**Outcome measures for functional neurological disorder – a review of the theoretical complexities**

Timothy R Nicholson MD, PhD\*1, Alan Carson MD2,3, Mark J Edwards MD, PhD4, Laura H Goldstein PhD1, Mark Hallett MD, PhD5, Bridget Mildon6, Glenn Nielsen BSc, PhD4, Clare Nicholson MSc7, David L Perez MD, MMSc8, Susannah Pick PhD1, Jon Stone, PhD2 and the FND-COM (Functional Neurological Disorders - Core Outcome Measures) group\*\*.

1. Institute of Psychiatry Psychology & Neuroscience, King’s College London, UK

2. Centre for Clinical Brain Sciences, University of Edinburgh, UK

3. Department of Rehabilitation Medicine, Astley Ainslie Hospital, Edinburgh, UK

4. Neuroscience Research Centre, St George’s University of London, London, UK

5. Human Motor Control Section, NINDS, Bethesda, Maryland, USA

6. CEO, FND Hope International

7. National Hospital for Neurology & Neurosurgery, University College London Hospitals NHS Foundation Trust, London, UK

8. Departments of Neurology and Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

Word count (excluding abstract/refs/figs): 4488

Keywords: functional neurological disorder, conversion disorder, psychogenic, outcome measure

\*Corresponding Author: PO68, Section of Cognitive Neuropsychiatry, Institute of Psychiatry Psychology & Neuroscience, De Crespigny Park, London SE5 8AF, UK. timothy.nicholson@kcl.ac.uk

\*\*FND-COM group collaborators: David Anderson, Ali Asadi-Pooya, Selma Aybek, Gaston Baslet, Bas Bloem, Richard J Brown, Trudie Chalder, Maria Damianova, Anthony S David, Steve Epstein, Alberto J Espay, Beatrice Garcin, Joseph Jankovic, Eileen Joyce, Richard A Kanaan, Kasia Kozlowska, Kathrin LaFaver, W Curt LaFrance Jr, Anthony E Lang, Alex Lehn, Sarah Lidstone, Carine Maurer, Francesca Morgante, Lorna Myers, Markus Reuber, Karen Rommelfanger, Petra Schwingenshuh, Tereza Serranova. Paul Shotbolt, Glenn Stebbins, Marina AJ Tijssen, Michele Tinazzi.

**Abstract**

The development and selection of optimal outcome measures is increasingly recognized as a key component of evidence-based medicine, particularly the need for the development of a standardized set of measures for use in clinical trials. This process is particularly complex for functional neurological disorder (FND) for several reasons. FND can present with a wide range of symptoms that resemble the full spectrum of other neurological disorders. Additional physical (e.g. pain, fatigue) and psychological (e.g. depression, anxiety) symptoms are commonly associated with FND, which also can be highly disabling with implications for prognosis, and warrant concurrent assessment, despite an unclear etiological relationship with FND. Furthermore, several unique clinical aspects of FND make it likely that the usual prioritization of “objective” (or clinician-rated measures), over “subjective” (or patient-rated measures) might not be appropriate. Self-report measures may be more clinically meaningful in this population. Despite being a common and disabling disorder, there has been little research into outcome measures in FND and to date trials have largely used measures designed for the assessment of other disorders. An international ‘Core Outcome Measure’ group (FND-COM) has been established to develop a consensus battery of outcomes for FND: a ‘core outcome set’. This perspective article reviews the process of outcome measure development and selection before considering the specific features of FND impacting on the development of a core outcome set, and a research agenda to optimize outcome measurement in this complex neuropsychiatric disorder.

**Introduction**

 Despite being a common and disabling condition, functional neurological disorder (FND), also known as conversion disorder, has been relatively neglected by the research community{1}. Until recently there were few clinical trials of treatment, and pathophysiological and etiological investigations were limited,{2} despite FND being the second commonest reason for a new outpatient referral to neurology{3}, and having high rates of disability and consequent healthcare utilization{4}.

Thankfully this situation has started to change{5}. Over the last decade patient groups and an international society, the Functional Neurological Disorder Society (FNDS){6}, have been established; two landmark developments in the history of the disorder. There has also been increased research attention and funding resulting in accumulating evidence for the efficacy of specific interventions for FND. In particular cognitive behavioural therapy (CBT) - both conventional and CBT-informed psychotherapy - for the seizure variant of FND, also known as dissociative or psychogenic non-epileptic seizures (PNES){7}{8}, and intensive outpatient physiotherapy for FND with movement disorders or limb weakness (‘motor symptoms’){9}. The first large-scale multicentre treatment trial for any FND symptom, evaluating conventional CBT for dissociative seizures, will be reporting results shortly{10}, and a similar-sized trial of intensive outpatient physiotherapy for motor symptoms is underway{11}. These and other planned trials have highlighted the lack of specific outcome measures for FND and the urgent need for the development of a consensus on which outcome measures are optimal for FND. This is particularly important to allow specific treatment modalities to be studied across countries, cultures and healthcare settings where clinical presentations, resources and values regarding aspects of recovery may vary, as well as facilitating the eventual pooling of data for meta-analyses. Furthermore, specialized FND services are emerging in many countries and cultural contexts, which will increasingly be expected to formally monitor patient progress and demonstrate cost-effectiveness.

This FND research need comes against the background of a general recognition across medical, neurological, psychiatric and psychological specialties of the importance of research into outcome measures, particularly with regards to the development and application of a core outcome set, or battery of outcome measures, that are disorder appropriate. A core outcome set establishes a minimum standardized list of data points allowing results to be compared, contrasted, and collated across trials. This standardization is being driven by international collaborations such as the COMET (Core Outcome Measures in Effectiveness Trials) initiative in Europe, which provides development guidance and a searchable database for completed core outcome sets{12}{13}{14}. In the USA there is a similar initiative focusing on the development of a Common Data Element (CDE) resource portal, coordinated by the National Institute of Neurological Disorders and Stroke (NINDS){15}, addressing a variety of conditions such as epilepsy and traumatic brain injury.

These initiatives have included work on some neurological conditions, however, there has been no specific focus on FND, stimulating the establishment of the FND-COM (FND Core Outcome Measure) group within the COMET framework{16}. The FND-COM group now has 45 members from 13 countries and includes the full range of relevant clinical and academic disciplines as well as patient group representation. Following two international consensus meetings, it became clear that there are several challenges in the development and selection of outcome measures for FND that are specific to this disorder, over and above the usual tasks inherent in outcome measure set development.

This perspective article reviews key concepts in outcome measure design and selection for any disorder, such as choosing what to measure and how to measure it. Regarding what to measure, the core symptoms of the disorder itself are clearly important, but it is also possible that associated symptoms - such as other physical (e.g. pain, fatigue) or psychological symptoms (e.g. depression, anxiety) - might also be of particular significance. These associated symptoms, however, are not focused on in this paper as they are the subject of other ongoing projects. We then illustrate the key features of FND that are pertinent to the design and selection of outcome measures and detail the specific challenges and complexities that FND poses, focusing on adults. Outcome measure options from related disorders are then discussed as examples that could inform that approach and choice in FND. We conclude with recommendations for how we might move forward as a clinical and scientific community in the development of a core outcome set for FND.

**Key concepts in outcome measure design and selection**

When designing or selecting outcomes measures it is important to initially consider what the optimal features of a measure might be for all disorders, and these have been variously defined by, for example by the COMET initiative{12}. It is critical that measures have high content (including face) validity, i.e. are representative of the disorder, to patients as well as other key stakeholders such as carers, relevant healthcare professionals, healthcare commissioners and funders. Other key features are that measures should also be reliable (have low measurement error), replicable over time and/or between raters, responsive (sensitive to change), culturally sensitive and relevant, and internally consistent (items are inter-related). Finally, they should be practical and easy to administer to minimize patient and clinician burden and keep costs low.

It is then useful to separate this task into two key decisions: what to measure and how best to measure it. While both aspects may differ significantly between disorders, there are key principles that apply to all.

*What to measure*

Symptoms of the disorder are usually the most intuitive aspect (domain) of disorders to measure; however, several other domains may be as or more meaningful. At the mechanistic level, biomarkers of disorders, if known, can be measured, e.g. acetylcholine receptor antibody levels in myasthenia gravis. Many ‘downstream’ effects can also be measured in terms of how the disorder affects physical function (e.g. ability to do daily tasks), social function, and quality of life.

Since the inception of the biopsychosocial approach, popularized by Engel’s classic paper in 1977{17}, there have been several attempts to classify outcomes in this manner. Wilson and Cleary's ‘taxonomy’{18} identified five domains: ‘biological / physiological’, ‘symptom’, ‘function’, ‘health perception’ and ‘quality of life’. The World Health Organization (WHO) has developed the International Classification of Functioning, Disability and Health, which is known as the ‘ICF’ to highlight its intended focus on function (rather than disability){19}. The ICF describes three similar domains to Wilson and Cleary: ‘body function / structure’ (corresponding to biological / physiological), impairment (corresponding to symptoms), ‘activity limitation’ (corresponding to function). It also describes the additional domain of ‘participation restriction’ referring to the inability to be involved in life situations – for which both neurological and psychiatric examples are helpfully given{20}. Spinal injury associated paralysis can limit activities such as using public transportation and therefore participation in religious activities. Panic disorder can limit activities such as being able to go out and therefore participation in social relationships, both due to symptoms themselves and also people’s reactions to them - thereby accounting for more complex social factors and interactions.

The COMET initiative recently reviewed existing outcome measure systems with a focus on use in clinical trials{21} and proposed a new taxonomy with five domains, two of which overlap with the other classification systems (Wilson and Cleary’s taxonomy and the WHO ICF). The first is ‘physiological or clinical’ which is a combination of the first two domains of the other classifications and is subdivided into 23 categories of physiological or anatomical systems (cardiac, endocrine, neurological, psychiatric etc.). The second is ‘life impact’, which is equivalent to the function, quality of life and health perception domains of Wilson and Cleary’s taxonomy, but also includes other concepts such as patient adherence and satisfaction. Three other domains are not included in the other classifications. These are ‘resource use’, ‘adverse events’ and ‘mortality’, which are often measured in clinical trials. See Table 1 for a summary of how these different outcome domain taxonomies map onto each other in terms of terminology and concepts.

**<< Insert Table 1 >>: Comparison of outcome domain classifications**

In the last few decades there has also been increasing interest in patient-generated, also known as individualized or ‘idiographic’, outcome measures as opposed to the traditional generalized or ‘normothetic’ measures validated against population norms. Such individualized measures might better capture issues associated with personal relationships and employment difficulties, and as such can be seen as an alternative or complimentary type of measure.{22} Examples used across disorders include the Canadian Occupational Performance Measure (COPM){23} and the Psychological Outcome Profiles (PSYCHLOPS) measure.{24} An individualised measure has also been developed specifically for assessing physiotherapy in Parkinson’s disease – the Patient Specific Index for Physiotherapy in Parkinson’s Disease (PSI-PD){25} which has been used in a large trial.{26}

*How to measure*

There are often many different ways to measure the same outcome. For example, grip strength can be measured using a variety of methods and from several perspectives that are of variable objectivity: an instrument measuring grip force (a dynamometer); routine neurological examination (clinician grading of power), impression of strength on observing function (clinician or carer-rated); or patient self-report of their strength (by impression or activities). Similarly, seizure frequency can theoretically be measured either objectively, conventionally during continuous EEG and video monitoring (telemetry) but also potentially by other physiological monitoring (e.g., wearable devices), or subjectively by patient recall of seizure episodes (e.g., seizure log).

Objective measures are usually considered more reliable (having lower measurement error) and therefore generally prioritized in clinical trials. Objective measures are usually measured by clinicians, but it is important to clarify that the converse does not necessarily apply, in that some clinician rated measurements are not truly objective – for example the clinician grading of strength during neurological examination has a degree of subjectivity to the grade allocation and has corresponding poor inter-rater reliability{27}, as does a grading based on observation rather than clinical examination. Some measurements are inherently subjective, such as quality of life, but it can be argued that such measures may be at least as important as objective data points as they could be more meaningful to patients and correlate more closely to other important factors such as socio-economic outcomes.

**Key features of FND influencing outcome measurement**

 Several features of FND are particularly important in guiding outcome measure design and selection. We review how a diagnosis of FND is made before focusing on the wide variety of presenting symptoms, and how specific ‘positive clinical signs’ not only allow its differentiation from other disorders but also explain high rates of symptom variability, why patient report of symptoms can differ from those of clinicians, and the implications of these features.

*Diagnostic features*

Key developments occurred in the update from the DSM-IV to the current DSM 5 diagnostic criteria of FND{28}. A major advance is that the diagnosis is now a “rule in” diagnosis, based on the requirement that the neurological symptoms are associated with “clinical evidence of incompatibility between symptoms and recognized neurological or medical conditions”{29}, using clinical exam signs’{30}, that allow FND to be positively differentiated from other disorders, rather than defined by the absence of another condition, and that have high rates of inter-rater reliability{31}. Another key change introduced in DSM-5 in comparison to the previous edition was moving the requirement of identifying preceding psychological stressors to a clinical note for the condition – such that this feature is still retained as a specifier. The recently published ICD-11 criteria have endorsed similar changes{32}. See Box 1 for the DSM-5 diagnostic criteria.

**Box 1:** DSM-5 functional neurological (symptom) disorder diagnostic criteria{28}

1. ≥ 1 symptom of altered voluntary motor or sensory function.
2. Clinical evidence of incompatibility between symptom(s) and recognized neurological or medical conditions [‘*positive clinical signs’*]
3. Symptom or deficit is not better explained by another medical or mental disorder.
4. Symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.

Specify:

* Symptom type:
* Weakness or paralysis
* Abnormal movement (e.g. tremor, dystonia, myoclonus, gait disorder)
* Swallowing symptoms
* Speech symptoms
* Attacks or seizures
* Anaesthesia or sensory loss
* Special sensory symptom (e.g. visual, olfactory or auditory)
* Mixed symptoms
* Acute (< 6 months) or persistent (> 6 months).
* With or without psychological stressor (associated with onset of symptoms).

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

There are positive clinical signs for the various symptom presentations, each with varying degrees of usefulness. Hoover’s sign of functional leg weakness, is a good example of a clinically useful sign with good reliability and specificity{31} and describes hip extension weakness that normalizes when it is triggered (automatically) by contralateral hip flexion. A functional tremor sign is elicited in response to an externally cued rhythmic movement, which may lead to tremor ‘entrainment’ or cessation. Patterns of PNES can also be differentiated from epileptic seizures based on semiological features{33}{34}. Functional sensory deficits are typically of a non-neuroanatomic pattern that otherwise cannot be explained by anything other than FND, e.g. a tubular visual field that is incongruous with the laws of optics. Crucially, the presence of these signs allows FND to be diagnosed, even in the presence of another neurological condition, such as multiple sclerosis or epilepsy. These positive clinical signs are dealt with in more detail below, as they, and other etiological factors, have particular implications for outcome measure selection and development.

*Core symptom heterogeneity*

As detailed in Box 1, there are symptom specifiers covering the ‘core’ symptoms types, including seizures (also referred to as attacks), weakness/paralysis, other movement disorders (e.g. tremor, dystonia, gait abnormalities or myoclonus) and sensory dysfunction (including somatosensory, visual or auditory impairment). ICD-11 has similar symptom subtypes – the most notable difference being the inclusion of a cognitive symptom subtype that is not part of the DSM-5 criteria{35}{36}. Many patients with FND have several core symptoms, either simultaneously or over time, for which the ‘mixed’ category in DSM-5 is appropriate. As such, FND can present with a wide variety of neurological symptoms in many different combinations{37} that are likely to have varying contributions to loss of function, disability and quality of life. It is also hypothesised that symptom replacement (or substitution) can occur, in that the resolution of one symptom can be followed by the appearance of another, although there is not convincing data to support this occurring{38},

Such symptom heterogeneity raises the question of what symptoms, or combination of symptoms, should be measured in a given individual, as well as in groups, for both research studies and clinical practice. In answering these questions it would be important to consider (i) which symptoms are most troubling for the patient; (ii) if multiple symptoms are to be measured, is it possible to create a weighted global score for comparison between individuals and groups; and (iii) is it possible to create a valid single measure of FND symptom severity.

*Physical and psychological comorbidities*

Beyond these core symptoms, many other physical and psychological symptoms are commonly reported in FND that have been shown to negatively impact health-related quality of life{39}{40} and clinical outcomes{41}{42}. These symptoms include pain, fatigue, sleep disturbance, poor concentration, bladder and bowel dysfunction and psychological symptoms such as depression, anxiety, panic, dissociative phenomena (e.g. depersonalisation), and post-traumatic stress symptoms{43}{44}. These concurrent symptoms can be and often are, amongst the most severe and disabling symptoms reported by patients – sometimes more so than the presenting FND symptom, itself. For example, in one study functional movement disorder patients pain, anxiety and cognitive symptoms{45}, and in another study fatigue and depression{46}, correlated strongly with quality of life in a way that the movement disorder symptoms did not. Similarly, for adults with PNES, depression and a range of other characteristics, such as dissociation, escape-avoidance coping and aspects of family dysfunction, were important associates of quality of life, although this may at least in part be due to particular quality of life scales containing items asking about anxiety, depression and pain{39}.

It is unclear if comorbid symptoms are an intrinsic part of the disorder or just common comorbidities. In the case of depression and anxiety, they can clearly be a secondary consequence of having the disorder, a predisposing vulnerability or both. In the case of post-traumatic stress disorder (PTSD) it potentially shares common pathophysiological elements with FND given that adverse life events are a shared risk factor{47}. The same could also apply to many other symptoms experienced by FND patients, such as dissociative symptoms, due to multiple overlapping risk factors and reflect different disorder subtypes. It is therefore potentially helpful to consider symptoms as occurring in ‘core FND’, ‘other physical’ and ‘psychological’ domains; see Figure 1.

**<< Insert Figure 1 >>:** **Schematic diagram of symptom domains in FND**

Such a wide range of core symptoms and comorbidities clearly presents challenges in choosing which aspects of the disorder to focus on for measuring outcomes. It is also a reminder of the importance of consulting patients individually and as a group about which symptoms are of most importance to them when selecting the outcomes collected, including the choice for a primary outcome measure for trials. Measurement of the severity of the core symptom on which the diagnosis is based therefore may not always best reflect the most important or meaningful change for a patient{48}.

*Variability of symptoms and signs*

The clinical signs described above illustrate how clinical features can be highly variable in FND in that there can be an instantaneous improvement, albeit briefly, with a clinical maneuver. It is sometimes helpful to explain this observed feature to patients, demonstrated on the FND exam. Contemporary theories for why these signs occur in FND propose that they arise from an abnormality in the way that the brain predicts motor and sensory activity, mediated in large part by dysfunctional attention to bodily symptoms.{49}{50}. Such models also integrate dysfunction of interoception, self-agency and motor control into their mechanistic account of FND{51}{2}, as well as aberrant stress response{52} and emotion processing{53}.

As such, high levels of symptom variability are a hallmark of the disorder-- this feature has important implications for outcome measurement. For example, when is the ideal time to measure function? That is, should leg weakness or tremor be measured during voluntary movement, when it could be highly impaired, or when distracted, when it could potentially normalize? A related issue is the variability of symptoms from one day to the next, and sometimes over shorter time periods, in people with FND, which has implications for timeframes for assessing symptoms. “In the moment” questions may not, therefore, accurately reflect the general (overall) state of the disorder, as might assessments covering short time periods such as the last few hours or days.

It is therefore more likely that assessments based over the last week (or longer unit of time) might give a more stable and reliable index of change despite there being potential trade-offs such as increased recall bias. This temporal variability is a particularly important issue for objective snapshot tests of motor symptoms, such as power (e.g. hand dynamometer), gait speed (e.g. 10-meter walk test), and endurance (e.g. 2-minute walk test). It is also noted that attention{54}, and therefore physical examination, tends to exacerbate such symptoms, such that routine clinical assessment may not accurately reflect the burden of a given symptom outside the context of the examination. There is also a very wide variation in the severity of symptoms experienced in FND - ranging from mild transient symptoms to amongst the most disabled and distressed patients seen in medicine - which is likely to produce ‘floor’ and ‘ceiling’ effects in symptom measurement.

*Differences between patient-rated and objective symptom measures*

There can also be marked discrepancies between an FND patient’s perception of their own symptom or function and that observed by clinicians or objectively measured. The most compelling evidence of this comes from a study comparing objectively measured tremor using an actigraphy watch, to patient self-report in FND patients relative to patients with tremor due to Parkinson’s disease, essential and dystonic tremors{54}. Patients with FND reported tremor 84% of the time, but the actigraphy watch recorded tremor for only 4% of the day – a nearly 20-fold overestimation. The neurological control group estimated they had a tremor 58% of the time, just over twice the amount they objectively had a tremor. Thus, although both groups significantly over-estimated their tremor, this is an order of magnitude more in FND. Importantly the disability reported by people with functional tremor in this study was greater than that reported by the other patient cohorts.

In support of this difference, a study of PNES patients found that they catastrophized their experiences whereas those with epilepsy normalized their experiences{55}. However, a recent similar study found less clear cut differences between objective tremor in FND and organic controls{56}. Ultimately it is possible that patients’ own reports are as clinically meaningful as objectively rated measures, which, depending on how they are performed, might conclude that a leg is not weak or that a tremor is not frequently present. Further research is needed to investigate the relationship between these different measures and their associations with other key outcomes such as function, quality of life and socio-economic outcomes.

*Other relevant features*

Qualitative research to date has also highlighted a number of common perceptions and experiences amongst patients with FND that contribute to the burden of illness and impaired quality of life{57}{58}{59}{60}. Capturing the distress associated with these experiences may be important to accurately measure the benefit of appropriate treatment. Relevant qualitative findings include: 1. A lack of understanding of one’s symptoms (and related illness beliefs) leading to feeling powerless and fearing a future with deteriorating health, 2. A perceived or experienced lack of appropriate support leaves many patients feeling abandoned and isolated, 3. Associated with this is the perception or experience that their diagnosis does not allow access to appropriate levels of social support such as financial benefits and allowances for disability, 4. Patients (and therapists) describe patient resources such as their level of self-compassion and mastery as of potential importance. Domains of measurement that can capture these important issues may include understanding, symptom threat, perceived support and self-efficacy as well as patient satisfaction.

**Examples from related disorders**

When considering outcome measure design and selection in FND it is potentially helpful to look at what has been designed and used in related disorders, although it isn’t clear which disorders are the best models for FND. Given that FND is the paradigmatic functional disorder at the interface of medicine, neurology, psychiatry, and psychology, a case for model disorders from these specialities can be made. There is also a clear rationale for considering other functional disorders, given the often significant overlap in clinical features between these disorders and FND..

Regarding neurological disorders, it may be beneficial to consider those that present with a wide range of neuropsychiatric and psychological symptoms similar to that seen in FND. Examples include multiple sclerosis and Parkinson’s disease that, despite a historical focus on motor function, are recognized to have many non-motor symptoms, including psychiatric, psychological and a range of cognitive symptoms, (e.g., depression, cognitive symptoms, among many others). An extensive scale has been developed for Parkinson’s disease, the latest version of which is the Movement Disorder Society revision of the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS){61}, and the International Consortium for Health Outcomes Measurement (ICHOM) has published a consensus outcome set for use in clinical practice{62} recommending seven domains: 1. Motor functioning, 2. Non-motor functioning, 3. Cognitive and psychiatric functioning, 4. Falls, 5. Hospital admissions, 6. Ability to work, 7 Health-related quality of life. The PSI-ID (Patient Specific Index for Physiotherapy in Parkinson’s Disease) mentioned above{25} is also a potentially an informative individualized approach for FND.

Huntington’s disease is another potential model and has a similar validated outcome measure, the Unified Huntington’s Disease Rating Scale (HDRS) {63}, but for which an outcome set has not yet been developed. Both the MDS-UPDRS and the HDRS are recommended in the NINDS Common Data Elements (CDE) initiative. For some subtypes of FND there is an obvious neurological disorder to consider, such as epilepsy for PNES. Although there has not been a published consensus outcome set for epilepsy in general there has been for childhood epilepsy{64}, studies in pregnant women with epilepsy{65} as well as a NINDS Common Data Elements publication{66} and research into the views of people with epilepsy and carers{67}. Most other FND subtypes do not have a single disorder that is of particular relevance.

In terms of potentially relevant mental health disorders, PTSD has a broad range of symptoms, including negative affect and dissociation that can overlap to some degree with FND. A range of outcome measures have been developed for PTSD, the latest and most comprehensive of which is the Clinician-Administered PTSD Scale (CAPS-5){68}, but there is not yet an agreed outcome set. Panic disorder has some clinical, phenomenological and potentially mechanistic overlap with FND, especially given that some dissociative seizure cases which have been compared to a state of ‘panic without panic’{69} and it is not uncommon for panic attacks to include focal neurological symptoms{70}. There is no consensus outcome set for panic disorder, but a joint ICHOM consensus outcome set has been developed for anxiety and depression{71} that is potentially of some relevance to aspects of FND.

Although parallels to FND may not be immediately obvious, obsessive compulsive disorder (OCD) is informative since its key outcome measure, the Yale-Brown Obsessive Compulsive Scale (YBOCS){72}, has several different components that might be applicable to FND. The YBOCS has a checklist for past and current symptoms as well as a current score for all obsessive symptoms and all compulsive symptoms measured over several domains (1. Frequency of symptom; 2. Interference with social / occupational function; 3. Distress; 4. Ability to resist, and 5; Subjective feeling of control).

In related functional disorders, a European group has recently published recommendations for somatic symptom disorder, bodily distress disorder and functional somatic syndromes{73} recommending six outcome domains: 1. Classification of disorder and comorbid mental problems, 2. Somatic symptoms (self-rated symptom intensity and interference with daily activities, both scored 0-10), 3. Psychobehavioural features (e.g. depression and anxiety), 4. Illness consequences (quality of life, disability and healthcare use), 5. Patient satisfaction, and 6. Unwanted negative effects. Good progress has also been made in fibromyalgia with the publication of a consensus core domain set{74} and a preliminary core outcome set for research{75}. There has also been some progress in developing consensus outcome domains for pain treatments in general{76} and an outcome set for chronic pain{77}.

Of note, patient-reported measures are prominent in the above core outcome sets and the primary outcome for a number of neurology and psychiatry clinical trials (e.g., headache, depression, anxiety and PTSD), underscoring the utility of self-reported symptom surveys. In conclusion, there was been variable progress in other disorders of potential relevance with respect to informing FND and there are many example disorders to consider, but no single disorder stands out as uniquely relevant. It will therefore be of use to continue to monitor outcome measure set developments in most of these disorders.

**Conclusions and future work**

FND poses particular questions and challenges to the development and selection of optimal outcome measures. It has many features that potentially impact on this process. First, the wide variety of core and associated symptoms means that it should not be assumed that a single core (‘primary’) FND symptom is the most meaningful aspect of the disorder to measure. As such, it might also be important to measure other concurrently present FND symptoms, as well as other physical and psychological symptoms.

Secondly, symptom variability across FND semiologies suggests that momentary assessment might be less reliable than longer-term assessments particularly in cases of paroxysmal or intermittent FND. Finally, the nature of FND means that subjective report measures may be potentially as clinically meaningful as objective outcome measures. The U.S. Food and Drug Administration has also raised the profile and importance of patient-rated outcome measures in their guidance on medicinal product development{78}. However, there is a clear need to continue to study the relationship between subjective and objective outcomes measures in this patient group. In the interim, a complementary set of objective (clinician-rated, performance based) and patient-rated measures may collectively provide an adequate representation of symptom burden and associated disability.

In order to develop an optimal outcome set it will be important to formally assess the views of the full spectrum of stakeholders about these issues, notably patients and caregivers, as well as all the relevant clinicians who treat the disorder, particularly neurologists, psychiatrists, psychologists, psychotherapists, physiotherapists, occupational therapists, speech and language therapists, social workers, nurses and other allied clinicians such as family (primary care) physicians. Such work is currently being undertaken by the FND-COM group, in the form of a qualitative interview-based study exploring the views of patients, carers and experienced healthcare professionals on outcomes, recovery and outcome measurement in FND.

A systematic review of outcome measures in FND is underway to define those outcome measures that have been developed for FND, as well as which outcome measures have been selected most commonly for use in clinical trials to date. Such work will inform the development of initial consensus recommendations and eventually a formal Core Outcome Set according to COMET guidelines{79}. The potential need for the development of new outcome measures for FND needs to be considered, as well as the possibility of combining existing outcome measures to delineate a suggested battery of instruments. Work is also needed to study whether in particular FND sub-groups different outcome measures might be preferable; for example, in children or in those with particular comorbidities such as trauma-related conditions or learning disabilities. It is also possible that different cultures might benefit from different optimal outcome measures. Finally, it may be important to note that the most useful outcome measures for research may differ from those most useful for clinical practice, where there may be less concern for measurement psychometrics and greater focus on what is important for patients and healthcare commissioners. For example, patients might be more concerned with performance of activities of daily living (such as walking and social activities) and commissioners with cost-savings and employment status.

Medical science often searches for singular diagnostic and treatment approach to disorders. For FND, a neuropsychiatric disorder with highly variable semiologic manifestations, multiple comorbidities, and associated psychosocial elements, a single simple outcome measure may not be optimal. A concise battery of measures, both clinician-scored and self-reported, monitoring physical, psychological and social aspects of the disorder, ideally allowing comparison to other disorders, may be an approach to most meaningfully assess and monitor the whole person with FND.

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Box 2:** Summary points and recommendations

1. The range of core symptoms of FND and the high levels of associated other physical and psychological symptoms complicates the choice of the most important symptoms to measure. Consequently a measure of both the primary core symptom and a general measure of all FND symptoms should be obtained, along with measures of key other physical and psychological symptoms (see Fig 1), when practicable.
2. Temporal variability in symptoms means that ‘snapshot’ (momentary or ‘state’) assessments are likely to be less meaningful than assessments reflecting symptom severity over longer time periods (days or weeks).
3. The discrepancy between patient report and objective measures, relating to a diagnostic feature of FND, challenges the usual preference for objective measures. A complementary set of self-reported (subjective) and objective (e.g. performance base or some clinician-rated) measurements may provide a particularly robust core outcome measure set for this population and the basis of research into the relative benefits of each.
4. There is a need to develop an outcome measure set for FND including research into:
	1. Existing outcome measures that have been used in, or are available for use in, FND trials and clinical practice. The need for the development of an FND specific scale should be considered.
	2. Personalised outcome measures that might be suitable for FND
	3. Stakeholder views on outcome measures, specifically patients, carers and relevant healthcare professionals.
	4. How different cultures, ages and other patient characteristics might impact on optimal outcome measurement.

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Funding / Conflicts of interest**

D.L.P. has received honoraria from the American Academy of Neurology, Movement Disorder Society and Harvard Medical School.

M.H. may accrue revenue on US Patent for an Immunotoxin (MAB-Ricin) for the treatment of focal movement disorders and for a Coil for Magnetic Stimulation and methods for using the same (H-coil); in relation to the latter, he has received license fee payments from the NIH (from Brainsway). He is on the Medical Advisory Boards of CALA Health, Brainsway, and Cadent. He is on the Editorial Board of approximately 15 journals and receives royalties and/or honoraria from publishing from Cambridge University Press, Oxford University Press, Springer, and Elsevier. Grant research funds have come from Merz for treatment studies of focal hand dystonia, Allergan for studies of methods to inject botulinum toxins, Medtronic, Inc. for a study of DBS for dystonia, and CALA Health for studies of a device to suppress tremor.

J.S. reports independent expert testimony work for personal injury and medical negligence claims and receives royalties from UpToDate for articles on functional neurological disorder and runs a free non-profit self-help website, [www.neurosymptoms.org](http://www.neurosymptoms.org).

L.H.G reports salary support from the UK National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre at the South London and Maudsley NHS Foundation Trust and King’s College London. T.R.N. and S.P. are also funded by a NIHR clinician scientist fellowship. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

**References**

1. Espay AJ, Aybek S, Carson A, et al.: Current concepts in diagnosis and treatment of functional neurological disorders. JAMA Neurol. 2018;

2. Voon V, Cavanna AE, Coburn K, et al.: Functional Neuroanatomy and Neurophysiology of Functional Neurological Disorders (Conversion Disorder). J. Neuropsychiatry Clin. Neurosci. 2016;

3. Stone J, Carson A, Duncan R, et al.: Who is referred to neurology clinics? - The diagnoses made in 3781 new patients [Internet]. Clin. Neurol. Neurosurg. 2010; 112:747–751Available from: http://dx.doi.org/10.1016/j.clineuro.2010.05.011

4. Carson A, Stone J, Hibberd C, et al.: Disability, distress and unemployment in neurology outpatients with symptoms “unexplained by organic disease” [Internet]. J Neurol Neurosurg Psychiatry 2011; 82:810–813Available from: http://www.ncbi.nlm.nih.gov/pubmed/21257981

5. Carson AJ, Brown R, David AS, et al.: Functional (conversion) neurological symptoms: research since the millennium [Internet]. J Neurol Neurosurg Psychiatry 2012; 83:842–850Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\_uids=22661497

6. FND Society [Internet][cited 2019 Apr 9] Available from: www.fndsociety.org

7. Goldstein LH, Chalder T, Chigwedere C, et al.: Cognitive-behavioral therapy for psychogenic nonepileptic seizures: a pilot RCT [Internet]. Neurology 2010; 74:1986–1994Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\_uids=20548043

8. LaFrance Jr. WC, Baird GL, Barry JJ, et al.: Multicenter pilot treatment trial for psychogenic nonepileptic seizures: a randomized clinical trial [Internet]. JAMA Psychiatry 2014; 71:997–1005Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\_uids=24989152

9. Nielsen G, Buszewicz M, Stevenson F, et al.: Randomised feasibility study of physiotherapy for patients with functional motor symptoms. J. Neurol. Neurosurg. Psychiatry 2017;

10. Goldstein LH, Mellers JDC, Landau S, et al.: COgnitive behavioural therapy vs standardised medical care for adults with Dissociative non-Epileptic Seizures (CODES): A multicentre randomised controlled trial protocol. BMC Neurol. 2015;

11. Nielsen G et. a.: Physio4FMD trial [Internet]2018; [cited 2019 Apr 1] Available from: http://www.isrctn.com/ISRCTN56136713?q=nielsen&filters=&sort=&offset=3&totalResults=26&page=1&pageSize=10&searchType=basic-search

12. Prinsen CAC, Vohra S, Rose MR, et al.: How to select outcome measurement instruments for outcomes included in a “Core Outcome Set” – a practical guideline [Internet]. Trials 2016; 17:449Available from: http://trialsjournal.biomedcentral.com/articles/10.1186/s13063-016-1555-2

13. Williamson PR, Altman DG, Bagley H, et al.: The COMET Handbook: Version 1.0. Trials 2017; 18

14. COMET\_database: COMET website

15. NIH: NIH Common Data Element (CDE) Resource Portal [Internet][cited 2019 Apr 1] Available from: https://commondataelements.ninds.nih.gov/ProjReview.aspx#tab=Introduction

16. Nicholson TRJ: FND-COM COMET initiative [Internet]2017; Available from: http://www.comet-initiative.org/studies/details/951?result=true

17. Engel GL: The need for a new medical model: A challenge for biomedicine. Science (80-. ). 1977;

18. Wilson IB, Cleary PD, McDowell I NC, et al.: Linking Clinical Variables With Health-Related Quality of Life [Internet]. JAMA 1995; 273:59[cited 2017 Jan 13] Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.1995.03520250075037

19. Arthanat S, Nochajski SM, Stone J: The international classification of functioning, disability and health and its application to cognitive disorders [Internet]. Disabil Rehabil 2004; 26:235–245Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\_uids=15164957

20. WHO: ICF Beginners Guide [Internet]2002; [cited 2019 May 28] Available from: https://www.who.int/classifications/icf/icfbeginnersguide.pdf

21. Dodd S, Clarke M, Becker L, et al.: A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. J. Clin. Epidemiol. 2018;

22. Ashworth M, Guerra D, Kordowicz M: Individualised or Standardised Outcome Measures: A Co-habitation? Adm. Policy Ment. Heal. Ment. Heal. Serv. Res. 2019;

23. Law M, Baptiste S, Mccoll M, et al.: The Canadian Occupational Performance Measure: An Outcome Measure for Occupational Therapy. Can. J. Occup. Ther. 1990;

24. Ashworth M, Robinson SI, Godfrey E, et al.: Measuring mental health outcomes in primary care: The psychometric properties of a new patient-generated outcome measure, “PSYCHLOPS” ('psychological outcome profiles’). Prim. Care Ment. Heal. 2005;

25. Nijkrake MJ, Keus SHJ, Quist-Anholts GWL, et al.: Evaluation of a patient-specific index as an outcome measure for physiotherapy in Parkinson’s disease. Eur. J. Phys. Rehabil. Med. 2009;

26. Munneke M, Nijkrake MJ, Keus SH, et al.: Efficacy of community-based physiotherapy networks for patients with Parkinson’s disease: a cluster-randomised trial. Lancet Neurol. 2010;

27. Vanhoutte EK, Faber CG, Van Nes SI, et al.: Modifying the Medical Research Council grading system through Rasch analyses. Brain 2012;

28. APA: Diagnostic and statistical manual of mental disorders : DSM-5 [Internet], 5th ed, Washington, DC, American Psychiatric Association, 2013Available from: http://online.statref.com/TOC.aspx?grpalias=JHU&FxId=37

29. Stone J, LaFrance WC, Brown R, et al.: Conversion disorder: Current problems and potential solutions for DSM-5. J. Psychosom. Res. 2011;

30. Daum C, Hubschmid M, Aybek S: The value of “positive” clinical signs for weakness, sensory and gait disorders in conversion disorder: a systematic and narrative review [Internet]. J Neurol Neurosurg Psychiatry Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\_uids=23467417

31. Daum C, Gheorghita F, Spatola M, et al.: Interobserver agreement and validity of bedside “positive signs” for functional weakness, sensory and gait disorders in conversion disorder: A pilot study. J. Neurol. Neurosurg. Psychiatry 2015;

32. WHO: ICD-11, 2018

33. Syed TU, Lafrance WC, Kahriman ES, et al.: Can semiology predict psychogenic nonepileptic seizures? a prospective study. Ann. Neurol. 2011;

34. Avbersek A, Sisodiya S: Does the primary literature provide support for clinical signs used to distinguish psychogenic nonepileptic seizures from epileptic seizures? J. Neurol. Neurosurg. Psychiatry 2010;

35. Pennington C, Hayre A, Newson M, et al.: Functional Cognitive Disorder: A Common Cause of Subjective Cognitive Symptoms. J. Alzheimer’s Dis. 2015;

36. Stone J, Pal S, Blackburn D, et al.: Functional (Psychogenic) Cognitive Disorders: A Perspective from the Neurology Clinic. J. Alzheimer’s Dis. 2015; 48:S5–S17

37. Matin N, Young SS, Williams B, et al.: Neuropsychiatric Associations With Gender, Illness Duration, Work Disability, and Motor Subtype in a U.S. Functional Neurological Disorders Clinic Population. J. Neuropsychiatry Clin. Neurosci. 2017;

38. McKenzie PS, Oto M, Graham CD, et al.: Do patients whose psychogenic non-epileptic seizures resolve, “replace” them with other medically unexplained symptoms? Medically unexplained symptoms arising after a diagnosis of psychogenic non-epileptic seizures. J. Neurol. Neurosurg. Psychiatry 2011;

39. Jones B, Reuber M, Norman P: Correlates of health-related quality of life in adults with psychogenic nonepileptic seizures: A systematic review. Epilepsia 2016;

40. LaFrance WC, Syc S: Depression and symptoms affect quality of life in psychogenic nonepileptic seizures. Neurology 2009;

41. Glass SP, Matin N, Williams B, et al.: Neuropsychiatric Factors Linked to Adherence and Short-Term Outcome in a U.S. Functional Neurological Disorders Clinic: A Retrospective Cohort Study. J. Neuropsychiatry Clin. Neurosci. 2017;

42. Gelauff J, Stone J, Edwards M, et al.: The prognosis of functional (psychogenic) motor symptoms: a systematic review [Internet]. J Neurol Neurosurg Psychiatry 2014; 85:220–226Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\_uids=24029543

43. Kranick S, Ekanayake V, Martinez V, et al.: Psychopathology and psychogenic movement disorders [Internet]. Mov Disord 2011; Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\_uids=21714007

44. Stone J, Warlow C, Sharpe M: The symptom of functional weakness: A controlled study of 107 patients. Brain 2010; 133:1537–1551

45. Věchetová G, Slovák M, Kemlink D, et al.: The impact of non-motor symptoms on the health-related quality of life in patients with functional movement disorders. J. Psychosom. Res. 2018;

46. Gelauff JM, Kingma EM, Kalkman JS, et al.: Fatigue, not self-rated motor symptom severity, affects quality of life in functional motor disorders. J. Neurol. 2018;

47. Ludwig L, Pasman JA, Nicholson T, et al.: Stressful life events and maltreatment in conversion (functional neurological) disorder: systematic review and meta-analysis of case-control studies. The Lancet Psychiatry 2018;

48. Reuber M, Mitchell AJ, Howlett S, et al.: Measuring outcome in psychogenic nonepileptic seizures: How relevant is seizure remission? Epilepsia 2005;

49. Edwards MJ, Adams RA, Brown H, et al.: A Bayesian account of “hysteria.” Brain 2012; 135:3495–3512

50. Van den Bergh O, Witthöft M, Petersen S, et al.: Symptoms and the body: Taking the inferential leap [Internet]. Neurosci. Biobehav. Rev. 2017; 74:185–203[cited 2017 Jan 31] Available from: http://www.ncbi.nlm.nih.gov/pubmed/28108416

51. Baizabal-Carvallo JF, Hallett M, Jankovic J: Pathogenesis and pathophysiology of functional (psychogenic) movement disorders. Neurobiol. Dis. 2019;

52. Keynejad RC, Frodl T, Kanaan R, et al.: Stress and functional neurological disorders: Mechanistic insights. J. Neurol. Neurosurg. Psychiatry 2018;

53. Pick S, Goldstein LH, Perez DL, et al.: Emotional processing in functional neurological disorder: A review, biopsychosocial model and research agenda. J. Neurol. Neurosurg. Psychiatry 2018;

54. Parees I, Saifee TA, Kassavetis P, et al.: Believing is perceiving: mismatch between self-report and actigraphy in psychogenic tremor [Internet]. Brain 2011; 135:117–123Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\_uids=22075068

55. Robson C, Drew P, Walker T, et al.: Catastrophising and normalising in patient’s accounts of their seizure experiences. Seizure 2012;

56. Kramer G, Dominguez-Vega ZT, Laarhoven HS, et al.: Similar association between objective and subjective symptoms in functional and organic tremor. Parkinsonism Relat. Disord. 2019;

57. Nielsen G, Buszewicz M, Edwards MJ, et al.: A qualitative study of the experiences and perceptions of patients with functional motor disorder. Disabil. Rehabil. 2018;

58. Rawlings GH, Reuber M: What patients say about living with psychogenic nonepileptic seizures: A systematic synthesis of qualitative studies. Seizure 2016;

59. Nettleton S, Watt I, O’Malley L, et al.: Understanding the narratives of people who live with medically unexplained illness [Internet]. Patient Educ Couns 2005; 56:205–210Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\_uids=15653250

60. Michaelis R, Niedermann C, Reuber M, et al.: “Seizures have become a means of somehow learning things about myself” — A qualitative study of the development of self-efficacy and mastery during a psychotherapeutic intervention for people with epilepsy. Epilepsy Behav. 2018;

61. Goetz CG, Tilley BC, Shaftman SR, et al.: Movement Disorder Society-Sponsored Revision of the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. Mov. Disord. 2008;

62. De Roos P, Bloem BR, Kelley TA, et al.: A Consensus Set of Outcomes for Parkinson’s Disease from the International Consortium for Health Outcomes Measurement. J. Parkinsons. Dis. 2017;

63. Kieburtz K, Penney JB, Corno P, et al.: Unified huntington’s disease rating scale: Reliability and consistency. Neurology 2001;

64. Crudgington H, Rogers M, Bray L, et al.: Core Health Outcomes in Childhood Epilepsy (CHOICE): Development of a core outcome set using systematic review methods and a Delphi survey consensus. Epilepsia 2019;

65. Al Wattar BH, Tamilselvan K, Khan R, et al.: Development of a core outcome set for epilepsy in pregnancy (E-CORE): a national multi-stakeholder modified Delphi consensus study. BJOG An Int. J. Obstet. Gynaecol. 2017;

66. Loring DW, Lowenstein DH, Barbaro NM, et al.: Common data elements in epilepsy research: Development and implementation of the NINDS epilepsy CDE project. Epilepsia 2011;

67. Noble AJ, Marson AG: Which outcomes should we measure in adult epilepsy trials? The views of people with epilepsy and informal carers. Epilepsy Behav. 2016;

68. Weathers FW, Bovin MJ, Lee DJ, et al.: The clinician-administered ptsd scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. Psychol. Assess. 2018;

69. Goldstein LH, Mellers JD: Ictal symptoms of anxiety, avoidance behaviour, and dissociation in patients with dissociative seizures [Internet]. J Neurol Neurosurg Psychiatry 2006; 77:616–621Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\_uids=16614021

70. Coyle PK, Sterman AB: Focal neurologic symptoms in panic attacks. Am. J. Psychiatry 1986;

71. Obbarius A, van Maasakkers L, Baer L, et al.: Standardization of health outcomes assessment for depression and anxiety: recommendations from the ICHOM Depression and Anxiety Working Group. Qual. Life Res. 2017;

72. Goodman WK, Price LH, Rasmussen SA, et al.: The Yale-Brown Obsessive Compulsive Scale: I. Development, Use, and Reliability. Arch. Gen. Psychiatry 1989;

73. Rief W, Burton C, Frostholm L, et al.: Core Outcome Domains for Clinical Trials on Somatic Symptom Disorder, Bodily Distress Disorder, and Functional Somatic Syndromes: European Network on Somatic Symptom Disorders Recommendations. Psychosom. Med. 2017;

74. Mease P, Arnold LM, Choy EH, et al.: Fibromyalgia syndrome module at OMERACT 9: Domain construct, in Journal of Rheumatology. 2009

75. Choy EH, Arnold LM, Clauw DJ, et al.: Content and criterion validity of the preliminary core dataset for clinical trials in fibromyalgia syndrome, in Journal of Rheumatology. 2009

76. Kaiser U, Kopkow C, Deckert S, et al.: Developing a core outcome domain set to assessing effectiveness of interdisciplinary multimodal pain therapy: The VAPAIN consensus statement on core outcome domains. Pain 2018;

77. Dworkin RH, Turk DC, Farrar JT, et al.: Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;

78. FDA: Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims [Internet]2009; Available from: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf

79. Kirkham JJ, Davis K, Altman DG, et al.: Core Outcome Set-STAndards for Development: The COS-STAD recommendations. PLoS Med. 2017;

**Table 1:** Comparison of outcome domain classifications

|  |  |  |  |
| --- | --- | --- | --- |
| **Wilson & Cleary** {17} | **WHO ICF** {18} | **COMET** {20} | **Concepts** |
| Biological / Physiological  | Body function/structure | Physiological or clinical | Physiological / biological |
| Symptom | Impairment | Physical, psychological & other symptoms |
| Function | Activity limitation | Life impact | Physical, psychological & social impacts |
| Quality of Life | - | Summary measure of quality of life |
| Health Perception | - | Subjective rating of general health |
| - | Participation restriction | - | Involvement in life situations |
| - | - | Resource use | Health/social costs |
| - | - | Adverse events | Treatment side effects |
| - | - | Mortality | Death |

**Key:** ICF = International Classification of Functioning, Disability & Health, COMET = Core Outcome Measures in Effectiveness Trials (initiative), WHO = World Health Organization.