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# Patient Reported Outcome Measures in Chronic Neuropathic Pain Clinical Trials – A Systematic Literature Review

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**Abstract:** In neuropathic pain clinical trials, the patient's perspective is often insufficiently reflected focusing mainly on pain intensity. Comparability of outcome assessment is limited due to heterogeneous patient reported outcome measures (PROMs).

The MEDLINE, CENTRAL, and Embase databases and reference lists of published meta-analyses were searched. Randomized controlled studies assessing treatment efficacy of drugs for chronic neuropathic pain were included. PROMs were assigned to recommended IMMPACT/NeuPSIG domains: pain intensity, pain other aspects, physical functioning, emotional functioning, global improvement and

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satisfaction, adverse events, participant disposition. Domains and PROMs were compared regarding the publication year and methodological quality of the studies.

Within the 251 included studies 200 PROMs were used with 27 being recommended by IMMPACT/ NeuPSIG. The number of domains was higher in high/moderate quality studies. The (sub-) domains 'physical functioning', 'global improvement and satisfaction', and 'neuropathic pain quality' were assessed more frequently in high/moderate quality studies and those published after 2011. Recent studies and those of better quality more often used the recommended PROMs.

Although neuropathic assessment via PROMs has improved, there is still a high heterogeneity. A standardized core set of outcome domains and should be defined to improve neuropathic pain treatment and to achieve better comparability of clinical trials.

**Perspective:** *This systematic literature review assesses the use of patient reported outcome measures (PROMs) in chronic neuropathic pain. The results show that there is still a high heterogeneity, highlighting the need for a standardized core set of outcome domains and PROMs to improve comparability of clinical trials and neuropathic pain treatment.*

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**Key words:** *Chronic neuropathic pain, patient reported outcome measures, domains, systematic review, randomized controlled trials.*

## Introduction

Neuropathic pain syndromes consist of mixed groups of patients presenting with a variety of pain qualities and sensory abnormalities. Probably the greatest unmet clinical need in these patients is the lack of pain control since less than 50% of them achieve partial pain relief with the currently recommended pharmacological treatments.<sup>2,16</sup> Such a poor therapeutic outcome is probably related to many reasons, but 1 of them could be an inadequate reflection of patients' perspective.<sup>3,6</sup> In fact, outcome assessment in clinical trials might not sufficiently reflect the most relevant symptoms for patients with neuropathic pain. In addition, if outcome assessment differs in clinical trials due to the use of different questionnaires, comparison of results is problematic.

One way to improve the comparability of study outcomes is the use of standardized meaningful outcome measures across studies in patients with the same condition.<sup>35</sup> In the absence of objective pain biomarkers, patient reported outcome measures (PROMs), defined as measurements based on reports that come directly from the patient without interpretation of the responses by a caregiver,<sup>33</sup> seem the most suitable because only patients are able to describe their symptoms and related disability in an appropriate manner.

Clinical trials on pain assessment and treatment efficacy mainly rely on patients' ratings of spontaneous pain intensity as the primary outcome parameter using various approaches such as categorical scales (eg, mild, moderate, severe), numerical rating scales (NRS), or visual analog scales (VAS). However, other factors such as physical and emotional functioning and quality of life, which can be assessed with specific PROMs, may also represent relevant treatment outcomes.<sup>26</sup> In this perspective, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommended a first set of core outcome domains and

measures for pain clinical trials.<sup>14,32</sup> Specific recommendations related to neuropathic pain trials were also published by experts from the European Federation of Neurological Societies (EFNS)<sup>10,11</sup> and the Special Interest Group on Neuropathic Pain (NeuPSIG) of the International Association for the Study of Pain (IASP).<sup>19</sup> More recently, specific recommendations for patient phenotyping in clinical trials of chronic pain, in particular neuropathic pain, were published by the IMMPACT group.<sup>15</sup> In general, all these recommendations are consistent regarding core domains which should be assessed in clinical trials, including: pain (intensity, quality, temporality), physical functioning (daily activities/well-being, sleep quality), emotional functioning, and patient global improvement and satisfaction with treatment. However, there were some differences regarding the specific recommended outcome measures. In particular, the most recent recommendations encouraged the use of PROMs more specifically validated in neuropathic pain patients.<sup>15,19</sup>

The present study was performed under the auspices of the Innovative Medicines Initiative (IMI) PainCare European project ([www.imi.europa.eu](http://www.imi.europa.eu); [www.imi-pain-care.eu](http://www.imi-pain-care.eu)) as part of the "Patient reported outcome measures to improve management of acute and chronic pain" (PROMPT) subtopic. The main hypothesis of PROMPT is that PROMs provide clinically valuable information which helps health care professionals to follow up on treatment success in real world conditions. The ultimate aim of this project is to define PROM-based specific criteria, which can be regarded as clinical biomarkers for various chronic pain conditions and may reflect distinct pain mechanisms that can be used for treatment response prediction.

As a first step in this project, we conducted a systematic literature review (SLR) on the use of PROMs in chronic neuropathic pain randomized controlled trials (RCTs). In addition, we assessed whether the publication of experts' recommendations by IMMPACT<sup>14,32</sup> and

NeuPSIG<sup>19</sup> had an impact on the assessment of outcome in clinical trials and whether the quality of the assessment was related to the overall methodological quality of the study.

## Methods

This SLR, which was included in the IMI PainCare project, was conducted in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA) 2009 guidelines and followed the Cochrane's methodology (PICOS: P, Population; I, Intervention; C, Comparator; O, Outcome; S, Study design). The review was preregistered at the prospective international register of systematic reviews, with 1 adjustment of the MEDLINE search string during conduct of the SLR (PROSPERO: CRD42020141824, [https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=141824](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=141824)).

### Eligibility Criteria

The inclusion and exclusion criteria were defined following the PICOS criteria.<sup>20</sup> Only peer-reviewed publications of RCTs assessing the efficacy of systemic or topical agents for chronic neuropathic pain with a duration of at least 3 months were included. The interventions included were systemic (oral, intravenous) or topical treatments (subcutaneous, cutaneous) with at least 2 weeks duration of treatment. Single administrations of drugs with long-term efficacy (eg, high concentration capsaicin patches or botulinum toxin type A injections) were included if the follow-up was at least 2 weeks. Only English-, French- or German-language studies were included.

Studies investigating less than 20 patients, conditions other than chronic neuropathic pain, eg, fibromyalgia or complex regional pain syndrome type I, as well as epidural or intrathecal treatment administration, 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 [Appendix Table 1](#).

### Search Strategy

The MEDLINE, CENTRAL, and Embase electronic databases were searched from the inception date of the respective database to April 2020. The search strings are shown in [Appendix 1](#). Additional records were identified by reviewing the reference list of the NeuPSIG meta-analysis by Finnerup et al.,<sup>16</sup> the recently published French recommendations<sup>23</sup> on treatment options for neuropathic pain, and by an additional hand search.

Titles and abstracts of all identified records were screened by 3 independent reviewers (JS, MS, MP) in a double-blind manner by use of the RAYYAN program (<https://rayyan.qcri.org/>).<sup>25</sup> Disagreements were resolved by discussion with the principal investigators of the study (EPZ, RB, DB).

Screening of the first ten full-text articles, inclusion/exclusion decision, data collection, risk of bias

assessment, and grading of study quality was performed independently by the same 3 reviewers (JS, MS, MP). Disagreements and differences in data extraction were discussed with the principal investigators (EPZ, RB, DB). For the remaining full-text review, reports were divided equally and screened independently by the same 3 assessors. Uncertainties were resolved after discussion with the other assessors and the principal investigators.

### Data Collection

For the data extraction, an excel spreadsheet and a corresponding explanation file with instructions were created. The following data from the included studies were extracted: publication year, funding by a pharmaceutical company, country of study conduction, information about the study design including also the number of investigated patients, the primary outcome, description of study population including disease entity, mean disease duration, mean pain duration, gender, age as well as information on interventions used (investigated treatment, comparators, way and duration of administration). A detailed list with all extracted data is given in [Appendix Table 2](#).

All PROMs were extracted from the included studies and classified according to the IMMPACT<sup>14,32</sup> and NeuPSIG<sup>19</sup> recommendations focusing especially on 6 core outcome domains: 'pain' (1, 2; see below), 'physical functioning' (3) including 'daily activities/well-being' (3a) and 'sleep' (3b), 'emotional functioning' (4), 'participant ratings of global improvement and satisfaction with treatment' (5) (here called 'global improvement and satisfaction' for simplicity), 'participant disposition' (6) as well as 'symptoms and adverse events' (7). As the main outcome domain in clinical trials is pain intensity, we decided to subdivide the domain 'pain' into 2 core domains, namely 'pain intensity' (1) and 'pain other aspects' (2). The domain 'pain other aspects' was then further subdivided according to the IMMPACT recommendations into the subdomains 'usage of rescue analgesics' (2a), 'neuropathic pain quality' (2b), 'unspecific pain quality' (2c), 'temporal aspects' (2d) and 'other aspects related to pain' (2e). PROMs covering other aspects ('others', 8) were also extracted as well as questionnaires or scales that were only used at baseline or as an inclusion/exclusion criterion.

### Risk of Bias Assessment

The risk of bias of each study was assessed according to the GRADE guidelines, ie, lack of allocation concealment, lack of blinding, incomplete accounting of patients and outcome events, selective outcome reporting bias, stopping early for benefit, use of non-validated outcome measures, and the carry-over effect in cross over trials rated as fulfilled (no limitation), not fulfilled (crucial limitation) and not clear (some limitation).<sup>18</sup> In order to ensure that the grading was carried out by each assessor as similarly as possible, the GRADE criteria were defined precisely ([Appendix Table 3](#)). The quality

of each study was then classified as 1 of 3 categories, ie, high, moderate, and low:

- High quality: no limitation (low risk of bias) for all GRADE criteria
- Moderate quality:
  - a crucial limitation for 1 criterion and/or
  - some limitation for 1 criterion or
  - some limitation for  $\geq 1$  criterion
- Low quality:
  - a crucial limitation for  $> 1$  criterion or
  - a crucial limitation for 1 criterion and some limitation for  $> 1$  criterion

## Data Analysis

As the aim of this SLR was the identification of PROMs that have been used in clinical trials on chronic neuropathic pain, data analysis was performed in a mainly descriptive manner.

First, all PROMs were listed according to the corresponding domain. The PROMs were divided into 2 groups, ie, those that were explicitly recommended by IMMPACT<sup>14</sup> or NeuPSIG<sup>19</sup> (Table 1) and those that were not explicitly recommended by 1 of these initiatives.

Second, the number of domains that were assessed by at least 1 recommended PROM were listed for each study. Note that no specific PROM was explicitly recommended for the domains ‘symptoms and adverse events’ and ‘participant disposition’. In contrast, for some of the subdomains, specific PROMs were recommended (‘pain quality’), or there was only 1 possible question to capture the domain (‘usage of rescue analgesics’).

Since the fastest way to harmonize PROMs in future clinical trials might be to favor those that have been used most frequently in previous, higher quality trials, we focused our analysis on studies with at least moderate methodological quality and compared them to those with low quality.

Sub-analyses were performed based on the publication year of the studies (before or after publication of the NeuPSIG recommendations<sup>19</sup>), the research design (parallel group vs other), the sponsoring (funded/sponsored by a pharmaceutical/industrial company vs not sponsored), the pain condition (polyneuropathy vs other) and the sample size ( $\geq 200$  vs  $< 200$ ).

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

## Results

The PRISMA flow diagram is shown in Fig 1. In total, 2693 possibly eligible articles were identified through database searching. After removing all duplicates, 1699 abstracts were screened for eligibility according to the predefined inclusion and exclusion criteria. In addition, 104 articles were identified by reviewing the NeuPSIG meta-analysis by Finnerup et al.<sup>16</sup> and the recently published French recommendations on treatment options for neuropathic pain<sup>23</sup> and by hand search. After

resolving all disagreements, 343 full-text articles were assessed for eligibility. Finally, 249 studies were included in the SLR. Articles comprising results of more than 1 study were considered as separate, ie, articles by Rowbotham et al. 2012,<sup>28</sup> Smith et al. 2014,<sup>29</sup> and Bramson et al. 2015<sup>9</sup> with 2 and 3 separate studies. Two studies performing secondary analyses on additional outcome measures of already included RCTs were considered together with the original article to avoid a loss of PROMs. Thus, the final number of analyzed studies was 251.

## Descriptive Analysis

In total, more than two thirds of the included studies (185, 73.7%) were RCTs with a parallel-group design, whereas 64 studies had a cross-over design (25.5%; 1 study with a within-patient design), and 2 studies had a different study design (1 study with a parallel-group and an additional comparator arm and afterwards a cross-over of non-responders, 1 study with an open-label arm before N-of-1 randomization). Thirty studies had an additional open-label or single-blind phase before or after the randomized phase (27 parallel-group trials and 3 cross-over trials). Nearly 90% (222 of 251) of all trials were double-blinded. Included patients were most frequently in the age group between 40 to 60 years (47.8%) followed by 60 to 80 years (32.7%). The gender distribution was approximately balanced on average across all studies (52.5% males; range: 0–96%). The majority of studies investigated peripheral neuropathic pain syndromes (223; 88.8%), whereas only 23 of all studies (9.2%) focused on central neuropathic pain and 4 (1.6%) on mixed central and peripheral neuropathic pain. Painful polyneuropathy was the most frequently investigated disease entity (45.0%). In total, 208 (82.9%) studies were placebo-controlled (13 of them with an active placebo), and 43 studies (17.1%) used a pharmacological and/or non-pharmacological comparator arm. The most frequently investigated drugs were calcium channel modulators (gabapentinoids) (26.3%). More than half of the studies (132; 52.6%) were sponsored or initiated by a pharmacological company.

A detailed list of study characteristics is given in Appendix Table 4. Results of the risk of bias assessment is shown in Appendix Table 5.

## Analysis of PROMs

The outcome assessment items used within the analyzed studies, ie, PROMs (recommended and not specifically recommended) as well as questionnaires and scales that were used only as inclusion/exclusion criterion or only at baseline, were sorted by the IMMPACT/NeuPSIG domains and are summarized in Table 2. The following sections will focus on PROMs.

In total, 200 PROMs were used in the analyzed studies, of which only 27 PROMs were recommended explicitly by IMMPACT and/or NeuPSIG. A detailed list with all validated PROMs, their objectives and characteristics is given in Appendix Table 6. A PROM was considered validated if a validation study could be found in the

**Table 1. Recommended PROMs According to the IMMPACT and NeuPSIG Guidelines**

DOMAIN	RECOMMENDED PROMs
Pain Pain intensity	11-point Numerical Rating Scale (0 = no pain, 10 = pain as bad as you can imagine) Categorical scale (non, mild, moderate, severe) Visual analogue scale (VAS) McGill Pain Questionnaire Visual analogue scale (MPQ-VAS) Brief Pain Inventory Numerical Rating Scale (BPI-NRS)
Rescue analgesics Pain quality	PainDetect Questionnaire (PD-Q) Douleur Neuropathique en 4 Questions (DN4) Self-administered Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) Neuropathic Pain Questionnaire (NPQ) Neuropathic Pain Symptom Inventory (NPSI) Neuropathic Pain Scale (NPS) McGill Pain Questionnaire (MPQ) NRS/VAS unpleasantness
Physical functioning	Brief Pain Inventory (BPI) The West Haven-Yale Multidimensional Pain Inventory (WHYMPI) 36-Item Short Form Survey (SF-36) Euroqol EQ-5D (EQ-5D) Pain Disability Index (PDI) Oswestry Disability Index (ODI) Roland-Morris Disability Questionnaire (RMDQ) Sickness Impact Profile (SIP) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Medical Outcomes Study Sleep scale (MOS Sleep) Daily Sleep Interference Scale (DSIS)
Emotional functioning	Pain Catastrophizing Scale (PCS) Beck Depression Inventory (BDI) Hospital Anxiety and Depression Scale (HADS) Profile of Mood States (POMS)
Global improvement and satisfaction	Patient Global Impression of Change (PGIC)

literature, regardless of its quality and the disease entity studied. Interestingly, while only 8 PROMs were used for 'pain intensity' 1) (5 recommended) the other domains were assessed more heterogeneously. In particular, 38 PROMs were used for 'pain other aspects' 2) and 81 different PROMs were used for 'physical functioning' 3) with 52 different PROMs (8 recommended) for 'daily activities/well-being' (3a) and 29 PROMs (2 recommended) for 'sleep' (3b).

While nearly all studies used at least 1 PROM for 'pain intensity' 1) (98.4%), the other domains were considered less frequently. A PROM for 'pain other aspects' 2) was used in 176 studies (70.1%). However, its subdomains (2a–e: rescue analgesic use, neuropathic pain quality, and unspecific pain quality) were assessed in about 1 quarter of the studies. In total, 199 studies (79.3%) used at least 1 PROM for 'physical functioning' 3) with the subdomain 'daily activities/well-being' (3a) assessed in 168 studies (66.9%) and 'sleep' (3b) in 119 studies (47.4%). 'Emotional functioning' 4) was covered by 86 studies (34.3%) and 'global improvement and satisfaction' 5) by 137 studies (54.6%).

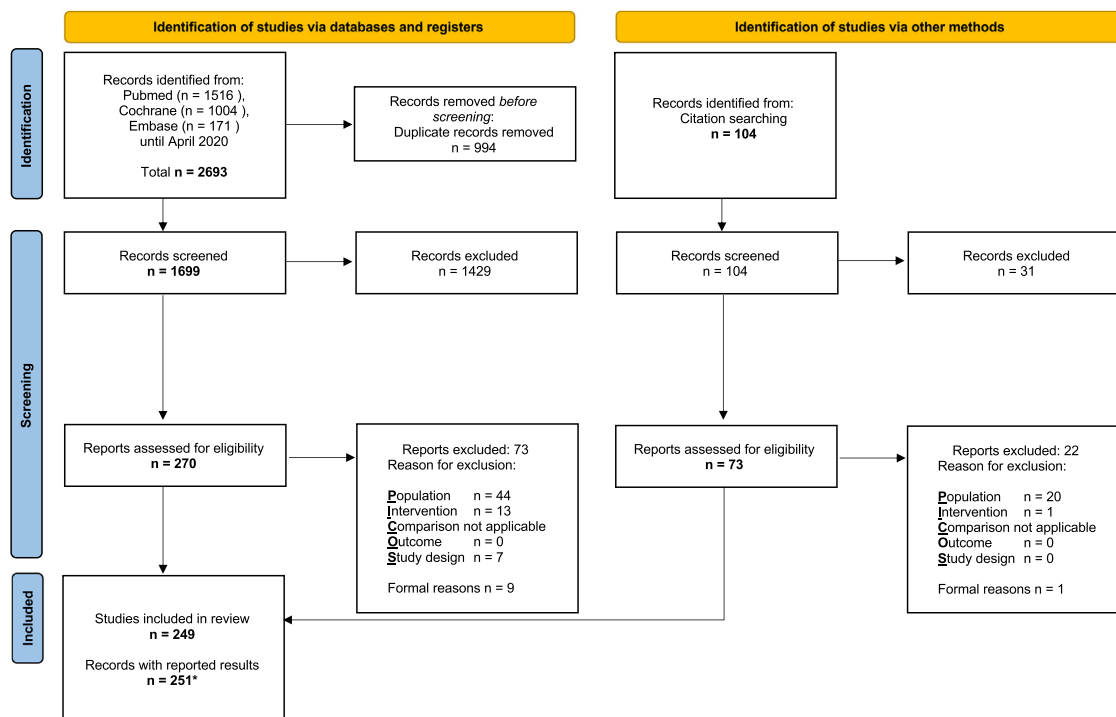
### High/Moderate Quality Studies

Most of the studies (157; 62.5%) had a moderate methodological quality, whereas 60 studies (23.9%) were of high and 34 (13.5%) of low quality based on

the risk of bias grading<sup>18</sup> (Appendix Table 3 and 5). Although we decided to strictly define the grading criteria to avoid internal disagreements, this approach remains semi-objective, leading to a large proportion of disagreements regarding the classification as high or moderate quality. Thus, moderate and high quality studies were combined into 1 group (n = 217) and compared against low quality studies (n = 34).

### Specific PROMs

Table 3 lists the applied PROMs sorted by the IMMPACT domains according to their frequency in high/moderate quality studies. While for some domains the same PROM was used in more than half of the studies, other domains showed a very heterogeneous picture with the use of many different PROMs. While, for example, only 8 different PROMs were used to measure 'pain intensity' (1), 'daily activities/well-being' (3a) was assessed by 42 different questionnaires. The NRS was by far the most frequently used PROM to measure 'pain intensity' (1) (70.5%). However, only 14 (6.5%) of the studies used the recommended NRS version, ie, both the recommended range (0–10) and the recommended wording ("no pain", "pain as bad as you can imagine"). Instead, most of the studies (139, 64.1%) used a different wording like "no pain" to "worst pain imaginable" or "unbearable pain", or the wording was not reported. Other recommended



**Figure 1.** PRISMA flow diagram of study selection. \*2x2 studies were matched due to secondary analysis of additional PROMS; 3 studies included results of different trials and were analyzed separately.

PROMs for ‘pain intensity’, ie, the 11-point NRS subscale of the Brief Pain Inventory (BPI; 25.8%) and the VAS of the McGill Pain Questionnaires (MPQ; 29.5%) or other VAS were used at least by about 1 quarter of the studies. Likewise, the recommended PROM for ‘global improvement and satisfaction’ (5), ie, the patient global impression of change (PGIC), was used by nearly half of high/moderate quality studies (49.8%).

Regarding ‘daily activities/well-being’ (3a), usage of PROMs was more heterogeneous, ie, the recommended 36-item Short Form Survey (SF-36) or the BPI quality part were used in less than one third of the studies (28.6 and 27.6%), and the EuroQol-5D (EQ-5D) by only 16.1% of the studies. Regarding ‘emotional functioning’ (4), less than 15% of all studies used the same PROM. The Pain Catastrophizing Scale (PCS), which is 1 of the PROMs recommended by NeuPSIG,<sup>19</sup> was used by only 1 high/moderate quality study.

Interestingly, in some studies, 1 domain was also investigated by several PROMs. For example, more than half of the high/moderate quality studies (54.8%; 119/217) used more than 1 PROM to assess ‘pain intensity’ (1). A combination of the NRS and the BPI NRS subscale was used in 46 high/moderate quality studies.

**Domains**

While the percentages of studies using at least 1 PROM per domain was similar in high/moderate quality studies compared to the totality of studies (see above), the comparison of high/moderate versus low quality studies revealed some differences (Fig. 2A–C).

For the domains ‘pain intensity’ (1) and ‘emotional functioning’ (4), there were only slight differences. However, more differences in the assessment of ‘pain

other aspects’ (2) were found (Fig 2B). In particular, a specific neuropathic pain questionnaire was used by 24.4% of high/moderate quality studies but only by 11.8% of low quality studies. The same tendency was observed for unspecific pain quality questionnaires, although differences were less pronounced (29.5% vs. 20.6%). Interestingly, for ‘other aspects related to pain’ (2e) (excluding pain quality), the opposite could be observed, ie, these were more frequently assessed by low quality studies compared to high/moderate quality studies. Moreover, ‘physical functioning’ (3) (see Fig. 2A and C for subdomains) and ‘global improvement and satisfaction’ (5) were examined more frequently in high/moderate quality studies compared to low quality studies. For example, while more than half of the high/moderate quality studies examined the global improvement of patients, this domain was included in only 29.4% of the low quality studies.

**Recommended PROMs**

The number of studies that have investigated the individual domains decreases considerably if one focuses only on the PROMs that are explicitly recommended. For example, a recommended PROM for ‘pain intensity’ was only used in 149 high/moderate quality studies (68.7%). The observed differences between high/moderate and low quality studies became even more distinct (Fig 3).

The number of domains, that were assessed by at least 1 recommended PROM within the included studies is shown in Fig 4. In total, only 5 high/moderate quality studies (2.0%) investigated all 6 domains. In contrast, none of the studies of low methodological quality included all 6

**Table 2. Frequencies of PROMs that were used in the Included Studies According to the IMMPACT Domains (n, %)**

DOMAIN	USED AS PROM	USED AT BASELINE ONLINE	USED AS INCLUSION/EXCLUSION CRITERION ONLINE
<b>Pain</b>			
<b>1: Pain intensity</b>			
Numerical Rating Scale (NRS)	160 (63.7)	0	0
NRS with recommended range	156 (62.2)	0	5 (2.0)
NRS with recommended wording	16 (6.4)	0	2 (0.8)
NRS with recommended wording and range <sup>†</sup>	16 (6.4)	0	0
NRS with other range	1 (0.4)	0	0
NRS with other wording	114 (45.4)	0	0
NRS range not reported	4 (1.6)	0	3 (1.2)
NRS wording not reported	30 (12.0)	0	5 (2.0)
Visual Analogue Scale (VAS) <sup>†</sup>	75 (29.9)	0	0
McGill Pain Questionnaire (MPQ) VAS <sup>†</sup>	69 (27.5)	2 (0.8)	5 (2.0)
Brief Pain Inventory (BPI) NRS <sup>†</sup>	62 (24.7)	0	0
Categorical scale	17 (6.8)	0	2 (0.8)
Categorical scale with recommended anchors <sup>†</sup>	1 (0.4)	0	0
Categorical scale with other anchors	14 (5.6)	0	2 (0.8)
Categorical scale with anchors not reported	2 (0.8)	0	0
NRS/VAS/categorical scale for the intensity of specific neuropathic pain qualities	16 (6.4)	0	0
Gracely Box Scale	10 (4.0)	0	0
Present Pain Intensity (PPI)	4 (1.6)	0	0
<b>2: Pain other aspects</b>			
<b>2a: Rescue analgesics</b>			
	60 (23.9)	0	0
<b>2b: Neuropathic pain quality</b>			
Neuropathic Pain Symptom Inventory (NPSI) <sup>†</sup>	28 (11.2)	0	0
Neuropathic Pain Scale (NPS) <sup>†</sup>	23 (9.2)	0	0
PainDETECT Questionnaire (PD-Q) <sup>†</sup>	5 (2.0)	1 (0.4)	1 (0.4)
Douleur Neuropathique en 4 Questions (DN4) <sup>†</sup>	1 (0.4)	1 (0.4)	9 (3.6)
Self-administered Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) <sup>†</sup>	1 (0.4)	1 (0.4)	4 (1.6)
Pain Quality Assessment Scale (PQAS)	1 (0.4)	0	0
Neuropathic Pain Questionnaire (NPQ) <sup>†</sup>	0	0	1 (0.4)
<b>2c: Unspecific pain quality</b>			
McGill Pain Questionnaire (MPQ) <sup>†</sup>	66 (26.3)	1 (0.4)	0
NRS/VAS for pain unpleasantness <sup>†</sup>	3 (1.2)	0	0
Patient assessment for Low Back Pain-Symptoms (PAL-S) and -Impact (PAL-I)	1 (0.4)	0	0
Other questionnaires	3 (1.2)	1 (0.4)	0
<b>2d: Temporal aspects</b>			
	12 (4.8)	0	0
<b>2e: Other aspects related to pain</b>			
NRS/VAS/VRS for pain relief	51 (20.3)	0	0
Global rating of pain relief	2 (0.8)	0	0
Integrated Pain Score (IPS)	1 (0.4)	0	0
Borg's Category Ratio (CR-10)	1 (0.4)	0	0
Other questionnaires	10 (4.0)	0	1 (0.4)
<b>3: Physical functioning</b>			
<b>3a: Daily activities and well-being</b>			
Brief Pain Inventory (BPI) <sup>†</sup>	66 (26.3)	0	0
36-Item Short Form Survey (SF-36) <sup>†</sup>	66 (26.3)	0	0
Euroqol EQ-5D (EQ-5D) <sup>†</sup>	38 (15.1)	0	1 (0.4)
Pain Disability Index (PDI) <sup>†</sup>	8 (3.2)	0	0
NRS/VAS pain interference	7 (2.8)	0	0
Oswestry Disability Index (ODI) <sup>†</sup>	6 (2.4)	0	0
12-Item Short Form Survey (SF-12)	5 (2.0)	0	0
Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (QOL-DN)	4 (1.6)	0	0
The West Haven-Yale Multidimensional Pain Inventory (WHYMPI)	4 (1.6)	0	0
WHYMPI as recommended <sup>†</sup>	0	0	0
Work Productivity and Activity Impairment Specific Health Problems Questionnaire (WPAI-SHP)	4 (1.6)	0	0

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Table 2. Continued

DOMAIN	USED AS PROM	USED AT BASELINE ONLINE	USED AS INCLUSION/EXCLUSION CRITERION ONLINE
Functional Independence Measure (FIM) instrument	3 (1.2)	0	0
Sickness Impact Profile (SIP) <sup>†</sup>	3 (1.2)	0	0
Craig Handicap Assessment and Reporting Technique (CHART)	3 (1.2)	0	0
Roland-Morris Disability Questionnaire (RMDQ) <sup>†</sup>	3 (1.2)	0	0
NRS/VAS daily activity	2 (0.8)	0	0
Sheehan Disability Scale (SDS)	2 (0.8)	0	0
Multiple Sclerosis Quality of Life-54 (MS-QoL-54)	2 (0.8)	0	0
International Spinal Cord Injury Basic Pain Data Set (ISCIBPDS)	1 (0.4)	0	0
Patient-Specific-Functional Scale (PSFS)	1 (0.4)	0	0
Walk-12	1 (0.4)	0	0
Shortened, restructured Treatment Outcomes in Pain Survey (S-TOPS)	1 (0.4)	0	0
Life Satisfaction Questionnaire 9 (LISAT-9)	1 (0.4)	0	0
Nottingham Extended Activities of Daily Living Scale (NEADL)	1 (0.4)	0	0
EORTC Quality of Life Questionnaire - Core Questionnaire (EORTC QLQ-C30)	1 (0.4)	0	0
EORTC Quality of life - Head and Neck Cancer Module (EORTC QLQ-H&N35)	1 (0.4)	0	0
Functional Assessment of Cancer Therapy - Gynecologic Oncology Group-Neurotoxicity (FACT&GOG-Ntx)	1 (0.4)	0	0
RAND 36-Item Health Survey	1 (0.4)	0	0
American Chronic Pain Association 10 point Quality of Life Scale	1 (0.4)	0	0
World Health Organization Quality of Life assessment instrument (WHOQOL-BREF)	1 (0.4)	0	0
Guy's Neurological Disability Scale (GNDS)	1 (0.4)	0	0
Functional Interference Estimate (FIE)	1 (0.4)	0	0
Linear Analogue Self-Assessment (LASA)	1 (0.4)	0	0
Peripheral Neuropathy Quality of Life Instrument (PN-QOL-97)	1 (0.4)	0	0
Edmonton Symptom Assessment System (ESAS)	1 (0.4)	0	0
Neuropathic Pain Impact on Quality-of-Life Questionnaire (NePI-QoL)	1 (0.4)	0	0
Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) <sup>†</sup>	1 (0.4)	0	0
NRS/VAS quality of life	1 (0.4)	0	0
Modified Fatigue Impact Scale (MFIS)	0	1 (0.4)	0
Other questionnaires	15 (6.0)	0	0
<b>3b: Sleep</b>			
Daily Sleep Interference Scale (DSIS) <sup>†</sup>	38 (15.1)	0	0
NRS/VAS sleep interference	27 (10.8)	0	0
Medical Outcomes Study Sleep scale (MOS Sleep) <sup>†</sup>	19 (7.6)	0	0
NRS/VAS sleep disturbance	15 (6.0)	0	0
NRS/VAS sleep scale	9 (3.6)	0	0
Chronic Pain Sleep Inventory (CPSI)	5 (2.0)	0	0
Insomnia Severity Index (ISI)	3 (1.2)	0	0
Jenkins Sleep Evaluation Questionnaire (JSEQ)	2 (0.8)	0	0
Pittsburgh Sleep Quality Index (PSQI)	1 (0.4)	0	0
Stanford Sleepiness Scale (SSS)	1 (0.4)	0	0
Leeds Sleep Evaluation Questionnaire (LSEQ)	1 (0.4)	0	0
Epworth Sleepiness Scale (ESS)	1 (0.4)	0	0
Pain and Sleep Questionnaire (PSQ)	1 (0.4)	0	0
Athens Insomnia Scale (AIS)	1 (0.4)	0	0
Other questionnaires	15 (6.0)	0	1 (0.4)
<b>4: Emotional functioning</b>			
Hospital Anxiety and Depression Scale (HADS) <sup>†</sup>	28 (11.2)	1 (0.4)	0
Profile of Mood States (POMS) <sup>†</sup>	24 (9.6)	0	0
Beck Depression Inventory (BDI) <sup>†</sup>	22 (8.8)	1 (0.4)	5 (2.0)
NRS/VAS depression or anxiety	5 (2.0)	0	0
Center for Epidemiologic Studies Depression Scale (CES-D)	5 (2.0)	0	0
Major Depression Inventory (MDI)	3 (1.2)	1 (0.4)	0
Beck Anxiety Inventory (BAI)	3 (1.2)	1 (0.4)	0
Zung Self-Rating Depression Scale (SDS)	2 (0.8)	0	0

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Table 2. Continued

DOMAIN	USED AS PROM	USED AT BASELINE ONLINE	USED AS INCLUSION/EXCLUSION CRITERION ONLINE
Pain Catastrophizing Scale (PCS) <sup>†</sup>	1 (0.4)	1 (0.4)	0
Generalized Anxiety Disorder Assessment (GAD-7)	1 (0.4)	0	0
Columbia-Suicide Severity Rating Scale (C-SSRS)	1 (0.4)	1 (0.4)	2 (0.8)
Depression, Anxiety, and Positive Outlook Scale (DAPOS)	1 (0.4)	0	0
Geriatric Depression Scale (GDS)	1 (0.4)	0	0
Mental Health Inventory (MHI)	1 (0.4)	0	0
Spielberger State-Trait Anxiety Inventory (SSTAI)	1 (0.4)	0	0
General Health Questionnaire (GHQ-12)	1 (0.4)	0	0
Patient Health Questionnaire (PHQ-9/-15/-8)	0	2 (0.8)	2 (0.8)
Brief Scale for Psychiatric problems in Orthopaedic Patients (BS-POP)	0	1 (0.4)	0
Mini-International Neuropsychiatric Interview (MINI)	0	0	4 (1.6)
<b>5: Global improvement and satisfaction</b>			
Patient Global Impression of Change (PGIC) <sup>†</sup>	112 (44.6)	0	0
Patient Global Impression of Improvement (PGI-I)	6 (2.4)	0	0
Satisfaction With Life Scale (SWLS)	3 (1.2)	0	0
Pain Treatment Satisfaction Scale (PTSS)	3 (1.2)	0	0
Patient-Rated Global Assessments of Treatment Benefit, Satisfaction, and Willingness to Continue (BSW)	3 (1.2)	0	0
Treatment Satisfaction Questionnaire for Medication (TSQM)	2 (0.8)	0	0
Self-Assessment of Treatment (SAT) Questionnaire	2 (0.8)	0	0
NRS subjective satisfaction of treatment	1 (0.4)	0	0
Global Perceived Effect (GPE)	1 (0.4)	0	0
Other questionnaires	18 (7.2)	0	0
<b>6: Participant disposition</b>			
Concomitant medication	16 (6.4)	0	0
Blinding	6 (2.4)	0	0
Other questionnaires	9 (3.6)	0	0
<b>8: Others</b>			
NRS/VAS spasticity rating	5 (2.0)	0	0
NRS/VAS intensity of neuropathy symptoms	5 (2.0)	0	0
NRS/VAS muscle stiffness and spasms	4 (1.6)	0	0
Karnofsky Performance Status Scale	2 (0.8)	0	2 (0.8)
Minnesota Multiphasic Personality Inventory (MMPI)	2 (0.8)	0	0
Neuropathy Symptom and Change (NSC)	2 (0.8)	0	0
Penn Spasm Frequency Scale (PSFS)	2 (0.8)	0	0
NRS/VAS neuropathic pruritus	1 (0.4)	0	0
Small Fiber Neuropathy and Symptoms Inventory Questionnaire (SFN-SIQ)	1 (0.4)	0	0
MOS Cognitive Functioning Scale (MOS Cog)	1 (0.4)	0	0
Other questionnaires	9 (3.6)	0	0
Neuropathy Total Symptom Score - 6 items (NTSS-6)	0	0	1 (0.4)
Michigan Neuropathy Screening Instrument (MNSI)	0	0	6 (2.4)

<sup>†</sup>recommended by IMMPACT and/or NeuPSIG

domains, and only 1 examined 5 domains. In total, 37.3% of the high/moderate quality studies investigated at least 4 domains by a recommended PROM compared to only 8.8% of studies with low quality.

### Combination of Domains

Although more than half of the high/moderate quality studies included at least 3 domains, the exact combination of domains differed between the studies. The most common, but overall rare, 3-way combination was 'pain intensity' (used in nearly all of the studies), 'pain quality', and 'physical functioning' (10/217; 4.6%). Overall, this combination was assessed by 29.5% of all high/moderate quality studies (64/217), including 10 studies

using 3 domains, 20 studies using 4 domains, 29 studies using 5 domains, and 5 studies using all 6 domains. A detailed overview of all domain combinations is given in [Appendix Figure 1](#).

### Additional Sub-Analyses

The comparison of studies that have been published before (n = 146) versus after the publication (n = 105) of the IMMPACT<sup>14</sup> and NeuPSIG recommendations<sup>19</sup> showed similar results as compared to the quality-dependent analysis, although the differences were less pronounced ([Fig. 5](#) and [6](#)). The domains 'physical functioning' with both subdomains related to 'daily activities/well-being' and 'sleep', and 'global

**Table 3. List of PROMs used in Studies with Moderate or High Methodological Quality (n, %)**

DOMAIN	USED AS PROM
<b>Pain</b>	
<b>1: Pain intensity</b>	
Numerical Rating Scale (NRS)	153 (70.5)
NRS with recommended range	149 (68.7)
NRS with recommended wording	14 (6.5)
NRS with recommended wording and range <sup>†</sup>	14 (6.5)
NRS with other range	1 (0.5)
NRS with other wording	111 (51.2)
NRS range not reported	4 (1.8)
NRS wording not reported	28 (12.9)
McGill Pain Questionnaire (MPQ) VAS <sup>†</sup>	64 (29.5)
Brief Pain Inventory (BPI) NRS <sup>†</sup>	56 (25.8)
Visual Analogue Scale (VAS) <sup>†</sup>	56 (25.8)
NRS/VAS/categorical scale for the intensity of specific neuropathic pain qualities	13 (6.0)
<b>Categorical scale</b>	
Categorical scale with recommended anchors <sup>†</sup>	1 (0.5)
Categorical scale with other anchors	9 (4.1)
Categorical scale with anchors not reported	2 (0.9)
Gracely Box Scale	6 (2.8)
Present Pain Intensity (PPI)	4 (1.8)
<b>2: Pain other aspects</b>	
<b>2a: Rescue analgesics</b>	
54 (24.9)	
<b>2b: Neuropathic pain quality</b>	
Neuropathic Pain Symptom Inventory (NPSI) <sup>†</sup>	27 (12.4)
Neuropathic Pain Scale (NPS) <sup>†</sup>	22 (10.1)
PainDETECT Questionnaire (PD-Q) <sup>†</sup>	4 (1.8)
Doleur Neuropathique en 4 Questions (DN4) <sup>†</sup>	1 (0.5)
<b>2c: Unspecific pain quality</b>	
McGill Pain Questionnaire (MPQ) <sup>†</sup>	61 (28.1)
NRS/VAS for pain unpleasantness <sup>†</sup>	2 (0.9)
Patient assessment for Low Back Pain-Symptoms (PAL-S) and -Impact (PAL-I)	1 (0.5)
Other questionnaires	2 (0.9)
<b>2d: Temporal aspects</b>	
8 (3.7)	
<b>2e: Other aspects related to pain</b>	
NRS/VAS/VRS for pain relief	41 (18.9)
Global rating of pain relief	1 (0.5)
Borg's Category Ratio (CR-10)	1 (0.5)
Other questionnaires	6 (2.8)
<b>3: Physical functioning</b>	
<b>3a: Daily activities and well-being</b>	
36-Item Short Form Survey (SF-36) <sup>†</sup>	62 (28.6)
Brief Pain Inventory (BPI) <sup>†</sup>	60 (27.6)
Euroqol EQ-5D (EQ-5D) <sup>†</sup>	36 (16.1)
Pain Disability Index (PDI) <sup>†</sup>	8 (3.7)
NRS/VAS pain interference	7 (3.2)
The West Haven-Yale Multidimensional Pain Inventory (WHYMPI)	4 (1.8)
WHYMPI as recommended <sup>†</sup>	0
Work Productivity and Activity Impairment Specific Health Problems Questionnaire (WPAI-SHP)	4 (1.8)
12-Item Short Form Survey (SF-12)	4 (1.8)
Oswestry Disability Index (ODI) <sup>†</sup>	4 (1.8)
Functional Independence Measure (FIM) instrument	3 (1.4)
Sickness Impact Profile (SIP) <sup>†</sup>	3 (1.4)
Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (QL-DN)	3 (1.4)

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**Table 3. Continued**

DOMAIN	USED AS PROM
Craig Handicap Assessment and Reporting Technique (CHART)	
NRS/VAS daily activity	2 (0.9)
Roland-Morris Disability Questionnaire (RMDQ) <sup>†</sup>	2 (0.9)
Sheehan Disability Scale (SDS)	2 (0.9)
International Spinal Cord Injury Basic Pain Data Set (ISCBPDS)	1 (0.5)
Walk-12	1 (0.5)
Shortened, restructured Treatment Outcomes in Pain Survey (S-TOPS)	1 (0.5)
Life Satisfaction Questionnaire 9 (LISAT-9)	1 (0.5)
Nottingham Extended Activities of Daily Living Scale (NEADL)	1 (0.5)
Functional Assessment of Cancer Therapy - Gynecologic Oncology Group-Neurotoxicity (FACT&GOG-Ntx)	1 (0.5)
RAND 36-Item Health Survey	1 (0.5)
American Chronic Pain Association 10 point Quality of Life Scale	1 (0.5)
World Health Organization Quality of Life assessment instrument (WHOQOL-BREF)	1 (0.5)
Guys Neurological Disability Scale (GNDS)	1 (0.5)
Functional Interference Estimate (FIE)	1 (0.5)
Multiple Sclerosis Quality of Life-54 (MS-QoL-54)	1 (0.5)
Peripheral Neuropathy Quality of Life Instrument (PN-QOL-97)	1 (0.5)
Neuropathic Pain Impact on Quality-of-Life Questionnaire (NePI-QoL)	1 (0.5)
Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) <sup>†</sup>	1 (0.5)
NRS/VAS quality of life	1 (0.5)
Other questionnaires	10 (4.6)
<b>3b: Sleep</b>	
Daily Sleep Interference Scale (DSIS) <sup>†</sup>	38 (17.5)
NRS/VAS sleep interference	26 (12.0)
Medical Outcomes Study Sleep scale (MOS Sleep) <sup>†</sup>	19 (8.8)
NRS/VAS sleep disturbance	14 (6.5)
NRS/VAS sleep scale	6 (2.8)
Chronic Pain Sleep Inventory (CPSI)	5 (2.3)
Insomnia Severity Index (ISI)	3 (1.4)
Jenkins Sleep Evaluation Questionnaire (JSEQ)	2 (0.9)
Pittsburgh Sleep Quality Index (PSQI)	1 (0.5)
Stanford Sleepiness Scale (SSS)	1 (0.5)
Leeds Sleep Evaluation Questionnaire (LSEQ)	1 (0.5)
Epworth Sleepiness Scale (ESS)	1 (0.5)
Pain and Sleep Questionnaire (PSQ)	1 (0.5)
Athens Insomnia Scale (AIS)	1 (0.5)
Other questionnaires	12 (5.1)
<b>4: Emotional functioning</b>	
Hospital Anxiety and Depression Scale (HADS) <sup>†</sup>	27 (12.4)
Profile of Mood States (POMS) <sup>†</sup>	23 (10.6)
Beck Depression Inventory (BDI) <sup>†</sup>	16 (7.4)
Major Depression Inventory (MDI)	3 (1.4)
Beck Anxiety Inventory (BAI)	3 (1.4)
Zung Self-Rating Depression Scale (SDS)	2 (0.9)
NRS/VAS depression or anxiety	2 (0.9)
Pain Catastrophizing Scale (PCS) <sup>†</sup>	1 (0.5)
Generalized Anxiety Disorder Assessment (GAD-7)	1 (0.5)
Columbia-Suicide Severity Rating Scale (C-SSRS)	1 (0.5)
	1 (0.5)

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Table 3. Continued

DOMAIN	USED AS PROM
Depression, Anxiety, and Positive Outlook Scale (DAPOS)	
Mental Health Inventory (MHI)	1 (0.5)
Spielberger State-Trait Anxiety Inventory (SSTAI)	1 (0.5)
General Health Questionnaire (GHQ-12)	1 (0.5)
Center for Epidemiologic Studies Depression Scale (CES-D)	5 (2.3)
<b>5: Global improvement and satisfaction</b>	
Patient Global Impression of Change (PGIC) <sup>†</sup>	108 (49.8)
Patient Global Impression of Improvement (PGI-I)	5 (2.3)
Satisfaction With Life Scale (SWLS)	3 (1.4)
Pain Treatment Satisfaction Scale (PTSS)	3 (1.4)
Patient-Rated Global Assessments of Treatment Benefit, Satisfaction, and Willingness to Continue (BSW)	3 (1.4)
Treatment Satisfaction Questionnaire for Medication (TSQM)	2 (0.9)
Self-Assessment of Treatment (SAT) Questionnaire	2 (0.9)
NRS subjective satisfaction of treatment	1 (0.5)
Global Perceived Effect (GPE)	1 (0.5)
Other questionnaires	12 (5.5)
<b>6: Participant disposition</b>	
Concomitant medication	14 (6.5)
Blinding	6 (2.8)
Other questionnaires	8 (3.7)
<b>8: Others</b>	
NRS/VAS spasticity rating	5 (2.3)
NRS/VAS muscle stiffness and spasms	4 (1.8)
NRS/VAS intensity of neuropathy symptoms	4 (1.8)
Karnofsky Performance Status Scale	2 (0.9)
Minnesota Multiphasic Personality Inventory (MMPI)	2 (0.9)
Neuropathy Symptom and Change (NSC)	2 (0.9)
Penn Spasm Frequency Scale (PSFS)	2 (0.9)
Small Fiber Neuropathy and Symptoms Inventory Questionnaire (SFN-SIQ)	1 (0.5)
MOS Cognitive Functioning Scale (MOS Cog)	1 (0.5)
Other questionnaires	5 (2.3)

<sup>†</sup>recommended by IMMPACT and/or NeuPSIG

improvement and satisfaction' were more frequently assessed in clinical trials that have been published after 2011 compared to those published before this date. For the other domains, these differences were less clear ('pain intensity') or even reversed ('pain other aspects', 'emotional functioning'). Interestingly, the use of specific neuropathic pain PROMs, in particular to assess neuropathic pain qualities, significantly increased after the publication of the NeuPSIG recommendations.<sup>19</sup> Thus, about 36% (of the studies published after 2011 (n = 105) included at least 1 specific PROM for 'neuropathic pain quality' like the Neuropathic Pain Scale (NPS), the Neuropathic Pain Symptom Inventory (NPSI), or the PainDETECT Questionnaire (PD-Q). By contrast, the use of unspecific pain quality questionnaires significantly decreased after the publication of these recommendations.

In addition, the percentage of studies assessing the single domains by at least 1 recommended PROM was higher in studies with a parallel group design, those that were sponsored by a pharmaceutical/industrial

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company and those with a larger sampler size of randomized patients compared to the respective counterpart (Appendix Figure 2). In particular, this was true for the domains 'physical functioning', 'emotional functioning' and 'global improvement and satisfaction'. Similarly, the number of domains assessed by at least 1 recommended PROM was higher in the industry-supported, larger and parallel design studies (Appendix Figure 3). In contrast, sub-analysis on the pain condition revealed no/different results (Appendix Figure 3).

## Adverse Events

In total, 27.5% of all studies used a scale or questionnaire to assess adverse events that occurred under the investigated treatment (Table 4). Most often, these were simple verbal scales with anchors such as mild/moderate/severe or light/moderate/bothersome/unacceptable. Specific questionnaires such as the Columbia Suicide Severity Rating Scale (C-SSRS) were used only by a minority of studies.

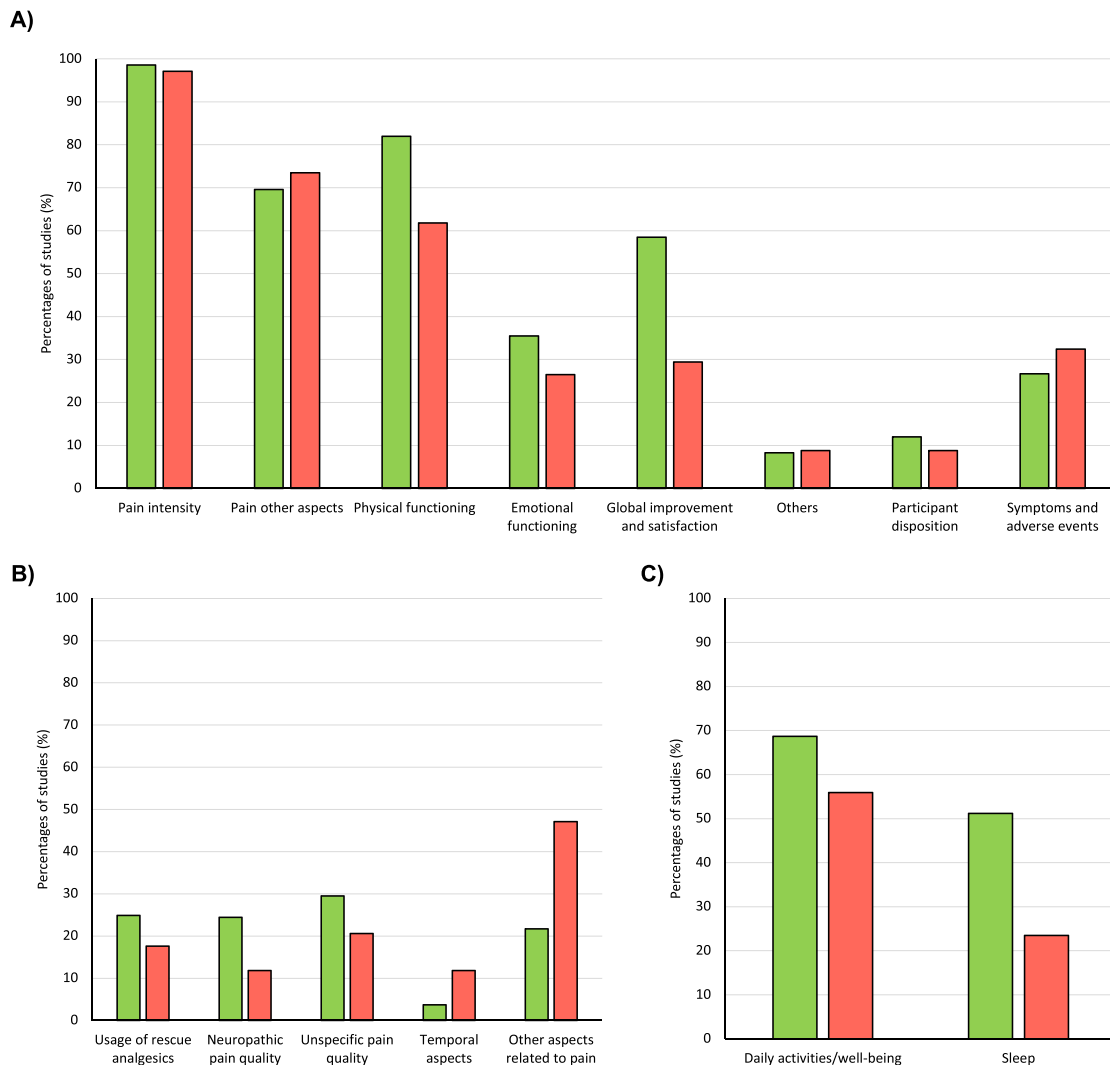
## Discussion

This SLR indicates that the number of domains and recommended PROMs used in neuropathic pain RCTs has increased over the last 2 decades, probably as a result of the publication of experts' recommendations. However, our study also indicates that still a minority of good quality studies are assessing more than 3 domains and that many different, so far non-recommended PROMs are still used. Thus, there is a large heterogeneity in outcome assessment on the domain and PROM level.

## Definition of Core Outcome Domains

A first step towards higher comparability of clinical studies is the definition of outcome domains for RCTs on chronic neuropathic pain. To address this, IMMPACT has recommended a core set of outcome domains including 'pain', 'physical functioning', 'emotional functioning', 'participants ratings of global improvement and satisfaction', 'symptoms and adverse events' and 'participant disposition' for chronic pain clinical trials regardless of the pain entity in 2003.<sup>32</sup> These recommendations based on expert consensus were generally well accepted by the community. Thus, most of these domains were endorsed with only minor changes by other experts, in particular neurologists involved in recommendations for the assessment of neuropathic pain.<sup>11,19</sup> The applicability of these recommendations and their impact on the design of neuropathic pain RCTs have however rarely been assessed.

As a potential consequence of these recommendations, our SLR shows that trials published after 2011 tend to examine more domains compared to those published before 2011. Nevertheless, only a minority of studies covered all recommended domains by at least 1 recommended PROM, including also studies published later than 2011. Overall, the less frequently assessed domains are 'sleep' (47.4%) and 'emotional functioning' (34.3%). Previous review articles that analyzed the use



**Figure 2.** Percentages of studies assessing the different IMMPACT/NeuPSIG domains by at least one PROM (regardless of whether the PROM was explicitly recommended) depending on their methodological quality (high or moderate quality (green)  $n=217$ , low quality (red)  $n=34$ ). (A) All main domains, (B) 'Pain other aspects' subdomains 'usage of rescue analgesics', 'neuropathic pain quality', 'unspecific pain quality', 'temporal aspects' and 'other aspects related to pain', (C) 'Physical functioning' subdomains 'daily activities/well-being' and 'sleep'.

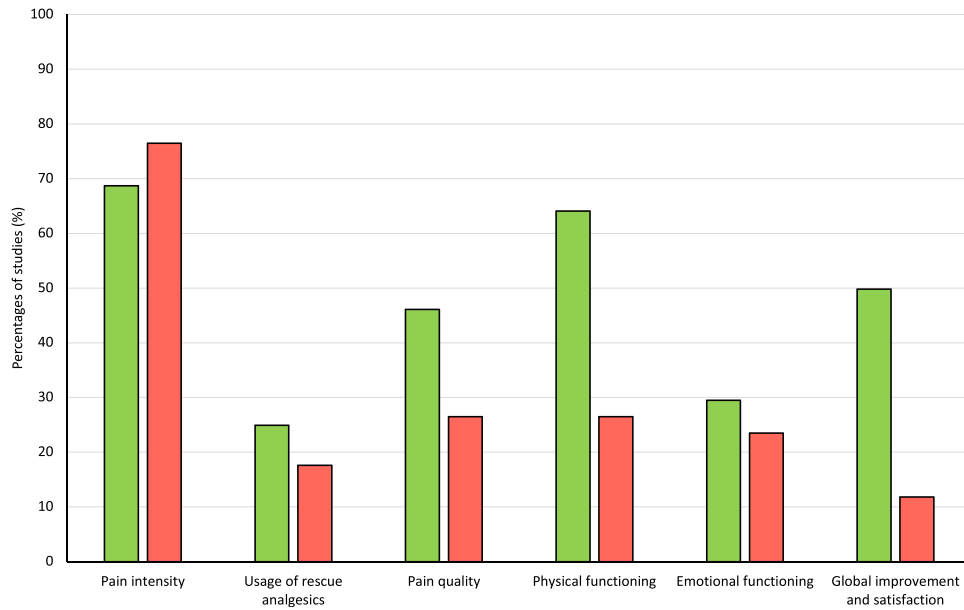
of IMMPACT domains in systematic reviews or meta-analyses of interventions for neuropathic pain revealed similar results, although with differences in the exact frequency. Mehta and colleagues<sup>22</sup> reported that 'physical functioning' was assessed in only 15% of trials, which is much lower compared to the results of Dosevovic et al.<sup>13</sup> (53%) and to those presented here. These differences could be due to several reasons. First, these analyses were based on SLRs rather than individual RCTs. Second, they extracted all outcome measures, not only PROMs but also other clinical outcome assessments. Finally, these previously published reviews searched databases only up to 2012 and 2015, respectively.

To identify the domains regarded by authors as the most relevant for chronic neuropathic pain trials, we focused our analyses on studies with at least moderate methodological quality. Although a larger number of domains were assessed in these studies in comparison with the low quality ones, there was a high variability

regarding the combinations of domains. The most frequently assessed domain was 'pain intensity' followed by 'physical functioning', 'pain other aspects', 'global improvement and satisfaction'. In particular, there was an increase in the assessment of neuropathic pain qualities in higher quality studies. This increase even gets more pronounced in more recent studies. By contrast, 'emotional functioning' and the subdomain 'sleep' were less frequently assessed.

### Definition of PROMs for Chronic Neuropathic Pain

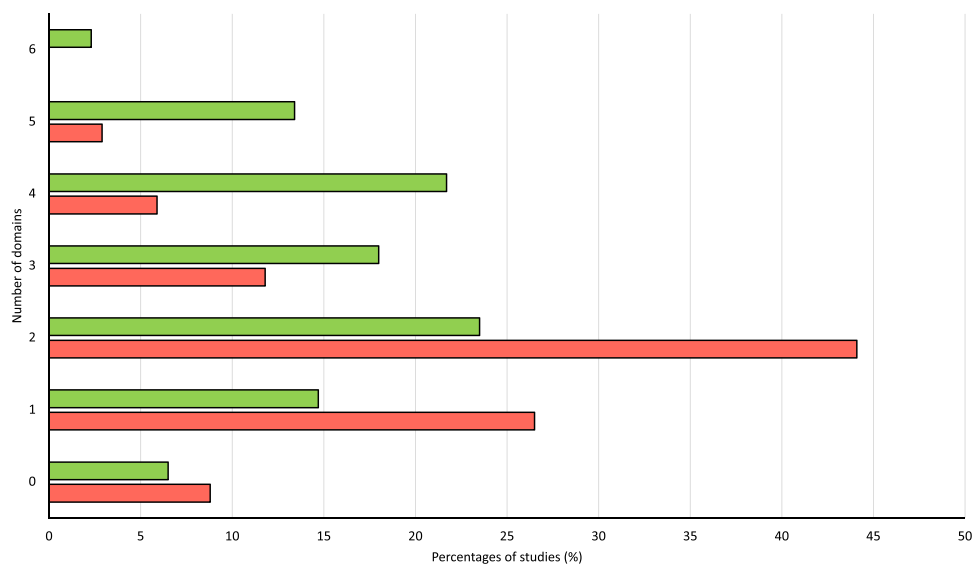
Recommendations of specific PROMs used to assess the proposed domains were made by certain expert groups, ie, by IMMPACT<sup>14</sup> and NeuPSIG.<sup>19</sup> The recommendations for specific PROMs were based on a number of criteria, including validity of content, reliability, validity, interpretability, respondent and administrator acceptability, etc.



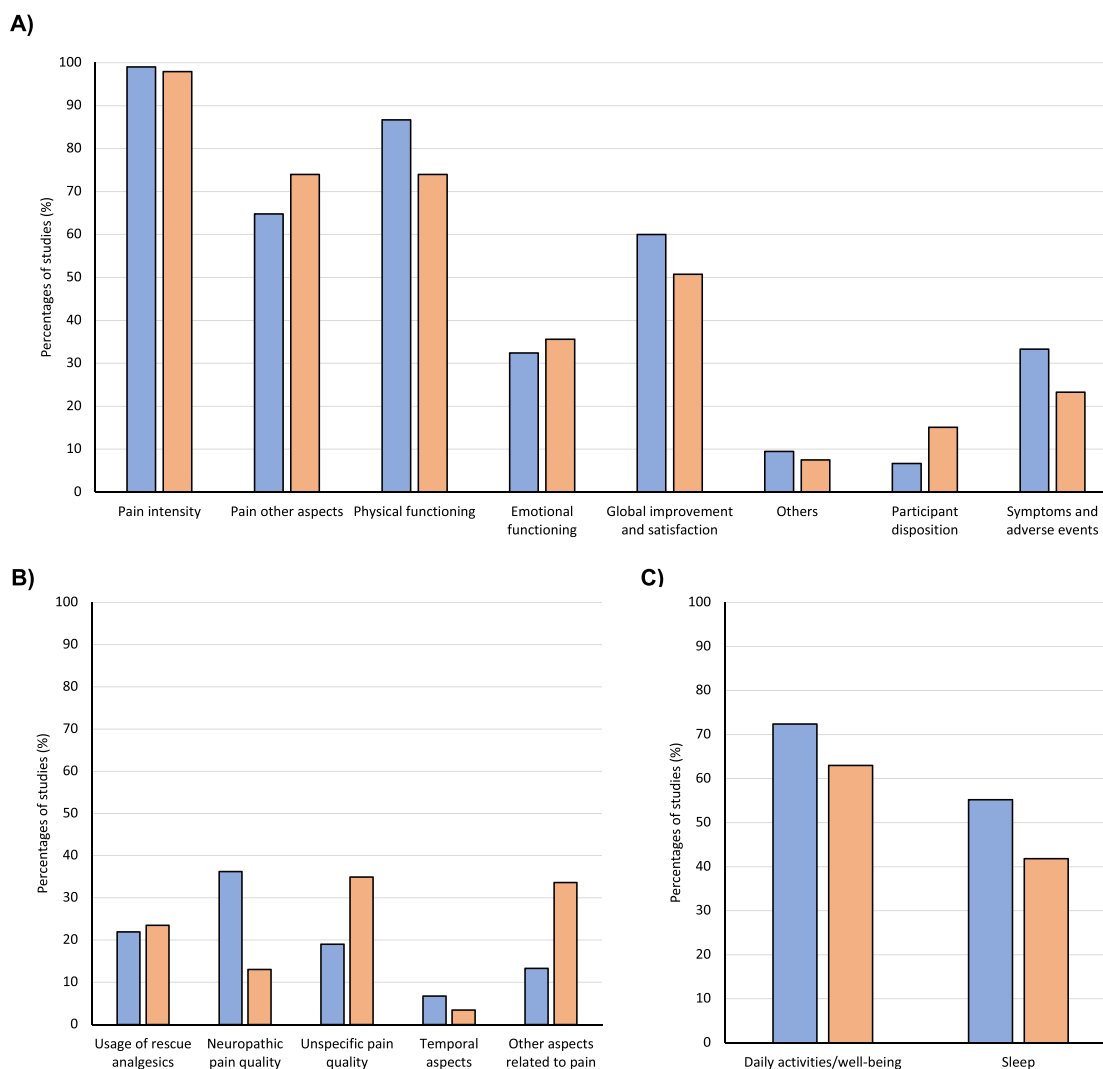
**Figure 3.** Percentages of studies assessing the different IMMPACT/NeuPSIG domains by at least one recommended PROM depending on their methodological quality (high or moderate quality (green) n = 217, low quality (red) n = 34).

Here again, although the IMMPACT and NeuPSIG recommendations had a lot in common, there were some differences. In general, the number of PROMs recommended for each domain by NeuPSIG was larger and included, when possible, PROMs specifically validated in neuropathic pain.<sup>19</sup> In the 251 articles analyzed here, a total of 200 different PROMs were identified, including 27 PROMs which were recommended explicitly by IMMPACT and/or NeuPSIG. This large number reflects the heterogeneity of the studies, which strongly decreases their comparability. Interestingly, however, our data indicate that the PROMs most frequently used in the good quality studies corresponded to those recommended by IMMPACT or NeuPSIG. As recommended, a NRS for ‘pain intensity’ was used in 71%, and the PGIC for ‘global improvement and satisfaction’ in almost half of the high/moderate quality

studies. Similarly, although they were not used in many studies, the PROMs used most frequently to assess ‘emotional functioning’ (Beck Depression Inventory [BDI], Profile of Mood States [POMS], Hospital Anxiety and Depression Scale [HADS]) corresponded to those recommended. By contrast, other tools recommended by NeuPSIG, such as the PCS or the Pain-coping Inventory, were rarely used. The same is true for the other subdomains such as ‘sleep’ or ‘daily activities and well-being’, although there was a larger heterogeneity in the PROMs used to assess these subdomains. This could be related to the fact that physical functioning comprises different aspects, eg, sleep, working ability, interference with daily activities, whereas pain intensity is quite clearly defined. Thus, 81 questionnaires were used for ‘physical functioning’, whereas ‘pain intensity’ was assessed with



**Figure 4.** Number of domains that were assessed by at least one recommended PROM depending on the methodological quality (high or moderate quality (green) n = 217, low quality (red) n = 34).



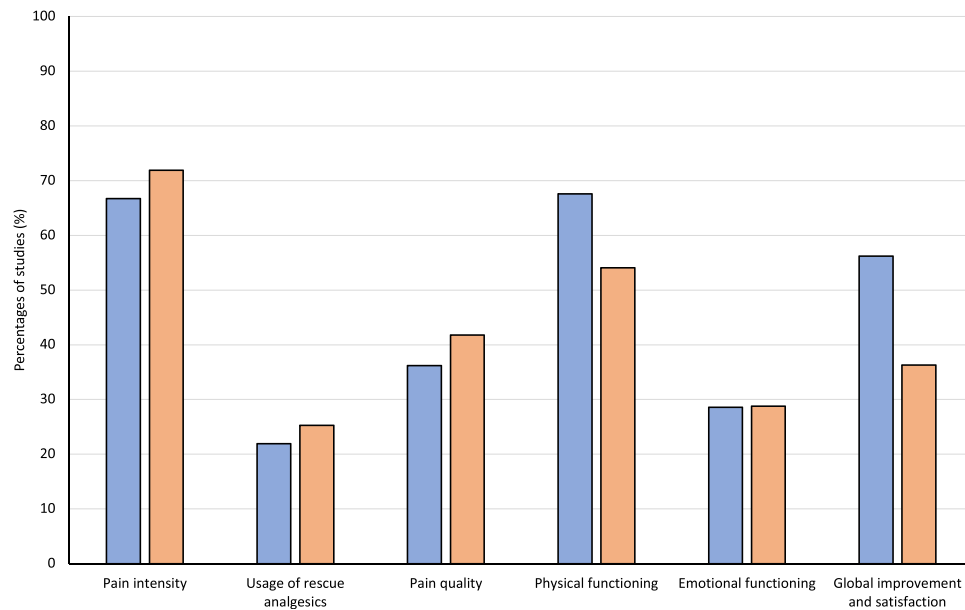
**Figure 5.** Percentages of studies assessing the different IMMPACT/NeuPSIG domains by at least one PROM (regardless of whether the PROM was explicitly recommended) depending on the publication year (after 2011 (blue)  $n = 105$ , before or in 2011 (orange)  $n = 146$ ). (A) All main domains, (B) 'Pain other aspects' subdomains 'usage of rescue analgesics', 'neuropathic pain quality', 'unspecific pain quality', 'temporal aspects' and 'other aspects related to pain', (C) 'Physical functioning' subdomains 'daily activities/well-being' and 'sleep'.

only 8 different PROMs. Our data also showed that specific neuropathic pain PROMs were more frequently used in recent studies, and in those with a higher quality. This was particularly true for questionnaires assessing neuropathic pain qualities like the NPS, NPSI, and PD-Q as recommended by NeuPSIG. By contrast, the use of questionnaires that generally ask about pain quality (not specifically neuropathic pain), such as the MPQ, has decreased.

### Prediction of Treatment Response

Questionnaires can be used not only as outcome parameters, but also at baseline to identify patients' subgroups and predict treatment outcome. In this context, pain experts have advocated a more personalized therapeutic approach to neuropathic pain based on clinical profiles consisting of specific combinations of symptoms and signs that may reflect pathophysiological mechanisms.<sup>4,5,7,17,27</sup> Accordingly, the latest IMMPACT

recommendations for patient phenotyping in chronic pain trials encouraged the use of specific questionnaires assessing neuropathic pain qualities.<sup>15</sup> Another potential interest of this approach could be the identification of specific sensory profiles which may reflect distinct pathophysiological mechanisms.<sup>8,30</sup> Consistent with these hypotheses, several studies using these questionnaires have shown that different analgesic drugs do not act uniformly on pain, but preferentially on specific signs or symptoms or combinations thereof.<sup>1,3,12</sup> Other patients' characteristics could also have predictive value to the treatment response. In particular, some studies have suggested that the severity of sleep disturbances, depression, anxiety, or catastrophizing at baseline could predict treatment responses in patients with neuropathic pain.<sup>21,31,34</sup> Although most of these data were based on post hoc analyses, they suggest that, besides pain intensity, neuropathic pain qualities, sleep disturbances, and mood should be more systematically assessed in future clinical trials.



**Figure 6.** Percentages of studies assessing the different IMMPACT/NeuPSIG domains by at least one recommended PROM depending on the publication year (after 2011 (blue) n = 105, before or in 2011 (orange) n = 146).

## Limitations

Our SLR comprises several limitations. First, our analysis is purely descriptive; we did not perform a meta-analysis and did not evaluate the psychometric properties of the extracted PROMs. Second, PROMs were assigned to already published domains instead of redefining domains based on our results. Third, data extraction and quality assessment were conducted by 3 reviewers, each assessing one third of the studies, which might have led to discrepancies, especially in quality rating. To

reduce discrepancies, the first ten studies were reviewed independently by the examiners, and extraction and quality assessment were conducted following standardized criteria. However, the quality assessment of the studies itself is subjective and can only provide a rough estimate. Although we followed the GRADE criteria,<sup>18</sup> this approach has several limitations; for example, the number of included patients is not part of these criteria. To mitigate these limitations, we decided to summarize moderate and high quality studies. Finally, our analyses may have underestimated the number of domains assessed in some studies. This could be due to the fact that our categorization of domains was rather stringent, whereas questionnaires like the BPI cover several domains, including physical, emotional functioning, and some aspects of disability. Also, some health-related quality of life questionnaires (eg, SF-36 or -12, EQ-5D) include items related to emotional and physical functioning.

**Table 4. List of Questionnaires used to Assess Adverse Events**

	USED (N, %)
<b>Simple scale</b>	
Mild/moderate/severe	16 (6.4)
Light/moderate/bothersome/unacceptable	8 (3.2)
NRS/VAS intoxication	3 (1.2)
1=not at all, 4=severe	1 (0.4)
Other scale	15 (6.0)
<b>Questionnaire</b>	
Columbia-Suicide Severity Rating Scale (C-SSRS)	6 (2.4)
Beck Depression Inventory (BDI)	4 (1.6)
Sheehan Suicidality Tracking Scale	3 (1.2)
Patient Assessment of Constipation Symptoms (PAC-SYM)	2 (0.8)
Opiate Withdrawal Scale	2 (0.8)
Constipation Assessment Scale (CAS)	1 (0.4)
Brief Pain Inventory (BPI)	1 (0.4)
NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE)	1 (0.4)
Linear Analogue Self-Assessment (LASA)	1 (0.4)
Patient Health Questionnaire (PHQ-9/-15/-8)	1 (0.4)
Quick Inventory of Depressive Symptomatology (QIDSSR)	1 (0.4)
Other questionnaire	9 (3.6)

## Conclusions and Future Steps

This SLR shows that neuropathic pain assessment via PROMs in clinical trials has significantly improved over the last years. However, our data also tend to confirm that the set of outcome domains recommended by IMMPACT and NeuPSIG is not systematically assessed even in good quality clinical trials. This may be due to the fact that the IMMPACT recommendations focus on chronic pain in general and not on chronic neuropathic pain in particular. The NeuPSIG recommendations are more specific for neuropathic pain conditions. However, although there is no 'gold'-standard available for the development of a core outcome set (COS), a stepwise approach containing systematic research and consensus processes is more and more accepted to be used.<sup>35</sup> In addition, patient involvement in the consensus process



of a COS is highly emphasized; this acknowledges the patient's perspective by establishing outcome assessments which matter to patients.<sup>26,35</sup> Furthermore, psychometric properties of PROMs need to be taken into account for selecting the best suited outcome measures.<sup>24</sup> For neuropathic pain, a Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) guided process defining a certain minimum of domains and PROMS might be a consequent next step.

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## Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jpain.2022.09.003>.

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