (29.2)	6 (7.7)
Studies using 2 PROMs	12 (6.3)	9 (8.0)	3 (3.8)
Studies using 3 PROMs	3 (1.6)	1 (0.9)	2 (2.6)
Studies using 4 PROMs	1 (0.5)	0	1 (1.3)
Studies using 5 PROMs	2 (1.0)	1 (0.9)	1 (1.3)
Generic measures of HRQOL	**53 (27.7)**	**40 (35.4)**	**13 (16.7)**
Studies using 1 PROM	48 (25.1)	38 (33.6)	10 (12.8)
Studies using 2 PROMs	5 (2.6)	2 (1.8)	3 (3.8)
SF-36	22 (11.5)	13 (11.5)	5 (6.4)
2 incompletely used			2 (2.6)
Short form: SF-12	4 (2.1)	3 (2.7)	1 (1.3)
Endometriosis health profile questionnaire (EHP-30)	19 (9.9)	14 (12.4)	5 (6.4)
9 incompletely used		7 (6.2)	2 (2.6)
Short form: EHP-5	6 (3.1)	5 (4.4)	1 (1.3)
4 incompletely used		4 (3.5)	0
Pain disability index (PDI)	1 (0.5)	1 (0.9)	0
Brief pain inventory	1 (0.5)	1 (0.9)	0
Nottingham health profile questionnaire	1 (0.5)	0	1 (1.3)
The duke quality of life scale	1 (0.5)	1 (0.9)	0
World Health Organization QOL-BREF (short-form)	2 (1.0)	2 (1.8)	0
VAS	1 (0.5)	1 (0.9)	0
QoL questionnaire	1 (0.5)	0	1 (1.3)
Gastrointestinal quality of life index (GQLI)	1 (0.5)	0	1 (1.3)
Self-constructed instruments	**1 (0.5)**	**0**	**1 (1.3)**
Daily activity	**8 (4.2)**	**5 (4.4)**	**2 (2.6)**
Endometriosis impact diary for productivity	2 (1.0)	0	2 (2.6)
2 incompletely used			2 (2.6)
Health related productivity questionnaire	2 (1.0)	2 (1.8)	0
Work and productivity impairment questionnaire—specific health problem version 2.0	2 (1.0)	1 (0.9)	1 (1.3)
1-5 scale interference of daily activities	1 (0.5)	1 (0.9)	0
Diary (difficulty of doing daily activity)	1 (0.5)	1 (0.9)	0
Self-constructed instruments	0	0	0
Sleep	**5 (2.6)**	**3 (2.7)**	**2 (2.6)**
Studies using 1 PROM	4 (2.1)	2 (1.8)	2 (2.6)
Studies using 2 PROMs	1 (0.5)	1 (0.9)	0
Akerstedt and Torsvall (incompletely)	1 (0.5)	0	1 (1.3)
Pittsburgh sleep quality index (PSQI)	2 (1.0)	1 (0.9)	1 (1.3)
VASQS	1 (0.5)	1 (0.9)	0
Diary	1 (0.5)	1 (0.9)	0
1-5 scale	1 (0.5)	1 (0.9)	0
Self-constructed instruments	0	0	0
Physical functioning other aspects	**11 (5.8)**	**7 (6.2)**	**4 (5.1)**
Studies using 1PROM	8 (4.2)	6 (5.3)	2 (2.6)
Studies using 2 PROMs	3 (1.6)	1 (0.9)	2 (2.6)
Breast cancer prevention trial symptom checklist (modified)	1 (0.5)	0	1 (1.3)
Index of sexual satisfaction	1 (0.5)	1 (0.9)	0
Sabbatsberg sexual rating scale	1 (0.5)	1 (0.9)	0
Sexual activity questionnaire	1 (0.5)	1 (0.9)	0
Female sexual function index (FSFI)	3 (1.6)	1 (0.9)	2 (2.6)
Inventory of social support and integration (incompletely used)	1 (0.5)	0	1 (1.3)
Marburg questionnaire for functional well-being	1 (0.5)	1 (0.9)	0

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Table 4 (*continued*)

	Used as PROM		
	All studies (n = 191)	**Studies of high/moderate quality (n = 113)**	**Studies of low quality (n = 78)**
Measure your own medical outcomes profile	1 (0.5)	1 (0.9)	0
Patient-reported outcomes Measurement information system fatigue short form 6a Questionnaire (short form)	1 (0.5)	1 (0.9)	0
Brief fatigue inventory	1 (0.5)	1 (0.9)	0
Piper fatigue scale-revised	1 (0.5)	0	1 (1.3)
Demand control questionnaire	1 (0.5)	0	1 (1.3)
Domain *"improvement and satisfaction"*			
Improvement and satisfaction	**27 (14.1)**	**23 (20.4)**	**4 (5.1)**
Studies using 1 PROM	26 (13.6)	22 (19.5)	4 (5.1)
Studies using 2 PROMs	1 (0.5)	1 (0.9)	0
Patient global impression of change (PGIC)	7 (3.7)	7 (6.2)	
Patient satisfaction	2 (1.0)		2 (2.6)
Questionnaire 1 incompletely used			1 (1.3)
5-point Likert scale	3 (1.6)	2 (1.8)	1 (1.3)
Other*	**12 (6.3)**	**11 (9.7)**	**1 (1.3)**
Domain *"adverse events"*			
Adverse events	**147 (73.8)**	**91 (80.5)**	**56 (71.8)**
Studies using 1 PROM	118 (61.8)	71 (62.8)	47 (60.3)
Studies using 2 PROMs	29 (15.2)	20 (17.7)	9 (11.5)
Diary	37 (19.4)	23 (20.4)	14 (17.9)
Kuppermann index	5 (2.6)	2 (1.8)	3 (3.8)
Checklist of side effects	3 (1.6)	3 (2.7)	0
Ferriman and Gallwey Score	2 (1.0)	2 (1.8)	0
VAS	2 (1.0)	2 (1.8)	0
Greene scale (modified)	1 (0.5)	1 (0.9)	0
Memory observation questionnaire	1 (0.5)	0	1 (1.3)
Global tolerability scale	1 (0.5)	1 (0.9)	0
Other*	**26 (13.6)**	**12 (10.6)**	**14 (17.9)**
Assessed but not indicated how	**101 (52.9)**	**64 (56.6)**	**33 (42.3)**

* "Questionnaire," "diary," and "subjective scale" (if not mentioned above separately).
† See supplemental digital content (Table 5, http://links.lww.com/PAIN/C69) for an overview of PROMs specifically addressing endometriosis.
‡ These PROMs were used only partly (subanalysis for pain).

sleep in 5 studies (2.6%; one study used 2 PROMs); 11 studies (5.8%) used *other PROMs* to assess *physical functioning*, mostly addressing sexual function.

The domain *improvement and satisfaction* was assessed in 27 studies (14.1%, 1 study [0.5%] used 2 PROMs; **Table 4**). The most frequently used PROMs for assessing this domain were the Patient Global Impression of Change (PGIC; 7 studies, 3.7%) and questionnaires without further specification asking for an "overall degree of satisfaction" (6 studies, 5.3%).

In total, 147 studies (73.8%; 29 studies used 2 PROMs) assessed *adverse events* (and/or side effects) that occurred under the investigated treatment (**Table 4**). Although most studies (101; 52.9%) did not indicate how this was measured, 37 (19.4%) used a "diary" without further specification and only 15 studies used specific scales or questionnaires, for example, the Kuppermann Index (5, 2.6%).

3.6. Endometriosis-specific patient-reported outcome measures

Two questionnaires for assessment of endometriosis-specific symptoms were mainly used: the Biberoglu and Behrman scale (used in 56 studies, 29.3%; 25 studies [13.1%] used it incompletely and 16 studies [8.4%] in a modified version) and the Andersch and Milsom questionnaire (used in 7 studies 4%; all used in modified versions). The Biberoglu and Behrman scale estimates pain intensity based on discomfort/need for analgesics for pelvic pain, loss in work efficiency for dysmenorrhea, and limitations regarding intercourse for dyspareunia.[29] The Andersch and Milsom scale, developed to assess dysmenorrhea, claims to assess pain severity based on questions related to work performance, systematic symptoms, and analgesic use.[16]

Only a few studies used other specifically endometriosis-related pain scales, such as the VRS-based endometriosis daily impact eDiary (2 studies, 1.0%) to assess *pain*. Regarding other domains, only a few endometriosis-specific PROMs were used, such as the Endometriosis Health Profile Questionnaire (EHP-30) and its short form (used in 19 studies [9.9%] and 6 studies [3.1%], respectively, compare supplemental digital content, Table 5, http://links.lww.com/PAIN/C69) were used as *generic measures of HRQOL*. The structured extraction of the assessment of bleeding patterns was difficult because this aspect was hardly described explicitly. Only 44 studies (23.0%) described the assessment of bleeding patterns at all, 24 of these among the *adverse events* assessment. 13 studies (6.8%) described this assessment using calendars or diaries. For a detailed overview of the different endometriosis-specific PROMs used, see supplemental digital content (see Table 5, http://links.lww.com/PAIN/C69).

Self-constructed questionnaires were indicated in a minority of all studies; 4 studies used 1 self-constructed instrument for *pain* and 1 study used a self-constructed instrument for *generic measures of HRQOL*. However, it has to be considered that many used scales and questionnaires, for example, 3 to 11 "point-scales" or "Likert-scales," were not further described and had no references and thus are likely to be self-constructed, too. In addition, many questionnaires were used in modified and/or incomplete versions (**Table 4**).

3.6.1. Quality-dependent analysis of the use of patient-reported outcome measures

Comparing the use of PROMs between studies of moderate-to-high vs low methodological quality revealed differences between these categories. Regarding *pain intensity*, more studies of moderate-to-high quality used VAS (65.5% vs 30.8%) and VRS (23.9% vs 10.3%), while studies of low methodological quality used more PROMs that were not clearly described (11.5% vs 0.9%) and self-constructed scales (0.9% vs 5.1%). *Rescue medication* was assessed more frequently in studies of moderate-to-high quality (45.1% vs 21.8%). Approximately one-third of all studies of moderate-to-high quality used PROMs of the subdomain *generic measures of HRQOL* (vs 16.7% of the low-quality studies). Here, the most frequently used PROMs, the SF-36 and SF-12, as well as the endometriosis-specific EHP-30 and EHP-5 were mainly used in studies of moderate-to-high methodological quality (30.9% vs 15.4%). For the assessment of *improvement and satisfaction*, the PGIC was only used in studies of moderate-to-high quality (7 studies, 6.2%) but not in low-quality studies. For the assessment of *adverse events*, almost all designated (eg, Ferriman and Gallway Score) and clearly described PROMs (eg, VAS or "diary") were used in studies of moderate-to-high quality, while the fraction of instruments that were not described clearly was larger in low-quality studies (17.9% vs 10.6%). However, both groups had a high proportion of studies that did not describe at all how *adverse events* were assessed (high/moderate: 56.6% vs low-quality: 42.3%).

3.6.2. Characteristics of endometriosis-specific patient-reported outcome measures including the quality of the development process of those most frequently used

The use of PROMs developed specifically for patients with endometriosis is highly relevant to address their specific needs. Characteristics of endometriosis-specific PROMs are listed in supplemental digital content (see Table 6, http://links.lww.com/PAIN/C69). Whereas the overall rating of the EHP-30 questionnaire (a questionnaire assessing HRQOL in patients with endometriosis) was adequate (subscales were rated "doubtful" to "very good"), the overall rating for the Biberoglu and Behrman scale (a scale used to assess pain levels in patients with endometriosis) development study was inadequate, as were all subscales (see supplemental digital content, Table 7, http://links.lww.com/PAIN/C69). In fact, the scale was basically used in an interventional study without any description of the development process.

4. Discussion

4.1. Domains assessed in clinical trials on chronic pelvic pain related to endometriosis

This systematic literature review revealed profound heterogeneity in both, domain assessment and PROMs used to evaluate symptoms in pain-related efficacy trials in endometriosis. The identified 5 domains (and subdomains) were categorized in accordance with the IMMPACT's outcome assessment recommendations for trials on chronic pain.[67] Although nearly all studies assessed the domain *pain intensity*, and approximately three-quarters assessed *adverse events*, other domains, such as *emotional functioning* (6.8%), *physical functioning* (29.8%), and *improvement and satisfaction* (14.1%) were considerably less frequently appraised. Despite the substantial impact that pain-related symptoms, such as those related to *emotional functioning*, exert on patients' quality of life, their assessment in the context of endometriosis is surprisingly inconsistent.[7,116,117] Chronic pain, acknowledged as a multidimensional entity and recognized as a disease by the WHO,[207] is overlooked in most clinical interventional trials related to endometriosis-associated pain. Merely one-third of studies assessed more than 3 domains, with *pain*, *physical functioning,* and *adverse events* as the predominant combination of domains. This neglects pain-related psychosocial symptoms, although it is well-established that pain severity alone is insufficient to evaluate how a patient's life is affected.[50,151,235] Alignment of perspectives from healthcare professionals and patients remains a challenge in numerous chronic pain conditions, including endometriosis,[71] but also other entities of chronic pelvic pain,[86,87] postsurgical pain,[30,131] chronic low back pain,[50] or fibromyalgia.[63] As recommended by COMET, the initial step toward achieving this alignment is defining the domains that warrant evaluation.[222]

4.2. PROMs assessed in clinical trials on chronic pelvic pain related to endometriosis

In addition to domains, this review explores PROMs used to assess the domains in pain-related efficacy trials in endometriosis. This not only guided to identify the assessed domains as advised by COMET and Young et al.[222,228] but also highlights heterogeneity in assessment strategies when different PROMs are used for the same (sub-)domain. Mirroring the diversity in domain usage, our results show a vast variety of used PROMs even within a single (sub-)domain, further complicating study comparison, restricting data for meta-analysis and recommendations, and hindering the evaluation of therapeutic effectiveness. Furthermore, many instruments lacked detailed descriptions, contributing to a high proportion categorized as "other" within the respective domains. Heterogeneity and insufficient PROM description, along with the use of incomplete or modified versions, further impede comparability. Approximately 73% of studies using the Biberoglu and Behrman scale (41/56) used modified or incomplete versions, often without any explanations for the nature and extent of modifications. Furthermore, the quality of PROMs used to assess a specific domain is critical. Here, guidance by COSMIN and COMET is essential to determine suitable instruments to measure defined outcome domains.[82,222] For *pain intensity* assessment, various unidimensional scales, such as NRS, VRS, and VAS, and—even within one form of scale—different anchors as descriptors of extremity were used, which might affect outcomes and hamper comparability.[107] However, following the IMMPACT recommendations and Hjermstad and colleagues, NRS, VRS, and VAS are still considered the most sensitive and suitable PROMs for *pain intensity* in trials in chronic pain and other types of pain.[67,107] Notably, many of the identified endometriosis-specific PROMs differ markedly from recommended scales in the pain field, with the most frequently used Biberoglu and Behrman scale deemed inadequately developed based on the COSMIN recommendations.[163,204] Thus, this instrument cannot be recommended for assessing pain in endometriosis clinical trials.[31,84] In addition, none of the endometriosis-specific PROMs differentiate appropriately between nociceptive and neuropathic pain.[174] Owing to evidence of both forms in patients with endometriosis, alongside tremendously different treatment options,[111,235] questionnaires for differentiation of neuropathic and nociceptive pain should be considered.[17,174]

4.3. Implications for the future

Presenting the vast diversity of outcome assessment in efficacy trials for chronic endometriosis-related pain, our comprehensive analysis of all domains and their respective PROMs reveals a devastating gap in addressing bio–psycho–social aspects crucial for patients with chronic pain in general and endometriosis in particular. Our results underscore the urgent need to define prioritized domains in clinical studies on pain-related interventions for endometriosis. Defining a core outcome set (COS) of domains and corresponding PROMs would improve study comparability, clinical and patient relevance, and thereby facilitate evaluation of treatment options. Moreover, it might improve communication between patients and health professionals through reflection and focusing on the experience of the patients and thus improve patient centred health care.[93] In addition, an inclusive consideration of the holistic bio–psycho–social framework encourages exploration of more comprehensive multimodal approaches to ascertain efficacy in the future. A very recent COS initiative, the INTEGRATE initiative, developed an overarching COS of domains for all chronic pain entities including the domains *pain*, *activities of daily living*, and *HRQOL*.[33]

Ideally, a COS representing a minimum of domains to be assessed in all clinical trials on endometriosis-related chronic pain should be developed with healthcare professionals and patients together. Such a process aligns closely with the recommendations outlined by the COMET and the COSMIN initiative.[163,222,223]

After consenting on a COS of domains (ie, the next step in forming a COS for endometriosis-related pain[222]), corresponding PROMs need to be searched and assessed for psychometric properties. Particularly pain-related PROMs seem lacking in development or validation in patients with endometriosis-related pain.[31] Additional evaluation of the development process of the Biberoglu and Behrman scale following COSMIN guidelines for assessing quality of a PROM[163,204] revealed an inadequate development process, indicating it unsuitable for recommendation within in a COS. By contrast, our analysis indicates a rather good quality of the development process of the HRQOL questionnaire EHP-30 based on the COSMIN risk of bias checklist. This finding aligns with a previous review on HRQOL measures for patients with endometriosis.[32]

4.4. Strength and limitations

To the best of our knowledge, this is the first and most comprehensive systematic literature research on the use of all domains and corresponding PROMs in clinical trials on chronic pelvic pain related to endometriosis in adults. One strength is its comprehensiveness, encompassing nearly 200 articles, extracting domains *and* PROMs, and performing analysis according to IMMPACT and study quality. To ensure accuracy, 4 reviewers were trained in data extraction, and ≥ 20% of studies were reviewed by multiple reviewers until a high level of agreement was reached. One limitation might be the exclusion of studies in adolescents and the search in only the large databases MEDLINE, CENTRAL, and Embase without considering databases such as PSychINfo or CONAHL. The results are largely consistent with previous literature reviews[31,87,149], which have described and evaluated outcome measures in patients with chronic pelvic pain (CPP), including endometriosis. However, their focuses differed, studying outcome assessment in CPP in general without considering endometriosis separately,[87] the use of PROMs in endometriosis populations, but mainly the subdomain *pain intensity*,[31] or analysing PROMs regarding their applicability and validity in endometriosis populations without performing comprehensive analysis of the status quo in the current literature.[149] Although some PROMs were developed specifically for patients with endometriosis, encompassing various domains beyond *pain*, some lack validation for this population.[31,149] Yet, none of these reviews considered all IMMPACT domains, thus overlooking the psychosocial aspects of pain-related symptoms.

We aimed to categorize domains in alignment with IMMPACT classifications as closely as possible. However, we acknowledge that categorizing certain PROMs, not referenced in literature, or applicable to multiple domains, might be debatable.[67] Furthermore, the classification of PROMs' short-forms, incomplete versions, or modifications was based on descriptions in the original publications. Various levels of precision in these descriptions of the content and intention of the used PROMs may have resulted in minor misclassifications.

5. Conclusions

This SLR identified an important variability in outcome domains and outcome measures (PROMs) used in endometriosis-related pain trials. Our findings provide evidence for a notable disparity between the assessment of *pain intensity* (almost all studies) and the assessment of other bio–psycho–social pain-related aspects (scarcely used). This basically ignores the fact that CPP related to endometriosis is a bio–psycho–social disease with multiple facets for patients. The measures used to assess these domains are heterogeneous across studies, with endometriosis-specific PROMs frequently used in incomplete or modified forms, hampering comparability. Particularly, the frequently used Biberoglu and Behrman scale lacks an adequate development process. To address these challenges, there is an urgent need to define and implement a common COS of domains, and successively one of high-quality PROMs for studies on endometriosis-related pain, relevant to all stakeholders including patients. This initiative is critical to improve study comparability and thus the reliability of meta-analysis, recommendations, and finally, patient care.

Conflict of interest statement

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