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Core outcome domains for clinical trials on somatic symptom disorder, bodily distress disorder and functional syndromes: Euronet-SOMA recommendations

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Abstract

Objective: The harmonization of core outcome domains in clinical trials facilitates comparison and pooling of data, and simplifies the preparation and review of research projects, and comparison of risks and benefits of treatments. Therefore we provide recommendations for the core outcome domains that should be considered in clinical trials on the efficacy and effectiveness of interventions for somatic symptom disorder, bodily distress disorder, and functional syndromes.

Methods: The **Euro**pean **Net**work on **soma**tic symptom disorders group (EURONET-Soma) of more than 20 experts in the field met twice in Hamburg to discuss issues of assessment and intervention research in somatic symptom disorder, bodily distress disorder, and functional syndromes. The consensus meetings identified core outcome domains that should be considered in clinical trials evaluating treatments for somatic symptom disorder and associated functional syndromes.

Results : The following core domains should be considered when defining ascertainment methods in clinical trials: (1) classification of somatic symptom disorder/bodily distress disorder, associated functional syndromes, and comorbid mental disorders (using structured clinical interviews), duration of symptoms, medical morbidity, and prior treatments (2) location, intensity, and interference of somatic symptoms, (3) associated psychobehavioral features and biological markers, (4) illness consequences (quality of life, disability, health care utilization, health care costs), (5) global improvement, treatment satisfaction, and (6) unwanted negative effects.

Conclusions: The proposed criteria are intended to improve synergies of clinical trials and to facilitate decision making when comparing different treatment approaches. These recommendations should not result in inflexible guidelines, but increase consistency across investigations in this field.

Words: 250

Key Words: somatization, somatoform, bodily distress, functional somatic syndromes, fibromyalgia, irritable bowel syndrome.

Abbreviations:

BDD Bodily Distress Disorder

BDS Bodily Distress Syndrome Checklist

CIDI Composite International Diagnostic Interview

DSM Diagnostic and Statistical Manual for Mental Disorders

EMA Ecological Momentary Assessment

EuroQoL European Quality of Life Group

HrQoL health related quality of life

IBS: Irritable Bowel Syndrome

IDCL International Diagnostic Check List

NAS Numeric Analogue Scale

IMMPACT Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials

PHQ Patient Health Questionnaire

QALY: Quality adjusted Life years

SCAN Schedules for Clinical Assessment in Neuropsychiatry

SCID Structured Clinical Interview for DSM-IV/DSM-5 disorders

SCL Symptom Check List

SOMS-7 Screening for Somatoform Symptoms, last 7 days

SSD Somatic Symptom Disorder

SSD-12 Somatic Symptom Disorder Scale

Ascertainment methods, addressed domains and outcome reports in intervention trials on bodily distress disorder (BDD), somatic symptom disorder (SSD)/somatoform disorders and functional syndromes vary substantially. This has impeded evaluations of the efficacy and effectiveness of suggested treatment approaches. Current interventions on somatic symptom and associated disorders reveal moderate effect sizes for psychological interventions (1, 2), but also for pharmacological interventions like tricyclic antidepressants (3), which can be a result of moderately effective treatments, but also of flaws of assessment strategies. Agglomeration of results of intervention trials (e.g., in meta-analyses) is blurred by assessment tools that are not sufficiently evaluated about their sensitivity to assess change, by a large variability of assessment tools, by a lack of including relevant core domains for comparability, and other factors (2, 4).

The development of a core set of outcome domains and quality criteria has been shown to improve comparison and pooling of data of intervention trials, while leaving investigators free to extend the core set with other instruments of their choice. In pain research, the introduction of the so-called IMMPACT criteria (5-7) led to a substantial improvement of the comparability and potential for accumulation of clinical trials. The introduction of quality criteria for intervention studies, such as the CONSORT criteria or the quality criteria of Cochrane analyses substantially improved the average quality of published clinical trials, and reduced the risk of publication of false-positive results. In the field of BDD, SSD and functional syndromes, the development of a recommended core set of outcome domains is still lacking, although assessment recommendations for single functional somatic syndromes have been published (e.g., for fibromyalgia (8)). Therefore the European Network on somatic symptom disorders (Euronet-SOMA) aimed to find a consensus for core domains to be assessed in the evaluation of interventions in the general field of somatic symptoms and associated disorders.

Methods

Two meetings of more than 20 European experts took place in Hamburg (Germany), and were organized by Bernd Löwe and his team in 2016. Several subgroups addressed different topics of research in somatic symptom disorder. Members of this subgroup were experienced in the conduct of clinical trials, and aggregation of different trial results. During the first session, we defined the clinical conditions of interest. After discussing different options, a consensus was reached to address somatic symptom disorder, bodily distress disorder, and associated functional syndromes. Reasons for this decision were the fact that these syndromes pretend to describe specific clinical conditions, although they are highly overlapping. The concept of somatic symptom disorder is defined in DSM-5; bodily distress disorder was originally defined by the Danish group of Per Fink, and it was shown that this definition covers most forms of somatization and functional somatic syndromes (9, 10). For several functional somatic syndromes, current definitions and classification

criteria exist (e.g., ROME-III criteria for irritable bowel syndrome (11); fibromyalgia criteria (12)). To develop a consensus for assessment domains, we analyzed the IMMPACT criteria, results of Cochrane and other meta-analyses in the field of SSD or BDD, recommendations for outcome measurement in specific syndromes, such as irritable bowel syndrome and fibromyalgia, general recommendations about the assessment of change in psychosomatic, psychiatric and psychological research, as well as specific results on the quality of assessing change of various assessment tools (e.g.,(13)).All participants of this specific working group were invited to name existing recommendations for outcome measurements of the corresponding groups. These nominations were collected and grouped to domains. The resulting proposal of domains was presented during the second meeting, and further discussed. These discussions led to further adaptations. After the second meeting, the resulting proposal was circulated twice to find a general agreement. Afterwards, this agreement was further circulated to the overall group, and finally harmonized. The final proposal was accepted by all group members. Of note, while recommendations for the assessment of trait variables and current state variables of somatic symptoms in particular for epidemiological research have been published elsewhere (4), more specific challenges of selecting tools for the assessment of change are addressed in this paper.

Results

All clinical trials of this field should consider reporting in agreement with the general quality criteria for clinical trials, such as the CONSORT criteria, with their specific recommendations. In particular, the description of interventions, the selection of participants, inclusion and exclusion criteria, the definition of concurrent treatments, the assessment of treatments during follow-up periods, randomization and blinding procedures, statistical management of missing values and drop-outs, adherence to treatment guidelines etc. are crucial pre-requisites to evaluate scientific rigor and clinical implications of these trials.

The CONSORT criteria suggest defining specific primary outcome variables. In addition to identifying the primary outcome of a trial, present recommendations add a broad variety of assessment domains relevant to SSRD/BDD, to facilitate the comparison and agglomeration of different clinical intervention effects. To accomplish this goal, we had to consider the broad variety of diagnoses, concepts, and approaches of this clinical group. We recommend the following domains to be addressed in clinical trials (for an overview see **Table 1**):

(1) Classification of disorder, comorbid mental and physical conditions

In a field where differing terminologies and classifications have all too often hampered transparency and comparability, a clear definition of the disorder in question and its comorbid aspects is of prime importance. While DSM-5 and/or

ICD-11 diagnoses should be adequately addressed, broader and/or additional ways of classification can be useful considering the limited duration of validity of current classification systems. For the purpose of classification, structured clinical interviews are the current gold standard of assessments in particular for mental disorders. Various evaluated methods exist with specific strength and limitations, such as the structured clinical interview for DSM classification SCID (14), the Composite International Diagnostic Interview (CIDI) (15), the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (16), among other interviews. A semi-structured approach such as the International Diagnostic Check Lists (IDCL) (17) can offer an economic alternative. In any case, a clear description of the selected sample and consideration of inclusion and exclusion criteria requires the use of one of these types of instruments. While a clear description of inclusion criteria is a prerequisite of high quality trials, investigators should be aware of the tremendous overlap of symptom profiles and other characteristics of functional somatic syndromes (10, 18). Therefore it is crucial to use broad-spectrum assessments for multiple symptoms or multi-symptomatic syndromes in addition to focusing on any particular symptom profile. Symptom onset, symptom duration, and treatment pre-experiences should be additionally investigated. A re-assessment at end-of-treatment and/or follow-up is strongly recommended. In combination with potential expert disability ratings (see below), these ratings should be done by raters blinded to the treatment selected for this patient - this could lead to expert ratings of remission and response rates.

The diagnosis of Somatic Symptom Disorder according to DSM-5 as well as the current ICD-11 proposal of Bodily Distress Disorder do not exclude the existence of comorbid medical conditions. SSD can be used as a diagnosis even if *all* somatic symptoms are explained on the background of a medical disease, such as cancer, because for the SSD diagnosis the burden of the symptoms is more relevant than the postulated etiology. Several functional somatic syndromes require that their core symptoms (e.g. abdominal pain in case of irritable bowel syndrome) are not mainly explained by a general medical disease. Nevertheless, also these functional syndromes often co-occur with physical diseases. Moreover, co-occurring medical conditions influence other relevant clinical outcome measures and health care use (19) Therefore it is crucial to assess the co-occurrence of physical diseases carefully. Binary checklists for somatic illnesses, such as the WHO checklist of chronic diseases in the SCAN (16) help to ensure that a comprehensive description of the somatic and psychological dimensions of the patient's medical status is given. In more severely affected or inpatient samples, the updated Charlson comorbidity index could also be relevant (20). Depending on the research question, repeated measurement could be useful.

(2) Assessment of somatic symptoms

While DSM-5 has shifted the focus of classification from the assessment of somatic symptoms to the consideration of concurrent psychosocial factors, clinical

trials should continue to assess the different facets of somatic symptoms (e.g., multiplicity of symptoms, location and type of symptoms, intensity, occurrence, duration, interference with daily activities) as change in symptoms will continue to be a central outcome feature of treatments for patients and physicians/ therapists alike. Although more sophisticating assessment tools are additionally necessary, we recommend the use of two numerical rating scales (NRS; see **Table 2**) to assess

- Symptom intensity
- Symptom interference with daily activities

The field of pain research has strongly benefited from using these two simple to use NRS. It allows comparing the efficiency of interventions between clinical trials. NRS have been shown to be sensitive to the assessment of change, valid, and simple to use (21) . A commonly used time frame for assessing somatic symptoms with a NRS is 7 days.

Self-rating scales should be used that are specifically evaluated to assess changes of somatic symptoms. While the Patient Health Questionnaire PHQ-15 is one of the most frequently used instruments to identify people at risk for somatization, its sensitivity to assess change was only sparsely evaluated (22). However, it has shown treatment effects in some evaluation trials (e.g., (23)). The somatization subscale of the Symptom Checklist SCL-90R is also frequently used, albeit its specificity for somatic symptom disorder is less clear (24). The Screening for Somatoform Symptoms (SOMS-7) has been evaluated for the sensitivity to assess change (25), but represents a very broad assessment tool. The Bradford Somatic Inventory (BSI) claims to be valid for multiple ethnic groups (26), which is an aspect that was frequently neglected during assessment tool evaluation. The Bodily Distress Syndrome Checklist (BDS) has been validated as a screening tool for bodily distress syndrome (27), but its sensitivity to assess change needs further evaluation.

In contrast to pain research, symptom diaries and other experience sampling methods are less frequently used in the field of SSD or BDD. However, they could provide information that goes far beyond self-rating scales, and new technologies are further facilitating their application (28)(e.g., ecological momentary assessments EMA). Multiple assessments allow the analysis of patterns of change, and the use of time-lag analyses. If diaries are used, it is recommended not only to use “negative” items (e.g., current symptom intensity), but also to address positive features (e.g., current ability to cope with symptoms, current ability to enjoy life despite of symptoms) (29).

(3) Psychobehavioral features

DSM-5 introduced classification-relevant psychobehavioral features of SSD, such as health anxiety, illness worry, excessive time and energy spent on the symptoms or health concerns. Therefore these features are part of the classification process (domain #1), but often they also determine significant parts

of the overall suffering of patients, and they also belong to potential mechanisms of symptom development and symptom maintenance. Therefore they also constitute a core outcome domain. Several assessment tools have been developed to investigate these features. The frequently used Whiteley-Index WI is a well-established and economic instrument to assess health anxiety (30), but also other instruments have demonstrated sensitivity to assess change in this field (31). New developments try to cover the full spectrum of the B-criteria of somatic symptom disorder (i.e., the cognitive, affective and behavioral impact of symptoms), e.g. the Somatic Symptom Disorder Scale (SSD-12) (32). Again, their sensitivity to assess change has to be further evaluated.

Anxiety and depression are frequently co-occurring psychopathological phenomena. Therefore the assessment of broader psychopathology beyond somatization is strongly recommended. Typical assessment tools are the SCL-90R, the anxiety and depression subscales of the Patient Health Questionnaire PHQ (33-35), or other self- and expert ratings on psychopathology (36, 37)

The assessment of psychological features of the disorders should also address potential *mechanisms of change/mediators*. Somatosensory amplification (38) describes the vicious circle of illness anxieties, attention focusing, and amplified perception of symptoms, and catastrophizing of symptoms (39). This mechanism shows close relationships with bodily vigilance (40). Fear avoidance has been shown to be one of the most powerful predictors of the development of symptom persistence/chronicity (41), and it is considered to be a major maintaining factor for these types of symptoms (42). Patients can show dysfunctional illness behavior that contributes to the maintenance of symptoms. Many interventions try to improve symptom coping skills, and reduction in fear avoidance or symptom catastrophizing partially mediates treatment effects across various syndromes (43, 44). These variables should be addressed accordingly. Illness beliefs in general, such as assumptions about the etiology of symptoms, suspected medical explanations, expected course and treatment responses are examples of components of illness beliefs. Some of these components can be dysfunctional (e.g. in contributing to high health expenditures (45)), and need to be changed during interventions. A typical instrument to assess these illness beliefs is the Illness Perception Questionnaire (46), which is also available in a shortened version (47). However, depending on the rationale of the treatment approach, other mechanisms of change can be postulated, and should be assessed accordingly (e.g., emotion regulation, attachment insecurity (48), reduction of avoidance behavior, reduction of symptom reinforcement via relatives, increase of acceptance and mindfulness, and communication skills). The assessment of mediators could be complemented with the evaluation of potential moderators (e.g., personality traits such as neuroticism or negative affectivity, gender, age).

(4) Illness consequences (Qualtiy of life and disability assessment)

Health related quality of life (HrQoL) is the most relevant outcome domain in this field, and its assessment should address issues such as physical functioning, psychological and emotional functioning, but also functioning in social roles. The most frequently used assessment tool for HrQoL is the Short Form SF-36 or its abbreviated version SF-12 (49, 50). This has been specifically adapted for the use in the field of SSD (51). As an alternative or extension to the assessment of HrQoL, assessments of disability are highly recommended. A frequently used assessment tool that is both economic and valid to assess change is the Pain Disability Inventory, which has been adapted to somatic symptoms in general (52). Also frequently used are the Sheehan Disability Scales (53). Finally, health care costs and health care utilization are considered to be of pivotal relevance in somatization syndromes, in particular because a substantial subgroup of patients is characterized by continuous health-care seeking. Although variables of health care use and costs are notoriously associated with statistical distribution and evaluation problems, their financial relevance should motivate to address this issue in clinical trials. In combination with health economic research questions, the assessment of quality-adjusted life years (QALY) is needed. For this purpose instruments such as the EuroQol (EQ-5D; (54)) or the SF-6D (55) can be used as an alternative to the SF-36. Recently, the reQOL has been developed which has been validated to give a better assessment of QOL in mental disorders (www.reqol.org.uk/p/overview.html).

(5) Consumer satisfaction

A global rating on treatment success from the perspective of the patient is also highly recommended. It is obvious that the definition of improvement by a patient can substantially differ from the improvements shown in symptom scales, or as evaluated via clinical expert ratings. Additionally, treatment satisfaction can also represent a variable that is of substantial relevance, but not identical to other suggested variables. The “recommendation item” (“Would you recommend this treatment to another person/a friend with similar problems?”) is one possible simple item that could be used in all clinical trials to assess treatment satisfaction. Consumer satisfaction scales have been developed for other clinical fields (56), but can be easily adapted to the focus group of this manuscript.

The effect of psychological interventions strongly depends on factors such as credibility of treatment, therapeutic relationship, and expectation of improvement. Therefore their assessment is recommended if psychological interventions are compared and evaluated. A brief scale to address these topics has been suggested (57). For the assessment of the quality of the therapeutic relationship, several screeners have been published (e.g. (58, 59)).

(6) Unwanted negative treatment effects

A scientifically-based treatment recommendation requires an evaluation of the expected positive treatment effects in relation to potential negative outcomes. However, even in pharmacology research, side effects are frequently assessed

with unsatisfactory methods (60, 61). Over the last century, psychotherapy research has also neglected the issue of unwanted negative effects (62). However, considering the vulnerable states of many patients with SSD/BDD as well as the many problematic experiences that patients report from past treatments, it is strongly recommended to assess unwanted negative effects during and after treatment. It is not considered sufficient just to add one or two open questions, and to rate their answers by experts about their relevance, as was frequently done in pharmacology research (63). More systematic assessments for negative effects are required both in psychological intervention trials and pharmacological intervention trials; just recently, assessment tools to ascertain negative effects of psychotherapy have been developed, although this field is just at the beginning of validating corresponding instruments (64, 65). In pharmacological trials, systematic and structured assessments should complement registrations that are more spontaneous and observation-based (65, 66).

Discussion

In this manuscript, we present consensus recommendations on which domains should be covered when planning the assessment tools in clinical trials in the field of SSD, BDD, and functional syndromes. While such a multidimensional approach should not replace other quality criteria of clinical trials (such as the definition of primary outcome variables), it should facilitate the comparability between clinical trials and help optimize the accumulation of results from different trials, e.g. in meta-analyses or Cochrane analyses.

A harmonization of assessments between clinical trials has the potential to not only substantially improve trial quality per se, but also the synergistic potentials between trials. It would be extremely helpful to have at least one or two very simple assessment methods that should be part of most clinical trials such as two suggested NRS on symptom intensity and interference with daily activities respectively (domain #2). Moreover, the definition of domains should also help to decrease the notorious lack of information, as soon as other than the primary variables are analyzed in meta-analyses. When features such as comorbid emotional problems, psychobehavioral features (domain #3) and illness consequences (quality of life and disability ; domain #4) are subject of agglomeration of trials, often less than 30% of the original trials provide full data (1). In such a situation, where the majority of published trials cannot be used, scientific and clinical progress will be unnecessarily delayed, and most conclusions from clinical trials must remain incomplete.. Moreover, a systematic consideration of potential mediators and moderators of interventions offers a basis for targeted treatment decisions. Therefore we expect a major breakthrough if these recommendations are considered in future clinical trials.

While the IMMPACT criteria and CONSORT criteria offer stimulating and thoughtful recommendations, a specific adaptation to the field of SSD, BDD, and functional syndromes is necessary. CONSORT offers a general quality framework for all clinical trials, which needed to be more specified for the field of interest of this paper. Specific domains of necessary ascertainments beyond the definition of primary, secondary outcome variables, and side effects are not specified in CONSORT criteria, but in our paper. IMMPACT has a strong focus on specific pain syndromes. While pain syndromes are also of relevance for many functional syndromes, the scope has to be broadened up for SSD, BDD and functional syndromes, to address the multiplicity of symptoms, the large overlap between different functional syndromes, and considering that for some functional syndromes, non-pain symptoms are crucial (e.g., chronic fatigue). Therefore, not surprisingly, some recommendations of our approach show similarity to IMMPACT recommendations (e.g., physical and emotional functioning; participant ratings of improvement and satisfaction with treatment; symptoms and adverse events), while others are adapted to the field of interest (e.g., classification issues; how to address somatic conditions; addressing overlap between functional syndromes; distinction between illness consequences and psychobehavioral mechanisms).

Another advantage of these recommendations is the inclusion of frequently neglected, yet highly relevant variables. The neglect of assessing unexpected negative effects in clinical trials investigating psychological interventions is one of the most impressive examples of blind spots in clinical research. However, if interventions increase the risk of somatic symptom turbulences, emotional crisis, suicidal ideation, or if patients feel that they are not taken seriously, such an intervention should be considered more critically compared to other interventions with similar benefits, but fewer of these negative effects. Therefore an adequate benefit-risk-evaluation requires not only the assessment of treatment advantages, but also of treatment-related problems (domain #5). These unwanted treatment outcomes may also influence patients' consumer satisfaction of the intervention, which is another important outcome (domain #6)..

When summarizing these recommendations, it also became evident that cultural adaptations of instruments are mostly lacking. This is all the more problematic, as somatic symptoms are embedded and experienced in the context of culture and language and thus differ in terms of type, location, intensity and ways of communicating them. Most intervention trials included patients with diverse backgrounds, and these effects of diversity can further add to uncontrolled variance if instruments are used without cultural equivalence or adaptation.

Publishing recommendations always bears the risk of over-standardization, while research progress needs some competition between conflicting approaches. Our aim is to provide a set of domains which are advantageous to address, rather than setting strict standards for future trials. Although we mention several specific assessment tools, this is only done to highlight examples for the field, while the genuine

recommendations primarily cover the six core domains. It remains up to the investigators to select assessment tools for these domains, but also to extend the suggested domains with other fields of interest. However, we want to encourage the use of multi-methodological approaches: the use of expert ratings can easily lead to over-estimations of intervention effects, and should always be complemented with validated self-ratings focusing on patient's perspective (67, 68).

Moreover we want to emphasize that in addition to statistical significance also clinical significance should be considered. Clinical significance accounts for the clinical relevance of individual patient's response to a treatment. There are many different methods of analyzing clinical relevance. For continuous data the reliable change index has been recommended since it incorporates the standard error of the measurement depending on the measurement's reliability . However the cut-off of the RCI>1.96 indicating reliable change is not feasible for the assessment of change of somatic symptom intensity, and is highly dependent on the variability of the assessment tool as well as the correlation of the assessment tool over repeated measures. For dichotomous data the number needed to treat for another beneficial outcome (NNTB) is often used which is defined as the number of participants that needed to be treated for one to benefit in a given time frame. Since clinical significance regarding the outcome domains has not been examined sufficiently for our field, empirical criteria of clinically significant change cannot be provided. We refer to a recommendation by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) which provides provisional criteria for interpreting the clinical importance of treatment outcomes in clinical trials of patients with chronic pain (69). For example, a decrease of 30% on a 0-10 NRS measuring pain intensity was defined as a moderately important change, and a decrease of ≥50% as a substantial improvement. The proposed multi-domain assessments will enable investigation of whether such improvements are paralleled by changes in other domains relevant to SSD, BDD and functional symptom disorders.

For the evaluation of clinical trials, there is no need to show improvements on all recommended domains for a single intervention, and in most cases it will be essential to establish an *a priori* primary outcome measure. However, it is important to realize that treatment effects can differ substantially between the specific domains. Treatments can substantially improve quality of life, although not change symptom intensity (e.g., if the focus is on acceptance strategies). The relevance of specific core domains can also vary depending on selection criteria and aim of the study: if, for instance, patients with abnormal health care use are selected for treatments, the effects on health care utilization can be of more relevance than the effect on comorbid emotional problems. Moreover, the relevance of each domain partially depends on one's theoretical perspective or clinical interest. For referring physicians, the improvement of symptoms could be of major interest, whereas the reduction of health care utilization could be more relevant for health care insurances. Similarly, working ability and role functioning are crucial from a societal perspective; and for the patient and significant others issues related to life satisfaction are likely to be

essential treatment outcomes. These examples highlight that the recommended core domains reveal relevant and necessary information to evaluate a specific treatment of interest in comparison to other treatments, and to reveal the relevant information for the specific interest group.

While the IMMPACt criteria of pain research stimulated the development of the EuronetSOMA criteria, the later ones try to extend this proposal, and to tailor it specifically to the field of somatic symptom disorder, bodily distress disorder, and functional syndromes. Specific recommendations are included how to address the diversity of included syndromes, how to address comorbid medical conditions, or how to assess unwanted negative effects of interventions. Beyond these more specific recommendations, the attempt to harmonize domains of evaluation methods is expected to accelerate progress of intervention research in this field. Therefore, we anticipate that the recommendations of core domains for outcome assessment in clinical trials of somatic symptom disorder will result in more consistency in trial design and output assessment with the goal of improving interpretability and generalizabilityof clinical trials in this field.

Conflict of Interest:

WR declares that he was part of the group inventing the Screening for Somatoform Symptoms SOMS-7 for outcome assessment in somatoform disorders, and of the INEP to assess negative effects of psychotherapeutic interventions. PF and AS invented the concept of bodily distress disorder, and PF was involved in the development of the Bodily Distress Syndrome Checklist. AT, WR, PH and BL were involved in the development of the SSI-12. All further authors declare no conflict of interest that could have influenced the content of this manuscript.

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References

1. van Dessel N, den Boeft M, van der Wouden JC, Kleinstauber M, Leone SS, Terluin B, Numans ME, van der Horst HE, van Marwijk H. Non-pharmacological interventions for somatoform disorders and medically unexplained physical symptoms (MUPS) in adults. Cochrane Database of Systematic Reviews. [Review]. 2014.
2. Kleinstäuber M, Witthöft M, Hiller W. Efficacy of short-term psychotherapy for multiple medically unexplained physical symptoms: A meta-analysis. Clinical Psychology Review. 2011;31:146-60.
3. Kleinstauber M, Witthoft M, Steffanowski A, van Marwijk H, Hiller W, Lambert MJ. Pharmacological interventions for somatoform disorders in adults. Cochrane Database of Systematic Reviews. 2014.
4. Zijlema WL, Stolk RP, Lowe B, Rief W, White PD, Rosmalen JGM, BioShaRe. How to assess common somatic symptoms in large-scale studies: A systematic review of questionnaires. Journal of Psychosomatic Research. 2013;74:459-68.
5. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;113:9-19.
6. Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, Cleeland C, Dionne R, Farrar JT, Galer BS, Hewitt DJ, Jadad AR, Katz NP, Kramer LD, Manning DC, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robinson JP, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Witter J. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain. 2003;106:337-45.
7. Turk DC, Dworkin RH, Burke LB, Gershon R, Rothman M, Scott J, Allen RR, Atkinson JH, Chandler J, Cleeland C, Cowan P, Dimitrova R, Dionne R, Farrar JT, Haythornthwaite JA, Hertz S, Jadad AR, Jensen MP, Kellstein D, Kerns RD, Manning DC, Martin S, Max MB, McDermott MP, McGrath P, Moulin DE, Nurmikko T, Quessy S, Raja S, Rappaport BA, Rauschkolb C, Robinson JP, Royal MA, Simon L, Stauffer JW, Stucki G, Tollett J, von Stein T, Wallace MS, Wernicke J, White RE, Williams AC, Witter J, Wyrwich KW. Developing patient-reported outcome measures for pain clinical trials: IMMPACT recommendations. Pain. 2006;125:208-15.
8. Williams DA, Kratz AL. Patient-reported outcomes and fibromyalgia. Rheumatic Disease Clinics of North America. 2016;42:317-23.
9. Fink P, Rosendal M, Olesen F. Classification of somatization and functional somatic symptoms in primary care. Australian and New Zealand Journal of Psychiatry. 2005;39:772-81.
10. Fink P, Schröder A. One single diagnosis, bodily distress syndrome, succeeded to capture 10 diagnostic categories of functional somatic syndromes and somatoform disorders. Journal of Psychosomatic Research. 2010;68:415-26.
11. Drossman DA, Dumitrascu DL. Rome III: New standard for functional gastrointestinal disorders. Journal of Gastrointestinal and Liver Diseases. 2006;15:237.
12. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB, Yunus MB. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis care & research. 2010;62:600-10.
13. Burton C, Chowdhury S. Outcome measures for intervention trials in somatic symptom disorders. Journal of Psychosomatic Research. [Meeting Abstract]. 2016;85:58-9.
14. Spitzer RL, Williams JBW, Gibbon M, First MB. The structured clinical interview for DSM-III-R (SCID). 1. History, rationale, and description. Archives of General Psychiatry. 1992;49:624-9.
15. Wittchen HU, Höfler M, Gander F, Pfister H, Storz S, Üstün TB, Müller N, Kessler RC. Screening for mental disorders: performance of the Composite International Diagnostic-Screener (CID-S). International Journal of Methods in Psychiatric Research. 1999;8:59-70.
16. WHO. SCAN. Schedules for Clinical Assessment in Neuropsychiatry, version 2.1. Geneva: World Health Organization, Division of Mental Health; 1998.

17. Hiller W, Zaudig M, Mombour W. International Diagnostic Check Lists for ICD-10 and DSM-IV. Bern: Verlag Hans Huber; 1997.
18. Schröder A, Sharpe M, Fink P. Medically unexplained symptom management. Lancet Psychiatry. 2015;2:587-8.
19. Sha MC, Callahan CM, Counsell SR, Westmoreland GR, Stump TE, Kroenke K. Physical symptoms as a predictor of health care use and mortality among older adults. American Journal of Medicine. 2005;118:301-6.
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Chronic Diseases. 1987;40:373-83.
21. Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, Fainsinger R, Aass N, Kaasa S, EPCRC. Studies comparing numerical rating Scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: A systematic literature review. Journal of Pain and Symptom Management. 2011;41:1073-93.
22. Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: Validity of a new measure for evaluating the severity of somatic symptoms. Psychosomatic Medicine. 2002;64:258-66.
23. Sattel H, Lahmann C, Gündel H, Guthrie E, Kruse J, Noll-Hussong M, Ohmann C, Ronel J, Sack M, Sauer N, Schneider G, Henningsen P. Brief psychodynamic-interpersonal psychotherapy for patients with multisomatoform disorder: A randomised controlled trial. British Journal of Psychiatry. 2012;100:60-7.
24. Escobar JI, Rubio-Stipec M, Canino G, Karno M. Somatic symptoms index (SSI): A new and abridged somatization construct. - Prevalence and epidemiological correlates in two large community samples. The Journal of Nervous and Mental Disease. 1989;177:140 - 6.
25. Rief W, Hiller W. A new approach to the assessment of the treatment effects of somatoform disorders. Psychosomatics. 2003;44:492-8.
26. Mumford DB, Bavington JT, Bhatnagar KS, Hussain Y, Mirza S, Naraghi. The Bradford Somatic Inventory. British Journal of Psychiatry. 1991;158:379-86.
27. Busdtz-Lilly A, Fink P, Ornbol E, Vestergaard M, Moth G, Christensen KS, Rosendal M. A new questionnaire to identify bodily distress in primary care: The "BDS checklist". Journal of Psychosomatic Research. 2015;78:536-45.
28. Mehl MR, Conner TS. Handbook of Research Methods for Studying Daily Life. New York: Guilford; 2011.
29. Flor H, Turk DC. Chronic pain: An intergrated biobehavioral approach. Seattle, WA: IASP Press; 2011.
30. Conradt M, Cavanagh M, Franklin J, Rief W. Dimensionality of the Whiteley Index: Assessment of hypochondriasis in an Australian sample of primary care patients. Journal of Psychosomatic Research. 2006;60:137-43.
31. Weck F, Bleichhardt G, Hiller W. Screening for Hypochondriasis With the Illness Attitude Scales. Journal of Personality Assessment. [Article]. 2010;92:260-8.
32. Toussaint A, Murray AM, Voigt K, Herzog A, Gierk B, Kroenke K, Rief W, Henningsen P, Lowe B. Development and Validation of the Somatic Symptom Disorder-B Criteria Scale (SSD-12). Psychosomatic Medicine. 2016;78:5-12.
33. Martin A, Rief W, Klaiberg A, Braehler E. Validity of the Brief Patient Health Questionnaire Mood Scale (PHQ-9) in the General Population. General Hospital Psychiatry. 2006;28:71-7.
34. Löwe B, Schenkel I, Carney-Doebbeling C, Göbel C. Responsiveness of the PHQ-9 to psychopharmacological depression treatment. Psychosomatics. 2006;47:62-7.
35. Löwe B, Decker O, Müller S, Brähler E, Schellberg D, Herzog W, Herzberg PY. Validation and standardization of the generalized anxiety disorder screener (GAD-7) in the general population. Medical Care. 2008;46:266-74.
36. Beck AT, Ward CH, Medelson M, Mock F, Erbaugh F. An inventory for measuring depression. Archives of General Psychiatry. 1961;4:561-71.

37. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety:Psychometric properties. Journal of Consulting and Clinical Psychology. 1988;56:893-7.
38. Barsky AJ, Wyshak GL. Hypochondriasis and somatosensory amplification. British Journal of Psychiatry. 1990;157:404 - 9.
39. Severeijns R, Vlaeyen JW, van den Hout MA, Weber WE. Pain catastrophizing predicts pain intensity, disability, and psychological distress independent of the level of physical impairment. Clin J Pain. 2001;17:165-72.
40. Schmidt NB, Lerew DR, Trakowski JH. Body vigilance in panic disorder: Evaluating attention to bodily perturbations. Journal of Consulting and Clinical Psychology. 1997;65:214.
41. Chou R, Shekelle P. Will this patient develop persistent disabling low back pain? JAMA. 2010;303:1295-302.
42. Rief W, Mewes R, Martin A, Glaesmer H, Braehler E. Are psychological features useful in classifying patients with somatic symptoms? Psychosomatic Medicine. [Article]. 2010;72:648-55.
43. Frolund Pedersen H, Frostholm L, Sondergaard Jensen L, Ornbol E, Schröder A. Neuroticism and maladaptive coping in patients with functional somatic syndromes British Journal of Health Psychology. 2016;21:917-36.
44. Chalder T, Goldsmith KA, White PD, Sharpe M, Pickles AR. Rehabilitative therapies for chronic fatigue syndrome: a secondary mediation analysis of the PACE trial. Lancet Psychiatry. 2015;2:141-52.
45. Frostholm L, Petrie KJ, Ørnbøl E, Fink P. Are illness perceptions related to future healthcare expenditure in patients with somatoform disorders? Psychological Medicine. 2014;44:2903-11.
46. Moss-Morris R, Weinman J, Petrie KJ, Horne R, Cameron L, Buick D. The revised illness perception questionnaire (IPQ-R). Psychology and Health. 2002;17:1-16.
47. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. Journal of Psychosomatic Research. 2006;60:631-7.
48. Liu L, Cohen S, Schulz MS, Waldinger RJ. Sources of somatization: Exploring the roles of insecurity in relationships and styles of anger experience and expression. Social Science & Medicine. 2011;73:1436-43.
49. Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey - Construction of scales and preliminary tests of reliability and validity. Medical Care. 1996;34:220-33.
50. Ware JE. SF-36 health survey update. Spine. 2000;25:3130-9.
51. Schroder A, Rehfeld E, Ornbol E, Sharpe M, Licht RW, Fink P. Cognitive-behavioural group treatment for a range of functional somatic syndromes: randomised trial. British Journal of Psychiatry. 2012;200:499-507.
52. Mewes R, Rief W, Martin A, Glaesmer H, Braehler E. What is normal disability? – An investigation of disability in the general population. Pain. 2009;142:36-41.
53. Sheehan KH, Sheehan DV. Assessing treatment effects in clinical trials with the discan metric of the Sheehan Disability Scale. Int Clin Psychopharmacol. 2008;23:70-83.
54. Williams A. EuroQol — a new facility for the measurement of health-related qualityof life. Health Policy. 1990;16:199–208.
55. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. Journal of Health Economics. 2002;21:271-92.
56. Ivarsson B, Malm U. Self-reported consumer satisfaction in mental health services: Validation of a self-rating version of the UKU-Consumer Satisfaction Rating Scale. Nordic Journal of Psychiatry. 2007;61:194-200.
57. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. Journal of Behavior Therapy and Experimental Psychiatry. 2000;31:73-86.
58. Munder T, Wilmers F, Leonhart R, Linster HW, Barth J. Working Alliance Inventory-Short Revised (WAI-SR): Psychometric Properties in Outpatients and Inpatients. Clinical Psychology & Psychotherapy. [Article]. 2010;17:231-9.

59. Luborsky L, Barber JP, Siqueland L, Johnson S, NAJAVITS LM, FRANK A, DALEY D. The revised Helping Alliance questionnaire (HAQ-II): psychometric properties. The Journal of Psychotherapy Practice and Research. 1996;5:260.
60. Rief W, v. Lilienfeld-Toal A, Nestoriuc Y, Hofmann SG, Barsky A, Avorn J. Differences in adverse effect reporting in placebo groups in SSRI and tricyclic antidepressant trials. A systematic review and meta-analysis. Drug Safety. 2009;32:1041-56.
61. Pope A, Adams C, Paton C, Weaver T, Barnes TRE. Assessment of adverse effects in clinical studies of antipsychotic medication: survey of methods used. The British Journal of Psychiatry. 2010;197:67.
62. Crawford MJ, Thana L, Farquharson L, Palmer L, Hancock E, Bassett P, Clarke J, Parry GD. Patient experience of negative effects of psychological treatment: results of a national survey. British Journal of Psychiatry. 2016;208:260-5.
63. Rief W, Avorn J, Barsky AJ. Medication-attributed adverse effects in placebo groups. Implications for assessment of adverse effects. Archives of Internal Medicine. 2006;166:155-60.
64. Ladwig I, Rief W, Nestoriuc Y. What are the Risks and Side Effects to Psychotherapy? - Development of an Inventory for the Assessment of Negative Effects of Psychotherapy (INEP). Verhaltenstherapie. 2014;24:252-63.
65. Rief W, Barsky AJ, Glombiewski JA, Nestoriuc Y, Glaesmer H, Brähler E. Assessing general side effects in clinical trials: Reference data from the general population. Pharmacoepidemiology and Drug Safety. 2011;20:405-15.
66. Lingjaerde O, Ahlfors U, Bech P, Dencker S, Elgen K. The UKU side effect rating scale: A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatrica Scandinavica. 1987;76:1-100.
67. Cuijpers P, Li J, Hofmann SG, Andersson G. Self-reported versus clinician-rated symptoms of depression as outcome measures in psychotherapy research on depression: a meta-analysis. Clinical Psychology Review. 2010;30:768-78.
68. Rief W, Nestoriuc Y, Weiss S, Welzel E, Barsky AJ, Hofmann SG. Meta-analysis of the placebo response in antidepressant trials. Journal of Affective Disorders. 2009;118:1-8.
69. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, Haythornthwaite JA, Jensen MP, Kerns RD, Ader DN, Brandenburg N, Burke LB, Cella D, Chandler J, Cowan P, Dimitrova R, Dionne R, Hertz S, Jadad AR, Katz NP, Kehlet H, Kramer LD, Manning DC, McCormick C, McDermott MP, McQuay HJ, Patel S, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Revickl DA, Rothman M, Schmader KE, Stacey BR, Stauffer JW, Von Stein T, White RE, Witter J, Zavislc S. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. Journal of Pain. 2008;9:105-21.

Table 1: Overview on core domains to assess change in clinical trials on somatic symptom and associated disorders

Domain	***Specifications***
Classification of disorder and comorbid mental problems	Validated structured clinical interview including specific criteria for the most important associated syndromes (fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, etc.). Duration/onset of symptoms. Pre-treatments.
Assessment of somatic symptoms	2 NRS (0..10; see Table 2): - Symptom Intensity - Symptom Interference Self-rating symptom scales, Symptom diaries, EMA
Psychobehavioral features	B-criteria of DSM-5 Psychopathology (Depression, Anxiety) Potential mechanisms (health anxiety, psychobiological markers, a.o.)
Illness consequences	Quality of Life; disability Health care use
Consumer satisfaction	Treatment satisfaction; recommendation item; Therapeutic relationship; Expectations
Unwanted negative effects	Worsening of problems Unexpected new problems and symptoms Systematic side effects assessements

Table 2

Recommendations for 2 Numeric Analogue Scale Items to Be Used in Clinical Trials

Symptom Intensity:

During the last 7 days, the overall intensity of my bodily symptoms was:

No Symptoms at all — Worst possible symptoms

0 — 10

Symptom Interference:

During the last 7 days, my bodily symptoms interfered with daily life activities

Not at all — Interfered completely

0 — 10

Appendix

Recommendations for 2 Numeric Analogue Scale: Non-English examples

German:

* Symptom Stärke: Während der letzten 7 Tage war die Gesamtstärke meiner körperlichen Beschwerden: 0 = überhaupt keine Beschwerden – 10 = schlimmstmögliche Beschwerden

* Symptom Beeinträchtigung: Während der letzten 7 Tage haben mich meine körperlichen Beschwerden bei Alltagsaktivitäten beeinträchtigt: 0 = überhaupt nicht – 10 = extrem beeinträchtigt

Danish

*Symptomernes intensitet: Hvor intense har mine fysiske symptomer været i de sidste 7 dage?: 0 = slet ingen symptomer – 10 = værst mulige symptomer

*Symptomernes påvirkning: Hvor meget har mine fysiske symptomer påvirket mine dagligdags aktiviteter i de sidste 7 dage?: 0 = slet ikke påvirket – 10 = påvirket ekstremt meget

Dutch

*Intensiteit van symptomen: Gedurende de afgelopen 7 dagen was de globale intensiteit van mijn lichamelijke symptomen: 0 = helemaal geen symptomen – 10 = meest erge symptomen

*Belemmering door pijn: Gedurende de afgelopen 7 dagen hebben de lichamelijke symptomen mij belemmerd in mijn dagelijkse activiteiten: 0 = helemaal niet – 10 = volledige belemmering

French

*Intensité des symptoms: Pendant les 7 derniers jours, l'intensité globale de mes symptômes physiques était: 0 = pas des symptômes du tout – 10 = intensité des symptômes totales

*Interférence par symptoms: Pendant les 7 derniers jours, mes symptômes physiques interféraient avec mes activités journalieres: 0 = pas d'interférence du tout - 10 = interférence totale

Lithuanian

*Simptomu intensitāte: Pēdējo 7 dienu laikā manu ķermeņa simptomu intensitāte bija: 0 = nebija nekādu simptomu – 10 = vislielākā intensitātē

*Simptomu mijiedarbība: Pēdējo 7 dienu laikā mani ķermeņa simptomi traucēja dienas aktivitātēs: 0 = nemaz – 10 = vislielākā mērā

Norwegian

*Symptomenes intensitet: I løpet av de siste 7 dagene har intensiteten av mine kroppslige symptomer vært: 0 = ingen symptomer i det hele tatt – 10 = verst mulige symptomer

*Symptomenes påvirkning: I løpet av de siste 7 dagene har mine kroppslige symptomer påvirket mine daglige aktiviteter: 0 = ikke det det hele tatt – 10 = påvirket disse fullstendig

Russian

*Интенсивность симптома: В течение последних 7 дней общая интенсивность моих телесных симптомов была следующей: 0 = Отсутствие симптомов – 10 = Максимальная выраженность симптомов
*Ограничения вследствие симптома / Вмешательство симптома: Насколько сильно в течение последних 7 дней мои телесные симптомы мешали моей повседневной жизнедеятельности: 0 = Совсем не мешали – 10 = мешали постоянно