Draft: Consensus Conceptual Model of Early Parkinson's Disease

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A consensus conceptual model of meaningful symptoms and impacts for early Parkinson's Disease

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Word Counts
Title: 81
Number of references: 120 (main manuscript)
Number of tables: 14
Number of figures: 3
Supplemental online materials: 5
Word count abstract: 250
Word count paper: 5180

Keywords: early Parkinson's, conceptual model, framework, meaningful, symptoms, impacts

Funding Source: This study was funded by the Michael J Fox Foundation. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS or the U.S. Government.

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ONLINE ONLY

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Abstract

Background

A comprehensive, widely accepted, patient-centered conceptual model of Parkinson's disease (PD) is needed to improve therapeutic development and guide selection of relevant endpoints.

Objectives

To develop an evidence-based conceptual model of early PD, defined as <3 years since clinical diagnosis, that meets the needs of all relevant stakeholders, including people with PD, researchers, clinicians, industry, and regulators.

Method

A multi-stakeholder taskforce and patient advisory panel oversaw the systematic review and metasynthesis of qualitative and quantitative studies using JBI Mixed Methods Review criteria and GRADE-CERQual standards for assessment of evidence quality, with iterative taskforce and advisory meetings to develop the model.

Results

More than 340 symptoms and impacts were identified from 89 studies. These were grouped into ten symptom domains (Movement, Cognitive, Psychiatric, Sleep, Sensory, Speech, Digestive, Urinary, Sexual, Autonomic) and two impact domains (Physical functioning, Psychosocial functioning). Synthesis of findings tables (SOFT) indicate that a wide range of motor and non-motor symptoms are prevalent and bothersome in early PD, with strongest evidence for tremor, dexterity, gait, stiffness, and slow movements as well as cognitive changes, word finding

issues, mood and sleep alterations, urinary dysfunction, constipation, pain, and fatigue. These impact mobility (sports & exercise), self-concept, coping, effort of living, interpersonal interactions and important activities, with preliminary evidence of many understudied impacts.

Conclusion

This consensus-based conceptual model of early PD provides the most comprehensive catalogue of meaningful symptoms and impacts to date. The model and SOFT offer evidence-based tools for identification of concepts of interest and endpoints for clinical trials.

1. Background

Effective treatments to halt or delay progression of Parkinson's disease (PD) are urgently needed by patients and families [1]. Yet, development of new drugs is a time and resource intensive process accompanied by more failures than successes [2]. This is especially true for diseases with wide heterogeneity in symptom expression and unclear biological mechanisms of progression, such as PD[3]. Phenotypic variability makes selection of pertinent outcomes for trials particularly challenging, as different symptoms or impacts may be more (or less) important to different people at different points throughout their disease process [4, 5]. Yet, the success of clinical trials is dependent on having clinical outcomes assessments (COA) that are sensitive to treatment effects rather than natural variations in disease progression or situational context [6, 7]. This has created a critical need to know, with reasonable certainty, what experiences are typically most important to the majority of people with PD at a specified stage of disease (i.e., what—who—when). This summative, contextually-defined knowledge of individuals' lived experiences is essential to selection of outcomes that are meaningful from a real-world perspective and in alignment with the regulatory landscape [8, 9]. Recent qualitative work has greatly enhanced understanding of the lived experiences of people living with Parkinson's [4, 10-13], however there is no comprehensive nor widely accepted patient-centric conceptual model that can be used to guide the field. For this reason, following the 2022 PD Endpoints Roundtable [14], a global task force of experts and patient representatives was convened to develop a consensus-based conceptual model of meaningful symptoms and impacts for early PD from systematic review of the literature. The task force goals were to create a comprehensive yet parsimonious model that (1) aligned with current FDA guidance for patient focused drug

development (PFDD) [6-9], (2) could support future research and clinical trials, (3) and was adaptable to emerging knowledge and later-stages of disease. This paper reports methodological approaches and findings of the task force.

2. Methods

To ensure rigor in model development, best-practice guidelines were followed for each stage of model building, including systematic review of the literature, mixed methods evidence synthesis, and assessment of evidence quality [15-22]. These are shown in Figure 1 and described below.

2.1. Approach to model development

Guidelines by Brady et al. (2020) for the development of conceptual models to guide policy, practice, and research include three steps: (1) identifying resources (e.g., existing models, stakeholders, and literature-based sources), (2) considering the broad array of possible factors identified from resources, (3) narrowing down factors for inclusion on the basis of theory, stakeholder perspectives, and evidence [16]. A multistakeholder 14-person taskforce convened March of 2023, together with a 9-person patient and family advisory panel (Table 1), to develop the methods and approach to review of the literature (Step 1). Stakeholders included people affected by PD (patients and families), researchers, clinicians, PD advocacy groups, industry, and regulatory agencies (FDA). The purpose of the literature review was to identify *all* reported symptoms and impacts of early PD (Step 2), with ultimate intent to identify symptoms and impacts that were most meaningful in early-stage disease to inform the final model (Step 3).

2.2. Approach to systematic review for mixed methods evidence synthesis

Multiple guidelines exist for the conduct of quantitative systematic reviews and qualitative evidence synthesis [23-25]. Fewer guidelines exist for mixed methods (MM) synthesis which is essential to understanding complex real-world phenomena [15]. The task force elected

a *convergent integrated synthesis* approach to identify meaningful symptoms and impacts of early PD in both qualitative and quantitative studies [15, 26, 27]. JBI Mixed Methods Review criteria [15, 27] were used: (1) defining the review question using PICo (population, phenomena, context); (2) determining inclusion/exclusion criteria; (3) defining the search strategy (4) systematic assessment of methodological quality (5) data extraction (6) data synthesis; and (7) presentation of results.

2.2.1. Research Question: What symptoms and impacts are most meaningful in early PD?

Per recommendations from the patient panel, people affected by PD were defined as patients/people with PD (PwP) and their intimate social circle, referred to hereafter in this manuscript as "family." The terms "caregiver" and "care partner" were not used as most people with early PD do not have formal caregivers, and "partner" does not encompass the scope of people affected by PD, such as children and close friends.

Definition of symptoms and impacts. For this model, "symptoms" were considered to be the subjective or objective physical and mental features (i.e., signs/symptoms) occurring as a result of PD, leading or potentially leading to changes in day-to-day physical and psychosocial functioning, including both signs and symptoms of disease. "Functional impacts" were defined per FDA PFDD guidance as alterations in the way a person functions or feels as a consequence of disease[6].

Definition of early PD. There is no formal definition of early PD and most studies to date have utilized clinical diagnosis of PD with variable definitions of early-stage disease ranging from 0 to upwards of 6 years. For the model, early PD was defined as less than 3 years since diagnosis

(YSD) by expert consensus. The 3-year timeframe aligns with the target population of the Critical Path for Parkinson's consortium and with many clinical trials for early PD [28].

Definition of meaningful symptoms and impacts. Per patient panel and expert discussion, to be deemed "meaningful" a symptom or impact had to show evidence of being present (prevalent) as well as personally bothersome to people with early PD <3 years since clinical diagnosis.

2.2.2. Primary source inclusion & exclusion criteria

Sources were eligible for inclusion if they were: (a) primary published or unpublished qualitative, quantitative or mixed methods (MM) studies; (b) conducted within an early PD population as defined by source study authors; (c) reported any symptoms and/or impacts of early PD; and (d) contained data that were patient, family, observer, clinician reported or digitally measured. Studies focused on evaluating the effect of a specific medication or intervention were excluded, as were conference proceedings, due to insufficient data to reliably evaluate methods or findings. In longitudinal studies baseline measurement values were used.

2.2.3. Search strategy

For the literature review, any source with a study-defined "early PD" population was included to avoid overlooking potential sources during the search process. Four data bases were searched as shown in Supplement A. Search ***Strategy 1*** identified sources published within 10 years that referenced early PD and symptoms or impacts anywhere in the title or abstract (search date: May 2023). ***Strategy 2*** identified sources that used early PD and common terms for

qualitative research anywhere in the title or abstract *without* time limits. ***Strategy 3*** consisted of examining reference lists of relevant review articles for additional sources. ***Strategy 4*** used expert consultation to identify key sources > 10 years old or unpublished relevant datasets not captured in the first two search strategies. As shown in Figure 2, 2006 sources were returned, with 1301 duplicates. Abstracts were screened for 705 sources. Of these 554 were excluded and 151 were selected for full text review. Eighty-nine sources remained after eliminating studies without reportable data on symptoms or impacts within any early PD population. Of these, only 56 studies used samples that were strictly <3 years since diagnosis based on mean and SD. A complete list of sources screened and included/excluded is provided in Supplement E.

2.3. Approach to data analysis

All sources that met review inclusion criteria were systematically analyzed, and findings were weighted and aggregated to enable assessment of the total quality of evidence supporting each concept in early PD, as described below. Data extraction for *concepts* was performed on all studies of early PD (as defined by study authors; N=89; range 0-6 years since diagnosis), however, data regarding *frequencies* of concepts was limited to PD <3 years since diagnosis (N=56). This was done to maximize identification of potential concepts with reported frequencies specific to early PD based.

2.3.1. Data extraction

For mixed methods synthesis, JBI guidance recommends codifying quantitative data in a manner compatible with qualitative synthesis to reduce potential for inaccuracies in meta-

aggregation across methodologies [26]. Using a matrix spreadsheet (Supplement B), all studies were assessed individually for study aims, design, year of publication, sample size, PD stage, diagnostic criteria, years since diagnosis (mean, SD), comparison group, gender distribution, race/ethnicity, country of origin, data source, data collection instruments, PD medication use, Levodopa equivalent daily dose (LEDD), Hoehn & Yahr (H&Y), Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS UPDRS) part III total score if reported [29], any covariates, and a brief study synopsis.

Content coding. Each source was then analyzed to extract information about symptoms or impacts of early PD. Where given, frequencies for prevalence were extracted. For studies lacking frequencies but reporting between groups comparisons for *early PD vs. Control* (e.g., normative cohort, later PD cohort), statistically significant differences were indicated with "*****" and no statistically significant differences were indicated with "**-**". For studies reporting bothersomeness rather than prevalence, the percentage of people identifying the concept as being actively bothersome was reported in the matrix.

2.3.2. Development of the conceptual model schema

After content coding, all identified concepts were qualitatively analyzed to derive a best-fit conceptual schema that was intuitive, optimally parsimonious, and able to facilitate measurement consistency and reduce redundancy. Only concepts identified by systematic review were included in the modeling. Initial attempts to group by motor versus non-motor resulted in a poorly organized structure due to the large number of concepts identified and the

presence of many concepts with ambiguous classification (e.g., motor vs. non-motor; symptom vs. impact).

A series of 10 interactive sessions were held from September to November, 2023, to solicit feedback from all stakeholders (taskforce and patient panel) to derive a consensus-based schema that was intuitive and user-friendly for clinicians, researchers, PwP and families. Sessions were held online using a focus group format, with a moderator who summarized and synthesized perspectives in real time.

Using mapping approaches (Xmind app) with screen sharing, concepts were clustered by relatedness and organized into logical groupings [30, 31]. Where possible, full agreement was sought for all analytic decisions, with use of majority vote on best groupings (task force and patient panel) when 100% consensus was not achieved in online meetings. Similar concepts were merged and consensus term selected based on task force and patient panel agreement. Concepts that related to a broader concept were subsumed as dependent nodes to develop a branching structure moving from broad concepts to progressively more specific aspects of an experience (e.g., shuffling as an aspect of gait). Conceptual distinctness and relatedness were determined by stakeholder consensus regarding interpretation of literature review findings during online sessions. All conceptually distinct items were retained in the final model schema (Supplement C). Detailed documentation of stakeholder sessions and revisions to the schema was retained for an audit trail.

2.3.3. Weighting of primary sources preparatory to metasynthesis

The PFDD guidance series prioritizes *direct report* of patient experience from the target population (i.e., people with PD) [9]. When this type of data is limited or the patient population has reduced ability to reliably report experiences, supporting information may be obtained from caregivers, clinicians, or other key informants [8]. Based on discussion with the patient panel and task force members, a three-tiered approach was chosen for classification of primary sources. This was done to allow for prioritization of patient voice and weighted synthesis of findings across diverse methodologies and data sources as described below.

Tier 1 [4, 10-13, 32-34] comprised qualitative or mixed methods studies that evaluated symptoms and impacts of PD using an open-ended, iterative, and patient-driven approach, in which patients and/or family were asked to freely identify what symptoms or impacts the person experienced without constraints. Tier 1 was further subdivided to ***Tier 1A*** (studies reporting a symptom as being *bothersome* in early PD irrespective of prevalence) and ***Tier 1B*** (studies reporting symptoms as *present* in early PD irrespective of whether it is bothersome). Tier 1 sources were used as *primary evidence* for the conceptual model. Original study teams from Tier 1 sources were contacted to obtain detailed frequencies for symptoms and impacts if not fully presented in published manuscripts [4, 10-12, 32, 33].

Tier 2 and 3 [35-114] consisted of quantitative studies in which predetermined aspects of health were measured using quantitative approaches. ***Tier 2*** included studies that evaluated symptoms and impacts using patient reported outcome (PRO) measures selected by a study team in which a limited selection of symptoms or impacts were evaluated from the patient perspective. ***Tier 3*** included data from studies with clinician or observer reported symptoms or impacts (i.e., ClinRO, ObsRO). Sources reporting only cumulative scores on validated scales were

excluded as they lacked discrete data on symptoms or impacts. Tier2 and 3 studies were included as *supporting evidence* due to potential for bias in symptom reporting.

Pooling of same sample studies. Same sample studies were defined as separate publications that reported findings from the same (identical) participant sample (Supplement B). Findings were pooled from same-sample studies to ensure equal weighting during meta-synthesis. For pooling, redundant findings (e.g., demographics – diagnosis of depression) were reported once, while all unique findings retained. A total of 38 unique study samples were included in the final model.

2.3.4. Aggregation of data for early PD <3 years since diagnosis

Data aggregation was performed at the level of *unique samples* (N=38; Supplement E), rather than at the level of individual studies so that each unique sample was represented only once in the final meta-synthesis. Only samples with data for PD<3 years since diagnosis were included at this stage, based on the final model inclusion criteria. Data and frequencies for the full early PD sample (N=89, 0-6 years since diagnosis) vs. PD <3 years since diagnosis can be viewed in Supplement B.

The following metrics were calculated for each symptom and impact in early PD <3 years since diagnosis:

1. Number and percentage of unique samples that measured a concept (within and across all Tiers);

2. Average prevalence of concept (within and across Tiers 1B, 2, & 3 – sum of frequencies in all studies reporting prevalence/total number of studies reporting prevalence);
3. Number and percentage of unique samples disconfirming presence of concept (within and across all Tiers); and
4. Frequency which concept was reported as being actively bothersome (Tier 1A; sum of frequencies in studies reporting bothersomeness/total number of studies reporting bothersomeness).

2.3.5. Assessment of quality of evidence & synthesis of findings

Next, evidence synthesis was performed using GRADE-CERQual [17-22]. GRADE-CERQual is a standardized approach to assessment of confidence in the quality of evidence from qualitative studies and is endorsed by the World Health Organization and numerous government agencies for the development guidelines to shape public policy and research [23, 115, 116]. CERQual evaluates four primary areas: (1) methodological limitations, (2) coherence of findings, (3) adequacy of the data, and (4) relevance of the findings. These criteria are presented in **Table 2,** along with the operationalized approach to assessment. For this model, methodological limitations were addressed *a priori* using the Tiered approach, in which unique samples were weighted based on underlying methodological strengths and limitations.

2.4. Research community review

Lastly, to maximize potential for usefulness and adoption of the consensus model, the final model and manuscript were posted for research community review and feedback. (Pending)

3. Results

Sample characteristics. A total of 38 unique samples from publications during years 2013 to 2023 were included in the synthesis of findings and frequencies for the final model, which was strictly limited to early PD<3 years since diagnosis. All qualitative samples (Tier 1; 6 unique samples from 7 studies) were from the UK, USA, and Canada and included predominantly white participants (93-100%). Three of these reported bothersomeness; four reported prevalence; one reported both. Sample sizes ranged from 20 to 134 with one very large sample study of 8536 participants (Fox Insight/PD PROP). Tier 2 (N=13) and Tier 3 (N=19) sources included studies from UK, USA, Canada, Italy, Korea, Serbia, Thailand, Germany, India, China, Singapore, and the Netherlands, in which distribution of race/ethnicity was often not reported. Samples sizes ranged from 54 to 921 participants. The mean age range for all studies in all Tiers was 57-68 years. Gender distribution ranged from 40-74% male, most commonly approaching 60%. In 13 of 38 unique samples (34%), participants were taking PD medications (range 4-100%; mean LEDD 50-544). Medication use was not stated in 18% (7/38). Hoehn & Yahr score (H&Y) was reported by 27/38 samples, with mean H&Y<2 for all (100%) studies, but only 12/27 (44%) strictly ≤2 when factoring +2SD. MDS UPDRS III (motor) was reported in 25/38 studies and ranged from 9.2-27.0, which is consistent with early PD [117].

Concept characteristics. Approximately 340 symptoms and impacts were identified. Substantial variability was observed in terminology and classification of concepts, with certain concepts inconsistently classified as motor vs. non-motor, (e.g., restless leg, constipation, drooling, voice changes, swallowing), impact vs. symptom (e.g., anxiety, depression, frustration), or listed twice under both symptom and impact (e.g., handwriting, anxiety). Diverse terminology

was commonly used to describe conceptually similar ideas (e.g., depressed mood, feelings of sadness, negative feelings and emotions). Definitions were rarely provided for terms, requiring reviewers to infer what a concept likely comprised from common language use or from the context in the report (e.g., thermoregulation indicative of heat/cold intolerance vs. body temperature). Consequently, some redundancy due to potentially overlapping concepts might be present in the working model presented below.

Consensus conceptual model schema. Concepts were organized using a primary classification schema of Domain—Category—Concept—Experience, with secondary classification of motor or non-motor occurring at the measurement level, as depicted in Figure 3. Ten systems-based symptom domains were identified (Movement, Cognitive, Psychiatric, Sleep, Sensory, Speech, Digestive, Urinary, Sexual, Autonomic) in addition to two impact domains (Physical functioning; Psychosocial functioning). A map of the schema for each domain is presented in Supplement C. Comprehensive data tables and frequencies by source are presented in Supplement B, and Supplement D presents working definitions for each concept included in the model.

SOFT Reports. Synthesis of Findings Tables (SOFT 1 through 12) are presented for each symptom and impact domain, with subdivision by conceptual categories. SOFT reports show (1) issues of coherence in measurement and classification of concepts; (2) adequacy of data supporting conclusions; and (3) the relevance of each concept based on prevalence and extent to which the concept is bothersome in early PD<3 years since diagnosis.

From the SOFT reports, the most meaningful motor symptoms of early PD appear to include tremor, fine motor difficulties, gait & balance changes, stiffness, and slow movements—

all of which were observed to be prevalent (54-85%) and bothersome (24-57%) within 3 years from diagnosis. The SOFT reports also highlight multiple non-motor symptoms that are commonly experienced and meaningful to people with early disease. These commonly include cognitive and speech changes (e.g., word finding); mood changes such as anxiety, depressed mood, or negative feelings/emotions; alterations in sleep; sensory changes (e.g., increased pain and fatigue); urinary dysfunction; and digestive system changes (e.g., choking, constipation).

In addition to identifying common bothersome symptoms and impacts, multiple gap areas were observed, most often in the impact domains. Evidence from the review suggests that impact on mobility-related activities, such as physical exercise, may be a high priority area in early PD (70% prevalence; 31% bothersome). Other concepts, such as "Effort of Living" are comparatively new, with no data on prevalence (Tier 1B to 3) but Tier 1A evidence suggestive of a meaningful experience (29% bothersome). Other concepts that may be relevant at this stage include impacts on self-concept (35% bothersome), personal coping (29% bothersome), interpersonal interactions (e.g., relationships with others), sense of independence, profession, and hobbies—among others.

A final unexpected finding from the SOFT reports is the substantial research that has been conducted in areas that appear less meaningful to people with PD. Most common examples of this include drooling (30% prevalence; 0% bothersome) and loss of smell (29% prevalence; 2% bothersome).

4. Discussion

The consensus conceptual model presented here is the most comprehensive catalogue of meaningful symptoms and impacts in PD based on literature to date. This effort expands on prior models derived from individual studies [4, 10, 12, 13]. Key strengths of the present approach are exhaustive review and meta-synthesis of methodologically diverse studies, inclusion of all key stakeholders throughout the model building process, and use of an iterative consensus-based design. We believe that this has contributed to a maximally inclusive model reflective of the current state of the science, with an intuitive and easily understood interface. This approach can increase utility of the model, contribute to improved COAs for early PD trials, and enhance potential for broad uptake and harmonization of approaches across research, health care practice, and other endeavors.

4.1. Recommendations for use and limitations of SOFT reports

A major contribution of this study is the SOFT reports, which can serve as an evidence-based rationale for identification of concepts of interest for use in research or clinical assessment. It is important to note that these reports should be used with caution due to limitations inherent in the data, collection, and reporting processes of primary sources. Evidence was compiled from diverse sources, and methodological flaws in primary sources may have resulted in over, under, or selective reporting, which in turn affect aggregated frequencies for this study. Thus, the term "SOFT report" is intentional, and should serve as a reminder that data are not conclusive and should be treated as an estimation rather than an exact measurement. Future work will enable more accurate understanding of concepts in defined populations (e.g., NSD) over time.

Conduct multifaceted Concept of Interest (COI) assessments. Concepts of interest are the "aspect of an individual's clinical, biological, physical, or functional state, or experience that the assessment is intended to capture or reflect" [8]. Selection of meaningful concepts requires recognizing that "meaningfulness" is multifaceted. No single metric in the SOFT reports should be used in isolation to justify selection of COI. Consideration should be given to all metrics, including estimates of prevalence in the population, evidence that it is truly relevant to people with early PD, and the total weight of evidence (Grade/Level) that justifies the former conclusions. Gap areas may have insufficient data to justify inclusion or exclusion on the basis of SOFT reports.

Explore gap areas. It is important to note that absence of a concept in SOFT reports, or lack of specific supporting data does not imply absence of a meaningful experience in early PD, and might mean the concept has not been sufficiently studied or reported. Particular attention should be paid to concepts with limited or missing evidence, which was commonly the case in the psychosocial impacts domain. Further research will be needed in many areas to define the scope of these concepts and determine best approaches to measurement.

Evaluate coherence and disconfirming evidence. Close attention should also be paid to disconfirming evidence and discrepancies in findings. For instance, the categorical concept of "gait" appears to be highly relevant in early PD, but there is little data to indicate which aspects of walking (i.e., specific health experiences such as shuffling or sensation of foot being stuck to floor) are problematic, noticeable, or bothersome to people with PD. Disconfirming evidence existing side-by-side with confirming evidence may raise questions about cohesiveness of the concept and adequacy of prior measurement approaches (e.g., both confirming and

disconfirming evidence regarding dyskinesia in early PD in all Tiers). Conflicting evidence often highlights areas of limited or imprecise understanding that might benefit by further clarifying work. Identifying the specific patient experiences that comprise a concept will improve consistency in concept definitions and measurement approaches.

4.2. Pragmatic considerations in selection of COI

Change over time. SOFT reports can help identify what is important to people affected by PD but additional pragmatic considerations are needed during COI selection and development of measures for clinical trials. Once potential COI have been identified, it is important to consider measurability for clinical trials and if the experience is likely to significantly change within the time frame of the average trial (e.g., 6-18 months). Similarly, selection of the COI might be dependent on whether it is likely to be affected by a potential treatment, which is contingent on the mechanism of action of the treatment being evaluated. For example, "stigma" may be highly relevant to PwP (good evidence of being prevalent and bothersome), but is unlikely to change rapidly with treatment, thus is unsuitable for certain measurement situations.

Context of use. The context in which a COI will be used in drug development decision making will also affect choice. Important points to consider are universality and participant characteristics that may affect how an individual experiences it. Individual characteristics such as age, life-stage (pre/post retirement), gender, geographic location, and culture can affect the meaningfulness of certain concepts more than others. For example, the impact of PD on driving may be greater for people in rural areas than for urban residents, which affects the suitability of the concept for geographically diverse trials testing treatment efficacy. Similarly, COIs may be sex

specific (e.g., erectile dysfunction) and attention should be given to maximize applicability to both sexes. Culture may also play a key role in COI selection, however there is very limited data on this due to the predominance of white participants of higher socio-economic status in most trials to date.

Measurement validity. Other practical considerations include recall and social biasing. Some experiences may be more difficult to recall over time than others. Some concepts may be subject to social desirability bias (e.g., people may downplay or be reluctant to report experiences like panic attacks or sexual dysfunction), leading to potential for increased measurement error. Ability for participants to tell if a symptom is attributable to PD may also be an important consideration, which was highlighted by the patient panel. Ways to enhance validity in measurement should be considered during COI selection. Symptom concepts that are clearly linked to a functional impact may be particularly useful, allowing for triangulated assessment of the symptom and/or impact on function (e.g., what the person can or cannot do because of fatigue). This requires establishing an evidence-based connection between specific symptoms and related functional impacts and demonstrating the prevalence and meaningfulness of these sets of experiences to people with early PD.

4.3. Future directions

Need for diverse perspectives. This report highlights the marked lack of participant diversity in PD research to date, which is a well-known issue in the field [118]. All Tier 1 evidence was elicited from the UK, USA, and Canada, with samples that were >93% white. Tier 2 and 3 data contained greater diversity in country of origin but limitation to PD duration of <3 years

since diagnosis excluded a number of these studies from inclusion in final frequencies. This data has been retained and is available in Supplement B. Future work should aim to expand knowledge of meaningful symptoms and impacts in culturally, geographically, and racially diverse populations. This recommendation corresponds with FDA PFDD guidance [6-9]. In particular, evidence from countries in certain parts of Asia, Africa, and South America is limited and would help to inform the utility of the current conceptual model for more diverse populations. Similarly, evidence from cultural and racial minorities living within predominantly white countries is needed.

Lastly, only one study in the review reported the perspectives of family separately from patient perspectives with regards to most bothersome symptoms [33]. Due to the model parameters and significant differences in PwP vs. family perspectives, this data was removed from the final model frequencies as an outlier but is reported in Supplement B. Further research to understand the wholistic impact of PD on patients and their family might be warranted, given growing emphasis on family centric and palliative care.

Need for harmonization. Another key call to action is for harmonization of concepts and concept definitions, which will be needed to improve coherence in classification and measurement for future studies. All terms in the present model have been given preliminary working definitions derived from evidence-based resources [119, 120] and common language usage of terms [121] (Supplement D), with the recognition that these may require revision or refinement as the field matures. Revisions or additions to domains, categories or concepts should be made cautiously and grounded in rigorous evidence, with careful attention to existing items in the model. This will help to avoid redundancy and maximize parsimony. Where

possible, researchers will benefit by building on prior work instead of duplicating efforts. When needed, clear and compelling scientific justification should be provided for alternative terms for similar concepts. Finally, in selecting "best" terms, reflecting the experiences of the people living with PD should remain a top priority – which was unanimously emphasized by the patient advisory panel. Thus, where possible, patient centric terms that are understandable to most patients will be preferred over complex technical terms exclusive to the scientific community (e.g., slow movements vs. bradykinesia).

Expectation of evolution. It is expected that this model will evolve over time based on refinements and expansion of knowledge within early PD and later stages of disease. It is important to note that the conceptual categorization proposed here is not intended to be prescriptive. Clear documentation of rationales for alternative approaches to concepts, definitions, or classification will help with refinement overtime. Intermittent, systematic re-evaluation may also be necessary.

In particular, reevaluation will be needed to ensure alignment with emerging PD biological definition and staging systems for neuronal synuclein disease (NSD) [122]. The use of an integrated biological- and clinical-staging model (based on degree of functional impairment) can improve participant selection for future studies. Historically, patient experience studies have not used biomarkers to define target populations, and all studies in the present conceptual model relied on clinical PD diagnosis, which is not an entirely accurate reflection of disease duration. Thus, this model might not be generalizable to biologically staged NSD and people with the other neuronal synucleinopathies, such as Dementia with Lewy Bodies. Findings likely reflect

PD/NSD individuals with mild symptoms and slight functional impairment to mild functional impairment (NSD Stage 3 or 4). As such, the proposed conceptual model should be treated as "best fit now" to prevent loss of forward momentum while striving for greater harmonization. Future work will be needed to test the model in biologically defined NSD populations. This will allow for more precise understanding of what is important at each stage and can better support selection of stage-appropriate COI and COA for clinical trials.

4.4. Conclusions

A widely accepted consensus conceptual model is an essential initial step in development of meaningful and reliable fit for purpose COAs for clinical trials in early PD. Collaborative efforts, leveraging prior work, and consensus on key concepts is crucial to advancing the science, reducing inefficiency and duplication of efforts, and ultimately developing the disease modifying treatments that are so desperately needed. We believe the methods and outcomes described in this report can help address gaps in outcome measure development and selection in early PD trials and serve more broadly as a model for future efforts to develop conceptual models in diseases beyond PD.

References for Main Manuscript

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Tables for Print

Table 1. Stakeholder participation in development of the consensus conceptual model

Stakeholder group	Investment
People affected by PD • Patients • Families (Spouse/partners, children, close friends)	• ***Taskforce member***: PwP representative at monthly taskforce meetings to consult on approach, progress, and co-author final product • ***Advisory panel:*** Ethnically and gender diverse 9-member patient advisory panel convened to (A) review and advise on approach developed by task force; (B) provide iterative real-time feedback on model structure, terminology, presentation, and potential uses; (C) review and provide feedback on final manuscript and results; (D) co-authors on final manuscript. Panel characteristics:
Clinicians (Neurology, PCP, Nursing, Speech/PT)	**Multi-stakeholder task force convened monthly to:** • Co-develop approach • Monitor progress • Advise on data extraction and meta-synthesis • Critique and iteratively revise model and outputs • Co-author presentations, publications **Public Review Period** • One-month public review period to provide feedback on final report.
Researchers • Model developers; PD staging experts, Topical experts	
PD Advocacy Groups • Michael J Fox Foundation • Parkinson's UK	
Industry • Roche, AbbVie, GSK, Roche, Denali, UCB	
Representatives of professional agencies • Critical Path for Parkinson's • Movement Disorders Society	
Regulatory • FDA • National Council on Aging • CMS (Center for Medicare Services)	• Review and provide feedback on draft methods and results. • Review and provide feedback on final report

Table 2. Operationalized criteria for assessment of quality of evidence – GRADE-CERQual

CERQual Criteria	Operationalized definition	Approach to criteria	
Methodological limitations	Methodological limitations in approaches to identifying symptoms and impacts that may limit what type of information was reported – e.g. use of validated measures that only collect specific data (restricted), vs. qualitative interviews allow for unrestricted reporting.	Tiering system for weighted inclusion of sources by methodological adequacy: • Tier 1: Qualitative studies collecting unrestricted data directly from report of patients and family. • Tier 2: Quantitative studies measuring specific symptoms or impacts predominantly from the patient perspective. • Tier 3: Quantitative studies measure specific symptoms or impacts from the clinician or outside observer perspective. Highest priority is given to direct patient voice with unrestricted approach to exploring symptoms or impacts. Lower priority is given to Tier 2 and 3 sources due to methodology that resulted in restricted data collection.	
Coherence	Assessment of the agreement of the primary studies regarding the concepts of interest. Threats to coherence include: contradictory data, divergent classification, ambiguous or conflicting descriptions.	• No concerns – consistent and coherent classification of COI across studies • Minor concerns – 80 – 94%% coherence in classification • Moderate concerns – 50-74% coherence in classification • Severe concerns- <50% coherence in classification No or minor concerns preferred.	
Adequacy	Adequacy is the richness and quantity of data supporting the measurable presence of a COI in the early PD population as seen in primary sources. *Primarily*: Percentage of Tier 1 sources (direct patient voice) that reported the COI as being measurably present in an early PD population. *Secondarily*: Percentage of Tiers 2 and 3 that reported the COI as being measurably present in an early PD population. Evidence from Tiers 2 and 3 alone is *insufficient proof* of adequacy if lacking evidence in Tier 1.	*Primary classification of adequacy (Tier 1):* • Grade A = Strong evidence in Tier 1 • Grade B = Moderate evidence in Tier 1 • Grade C = Limited evidence in Tier 1 • Grade D = lacking evidence in Tier 1 • Grade X = No evidence in Tier 1 *Secondary classification of adequacy (Tier 2 & 3):* • 1 = with strong evidence in Tier 2 or 3 • 2 = with moderate evidence in Tier 2 or 3 • 3 = with limited evidence in Tier 2 or 3 • 4 = with very limited evidence in Tier 2 or 3 • x = No evidence in Tier 2 or 3 Grade A evidence preferred (ex. A1, A2).	*Thresholds are based on the <u>number of studies</u> reporting the concept:* • 1-24% = Very limited • 25-49% = Limited • 50-74% = Moderate • ≥ 75% = Strong
Relevance	Composite score indicating the extent to which evidence from the primary studies supports the concept as being actively <u>bothersome</u> to people with early PD, in addition to being commonly present in the population.	*Bothersome rating*: Average frequency at which concept is reported as bothersome in early PD among studies measuring frequency of the concept. • High, Medium, Low, or *NR* (not rated due to insufficient evidence) *Prevalence rating*: Estimate of presence of concept *in an early PD population* based on the average prevalence (% sample) reported in studies that the measured the construct. • % [Range] or NR (not rated due to insufficient evidence)	

SOFT 1. Movement Domain

Category/Concept	Coherence in Measurement & Classification		Adequacy of Data					Relevance of Concept		
	Concerns	Explanation	Tier 1 Grade	Tier 2 & 3 Level	Tier 1 6 Studies (%)	Tier 2 13 Studies (%)	Tier 3 18 Studies (%)	Bothersome mean %	Prevalence mean %	Prevalence [Range]
SLOW MOVEMENT										
Slow movement	-	No concerns; One Tier 3 study disconfirming presence in early PD	A+	4 -	100%	-	16%	29%	54%	[5-83%]
LOSS OF COORDINATION		Concept cateogy								
Loss of coordination	Moderate	Variably reported and may confound fine motor with gross motor	B	x	50%	-	-	10%	14%	[5-23%]
FINE MOTOR		Concept category								
Fine motor difficulties	-	No concerns; No disconfirming evidence	A	4	83%	-	5%	35%	85%	[71-95%]
STIFFNESS										
Stiffness/Rigidity	Minor	Variable terminology (stiff, tight, rigid); No disconfirming evidence	A+	4	100%	-	11%	24%	62%	[50-69%]
Range of motion	Minor	Inconsistent classification as symptom vs. impact; Limited evidence	D	x	33%	-	-	13%	17%	[5-28%]
Facial expression	-	No concerns; No disconfirming evidence	A+	x	100%	-	-	3%	18%	[13-27%]
Occulomotor changes	Moderate	Encompasses blinking and pupilomotor control; Definitions needed	D	4	17%	8%	5%	-	19%	-
WALKING, BALANCE & POSTURE	Minor	Variably measured as a composite concept blending walking and balance	B	4	67%	2	-	21%	57%	[30-75%]
Balance	-	No concerns; No disconfirming evidence	A+	4	100%	-	11%	20%	41%	[7-66%]
Gait changes	Minor	Variable approaches to measurement and multiple subconcepts limits synthesis	A+	4	100%	-	5%	32%	63%	[40-86%]
Shuffling	UA	Limited evidence in early PD <3 years	D	x	17%	-	-	-	11%	-
Dragging feet	UA	Limited evidence in early PD <3 years	D	x	17%	-	-	-	24%	-
Short step	UA	Limited evidence in early PD <3 years	D	x	17%	-	-	-	3%	-
Altered stance	UA	No evidence in early PD <3YSD	X	x	-	-	-	-	-	-
Altered turning	UA	Limited evidence in early PD <3YSD	D	x	17%	-	-	-	5%	-
Double support time	UA	No evidence in early PD <3YSD	X	x	-	-	-	-	-	-
Staggering	UA	No evidence in early PD <3YSD	X	x	-	-	-	-	-	-
Freezing	-	No concerns; No disconfirming evidence	B	4	50%	8%	5%	3%	6%	[4-16%]
Velocity	UA	No evidence in early PD <3YSD	X	x	-	-	-	-	-	-
Altered arm Swing	-	No concerns; No disconfirming evidence	B	x	50%	-	-	5%	55%	[38-71%]
Postural changes	-	No concerns; No disconfirming evidence	A+	x	100%	-	-	4%	15%	-
TREMOR										
Tremor	-	No concerns; No disconfirming evidence	A+	4	100%	15%	11%	57%	85%	[42-100%]
Sense of internal tremor	-	Sometimes confounded with "vibratory" sense	B	2	50%	-	-	1%	9%	[8-9%]
OTHER INVOLUNTARY MOVEMENT		Proposed concept category								
Cramping/spasm	-	Variable terminology (cramping, spasms, dystonia); No disconfirming evidence	A	x	83%	-	-	9%	30%	[20-41%]
Restless legs	Minor	Inconsistent classification as MS vs. NMS; One Tier 1 source disconfirming	B -	x	50%	-	-	1%	13%	[0-38%]
Twitching	Moderate	Inconsistent terminology (twitching, jerking); no disconfirming evidence	D	x	17%	-	-	-	30%	-
Dyskinesias	Severe	Inconsistent and disconfirming evidence all Tiers	B -	4 -	67%	8%	-	2%	11%	[0-2%]

Notes. *PD= Parkinson's disease; UA=Unable to assess due to limited data; YSD=Years since diagnosis of Parkinson's disease;* ***Tier 1 Grade*** *A+=100%, A=75-99%, B=50-74%, C=25-49%, D=1-24%, X=No studies supporting presence in early PD;* ***Tier 2 & 3 Level*** *1=75-100%, 2=50-74%, 3=25-49%, 4=1-24%, x=No Tier 2 or 3 studies supporting presence in early PD. Minus sign "-" in Grade or Level indicates presence of disconfirming evidence.*

SOFT 2. Cognitive Domain

Category/Concept	Coherence in Measurement & Classification		Adequacy of Data		Relevance of Concept		
	Concerns	Explanation	*Tier 1 Grade*	*Tier 2 & 3 Level*	*Bothersome mean %*	*Prevalence mean %*	*Prevalence [Range]*
MEMORY		Expert proposed concept category aligning with state of science					
Memory	Moderate	Unclear what is being measured for "memory" in many study reports	A+	3	14%	38%	[17-65%]
Forgetting to do things	UA	Limited evidence; No disconfirming evidence	X	4	-	-	-
Visual Memory	UA	Limited evidence; No disconfirming evidence	X	4	-	-	-
EXECUTIVE FUNCTION		Expert proposed concept category aligning with state of science					
Executive function	Moderate	No disconfirming evidence; Unclear how concept is being measured	B	4	3%	24%	-
Ability to multitask	UA	Limited evidence; No disconfirming evidence	C	x	3%	14%	-
LANGUAGE		Expert proposed concept category aligning with state of science					
Word finding	Minor	One large Tier 1 study found no evidence of bothersomeness at early stage	A-	x	17%	42%	[19-65%]
VISUAL SPATIAL		Expert proposed concept category aligning with state of science					
Depth perception	UA	Limited evidence; One Tier 1 study disconfirming presence in early PD <3YSD	D-	4	3%	25%	-
Finding way	UA	Limited evidence; no disconfirming evidence	C	x	4%	10%	-
ATTENTION & PROCESSING		Expert proposed concept category aligning with state of science					
Attention	-	No disconfirming evidence	B	x	11%	25%	[24-25%]
Concentrating	-	No disconfirming evidence	A+	4	11%	28%	[14-63%]
Slower thinking	-	No disconfirming evidence	B	x	12%	42%	[30-53%]
Mental alertness/fog	-	No disconfirming evidence	B	x	5%	24%	[8-40%]
DIAGNOSTIC CLASSIFICATION							
Mild cognitive impairment	Moderate	No disconfirming evidence, unclear if clinical classification or self-report	C	3	-	30%	[25-35%]
Dementia	Severe	No evidence supporting presence in PD <3YSD; Disconfirming evidence in Tier 2	X	x-	-	-	-

Notes. *PD= Parkinson's disease; UA=Unable to assess due to limited data; YSD=Years since diagnosis of Parkinson's disease;* ***Tier 1 Grade*** *A+=100%, A=75-99%, B=50-74%, C=25-49%, D=1-24%, X=No studies supporting presence in early PD;* ***Tier 2 & 3 Level*** *1=75-100%, 2=50-74%, 3=25-49%, 4=1-24%, x=No Tier 2 or 3 studies supporting presence in early PD. Minus sign "-" in Grade or Level indicates presence of disconfirming evidence.*

SOFT 3. Psychiatric Domain

Category/Concept	Coherence in Measurement & Classification		Adequacy of Data		Relevance of Concept		
	Concerns	Explanation	*Tier 1 Grade*	*Tier 2 & 3 Level*	*Bothersome mean %*	*Prevalence mean %*	*Prevalence [Range]*
MOOD & AFFECT		Expert proposed concept category					
Mood		No disconfirming evidence	B	4	25%	47%	[35-59%]
Apathy	Minor	One study Tier 3 disconfirming presence in early PD <3YSD	A	3 -	5%	23%	[5-58%]
Loss of interest	Moderate	Appears to overlap with concept of apathy	C	4	-	24%	[14-35%]
Anxiety	Minor	One study Tier 3 disconfirming elevated presence in early PD <3YSD	A +	3 -	21%	45%	[12-74%]
Social phobia	UA	No evidence in early PD <3YSD	X	x	-	-	-
Panic	UA	Minimal evidence in early PD <3YSD	D	x	-	14%	-
Depression/depressed mood	Moderate	Unclear if clinical diagnosis or symptoms of depressed mood	A +	3	8%	34%	[10-59%]
Low or flat mood	UA	Patient panel strongly advocates to retain concept as distinct from depression	C	4	-	27%	[19-38%]
Feelings of sadness	Moderate	Potential overlap with depression/depressed mood; Not reported in PD <3YSD	X	x	-	-	-
Loss of pleasure	UA	Minimal evidence in early PD <3YSD	D	x	-	30%	-
Negative feelings/emotions	UA	Patient panel strongly advocates to retain concept as distinct from depression	C	x	27%	30%	-
Death & suicidal thoughts	UA	Limited evidence in early PD <3YSD	C	x	1%	3%	-
Emotional lability	New	Category suggested by patient panel					
Pseudobulbar affect	UA	No supporting evidence in early PD; One study disconfirming in Tier 1	X -	x			
Irritability	UA	Patient panel advocates for inclusion as a symptom	D	4	1%	14%	[1-18%]
Euphoria	Minor	Limited evidence; One Tier 3 study disconfirming presence in early PD <3YSD	X	x -			
Agitation	UA	Minimal evidence in early PD <3YSD	X	4	-	13%	[12-13%]
BEHAVIORS		Expert proposed concept category					
Impulsive behaviors	UA	One Tier 1 study disconfirming presence in PD <3YSD; Very limited evidence	X -	4	-	10%	-
Medication use compulsion	UA	Very limited evidence in early PD <3YSD	X	4	-	2%	-
Buying compulsion	UA	Very limited evidence in early PD <3YSD	X	4	-	4%	-
Eating compulsion	UA	Very limited evidence in early PD <3YSD	X	4	-	5%	-
Sexual compulsion	UA	Very limited evidence in early PD <3YSD	X	4	-	5%	-
Punding compulsion	UA	Very limited evidence in early PD <3YSD	X	4	-	5%	-
Gambling compulsion	UA	Very limited evidence in early PD <3YSD	X	4	-	1%	-
Walkabout compulsion	UA	Very limited evidence in early PD <3YSD	X	4	-	1%	-

PSYCHIATRIC DOMAIN (SYMPTOMS)

Hobbyism compulsion	UA	Very limited evidence in early PD <3YSD	X	4	-	11%	-
Subsyndromal ICD	UA	Diagnostic classification: Minimal evidence in early PD <3YSD	X	4	-	10%	-
ICD	UA	Diagnostic classification: Minimal evidence in early PD <3YSD	X	4	-	25%	-
PSYCHOSIS		Expert proposed concept category					
Psychosis	UA	Minimal evidence in early PD <3YSD	X	x	-	-	-
Delusions	UA	Minimal evidence in early PD <3YSD	X	4	-	2%	-
Hallucinations	UA	Minimal evidence in early PD <3YSD	D	4	1%	4%	
PERSONALITY CHANGES		Expert proposed concept category					
Personality changes	UA	Very limited evidence in early PD <3YSD	D	4	1%	-	-
Persistence	Moderate	Concern for overlap with perseveration; No evidence early PD <3YSD	X	x	-	-	-
Reward dependence	UA	No evidence in early PD <3YSD	X	x	-	-	-
Disinhibitions	UA	Minimal evidence in early PD <3YSD	X	4	-	2%	-
Neuroticism	UA	No evidence in early PD <3YSD	X	x	-	-	-
Emotion recognition accuracy	UA	No evidence in early PD <3YSD	X	x	-	-	-
Novelty seeking	UA	No evidence in early PD <3YSD	X	x	-	-	-

Notes. *PD= Parkinson's disease; UA=Unable to assess due to limited data; YSD=Years since diagnosis of Parkinson's disease;* ***Tier 1 Grade*** *A+=100%, A=75-99%, B=50-74%, C=25-49%, D=1-24%, X=No studies supporting presence in early PD;* ***Tier 2 & 3 Level*** *1=75-100%, 2=50-74%, 3=25-49%, 4=1-24%, x=No Tier 2 or 3 studies supporting presence in early PD. Minus sign "-" in Grade or Level indicates presence of disconfirming evidence.*

SOFT 4. Sensory Domain

Category/Concept	Coherence in Measurement & Classification		Adequacy of Data		Relevance of Concept		
	Concerns	Explanation	*Tier 1 Grade*	*Tier 2 & 3 Level*	***Bothersome mean %***	***Prevalence mean %***	***Prevalence [Range]***
FIVE SENSES		Proposed concept category					
Vision	Moderate	Ambiguity in what is being measured	B	x	1%	9%	[5-11%]
Light sensitivity	UA	Very limited data	X	4	-	21%	[2-27%]
Double vision	UA	Limited data; One Tier 1 study disconfirming presence in early PD <3YSD	D -	4	-	5%	[3-7%]
Dry eyes	UA	Very limited data	D	x	-	3%	-
Taste	UA	Limited data	D	4	1%	25%	-
Smell	-	Strong evidence all Tiers	A	3	2%	29%	[16-50%]
Hearing	UA	Limited data	D	x	-	5%	-
Touch	Moderate	Inconsistent use in terminology for touch subconcepts	B	x	2%	16%	[1-29%]
Peripheral neuropathy	Moderate	Peripheral neuropathy (diagnosis) used interchangeably with numbness	D	4	-	27%	[15-38%]
Vibratory sense	Moderate	Vibratory sense colloquially confounded with tremor	X	4	-	55%	-
Numbness	Moderate	Peripheral neuropathy (diagnosis) used interchageably with numbness	C	x	3%	15%	
Temperature sensation	Severe	No evidence in early PD <3YSD; One Tier 1 study disconfirming; Inconsistent terms	X -	x	3%	-	-
Tingling	Moderate	Often reported as merged concept numbness/tingling	C	x	-	13%	[11-15%]
OTHER SENSATIONS		Proposed concept category					
Pain (general)	Minor	Non-specific - unclear what "pain" encompasses	A +	3	28%	38%	[8-59%]
Headaches	UA	Limited data	D	x	1%	-	-
Fatigue/lack of energy	Minor	Often reported as tired/fatigued; one Tier 3 study disconfirming	A +	3 -	28%	50%	[20-76%]
Physical fatigue	-	No disconfirming evidence	C	x	33%	35%	[33-35%]
Mental fatigue	-	No disconfirming evidence	B	x	1%	8%	[1-8%]
Breathlessness (dyspnea)	Moderate	No evidence supporting presence in early PD <3yrs; Disconfirming evidence in Tier 1	X -	x	-	-	-
Muscle weakness	-	No disconfirming evidence	B	x	4%	20%	[15-27%]
Heaviness	UA	Very limited data	D	x	-	5%	-
Temperature control	Severe	Confused with thermoregulation (autonomic); One Tier 1 study disconfirming	C -	4	2%	25%	[3-57%]
Heat intolerance	UA	No Tier 1 evidence; very limited data	X	4	-	19%	-
Cold intolerance	UA	No Tier 1 evidence; very limited data	X	4	-	27%	-

Notes. *PD= Parkinson's disease; UA=Unable to assess due to limited data; YSD=Years since diagnosis of Parkinson's disease;* ***Tier 1 Grade*** *A+=100%, A=75-99%, B=50-74%, C=25-49%, D=1-24%, X=No studies supporting presence in early PD;* ***Tier 2 & 3 Level*** *1=75-100%, 2=50-74%, 3=25-49%, 4=1-24%, x=No Tier 2 or 3 studies supporting presence in early PD. Minus sign "-" in Grade or Level indicates presence of disconfirming evidence.*

SOFT 5. Sleep Domain

Category/Concept	Coherence in Measurement & Classification		Adequacy of Data		Relevance of Concept		
	Concerns	Explanation	*Tier 1 Grade*	*Tier 2 & 3 Level*	*Bothersome mean %*	*Prevalence mean %*	*Prevalence [Range]*
SLEEP DISTURBANCES	Moderate	Inconsistent terms; One Tier 3 study disconfirming elevated presence in early PD	**A +**	**2 -**	**13%**	**52%**	[13-69%]
Sleep quality		Limited evidence	**D**	**x**	**-**	**16%**	-
Insomnia	-	Strong evidence for presence in early PD <3YSD	**B**	**3**	**22%**	**23%**	[5-59%]
Trouble falling asleep	-	Limited evidence	**D**	**x**	**2%**	**-**	-
Trouble staying asleep	-	No issues	**C**	**x**	**7%**	**41%**	-
Early morning awakening	UA	No evidence in early PD; One Tier 1 study disconfirming presence in early PD <3YSD	**X -**	**x**	**-**	**-**	-
Sleep duration and efficiency	UA	One Tier 3 study disconfirming; Unclear terminology; Needs definitions	**X**	**x -**	**-**	**-**	-
Sleep walking	UA	Limited evidence	**D**	**x**	**-**	**5%**	-
RSBD							
REM Sleep Behavior Disorder	Moderate	May encompass multiple experiences	**A +**	**3**	**5%**	**29%**	[11-39%]
Vivid dreams	Moderate	Unclear if different from RSBD	**B**	**3**	**7%**	**20%**	[7-31%]
Unpleasant dreams	Moderate	May or may not be component of RBSD; unclear category	**D**	**x**	**-**	**14%**	-
DAYTIME SLEEPINESS	Moderate	Unclear what level of sleepiness consistitutes excessive daytime sleepiness	**A +**	**4**	**8%**	**26%**	[3-54%]

Notes. *PD= Parkinson's disease; UA=Unable to assess due to limited data; YSD=Years since diagnosis of Parkinson's disease;* ***Tier 1 Grade*** *A+=100%, A=75-99%, B=50-74%, C=25-49%, D=1-24%, X=No studies supporting presence in early PD;* ***Tier 2 & 3 Level*** *1=75-100%, 2=50-74%, 3=25-49%, 4=1-24%, x=No Tier 2 or 3 studies supporting presence in early PD. Minus sign "-" in Grade or Level indicates presence of disconfirming evidence.*

SOFT 6. Speech Domain

Category/Concept	Coherence in Measurement & Classification		Adequacy of Data		Relevance of Concept		
	Concerns	Explanation	*Tier 1 Grade*	*Tier 2 & 3 Level*	***Bothersome mean %***	***Prevalence mean %***	***Prevalence [Range]***
SPEECH CHANGES	-	Concept category	**A +**	**4**	**14%**	**45%**	[7-66%]
Articulation	Moderate	One Tier 1 study disconfirming presence in early PD <3YSD	**C -**	**4**	**6%**	**29%**	[6-38%]
Verbal Fluency	Moderate	Unclear definition of term; May overlap with cognitive word finding	**D**	**x**	**-**	**5%**	-
VOICE CHANGES	-	Concept category	**B**	**x**	**2%**	**-**	-
Phonation	UA	Limited evidence; No disconfirming evidence	**X**	**4**	**-**	**-**	-
Monotone (Prosodic impairment)	UA	Limited evidence; No disconfirming evidence	**D**	**x**	**6%**	**31%**	[6-31%]
Quiet voice	-	No disconfirming evidence	**B**	**x**	**6%**	**66%**	[2-79%]
Voice quality	-	Important to retain per patient panel; Distinct from other voice changes	**B**	**x**	**6%**	**32%**	[6-49%]

Notes. *PD= Parkinson's disease; UA=Unable to assess due to limited data; YSD=Years since diagnosis of Parkinson's disease;* ***Tier 1 Grade*** *A+=100%, A=75-99%, B=50-74%, C=25-49%, D=1-24%, X=No studies supporting presence in early PD;* ***Tier 2 & 3 Level*** *1=75-100%, 2=50-74%, 3=25-49%, 4=1-24%, x=No Tier 2 or 3 studies supporting presence in early PD. Minus sign "-" in Grade or Level indicates presence of disconfirming evidence.*

SOFT 7. Digestive Domain

Category/Concept	Coherence in Measurement & Classification		Adequacy of Data		Relevance of Concept		
	Concerns	Explanation	*Tier 1 Grade*	*Tier 2 & 3 Level*	*Bothersome mean %*	*Prevalence mean %*	*Prevalence [Range]*
MOUTH & THROAT SYMPTOMS		Proposed concept category					
Saliva control		Proposed concept					
Drooling	Moderate	One Tier 1 study disconfirming presence in early PD <3 YSD	B -	2	-	30%	[13-49%]
Dry mouth	UA	One Tier 1 study disconfirming presence in early PD <3 YSD	C -	x	-	3%	-
Chewing & Swallowing	Moderate	Double barrelled; Unclear if experienced separably by PwP	A +	2	-	-	-
Chewing	UA	No disconfirming evidence	D	4	5%	22%	[14-30%]
Globus	UA	Sensory perception of obstruction; Not patient oriented	X	4	-	17%	-
Dysphagia	Moderate	Diagnostic classification may comprise multiple experiences; Not patient oriented	X	3	-	15%	[7-21%]
Impaired swallowing	Moderate	No disconfirming evidence; Overlap with choking	A +	3	-	22%	[1-35%]
Choking	Moderate	One Tier 1 study disconfirming presence in early PD <3YSD; Overlap with swallowing	D -	4	9%	19%	[13-28%]
Pain during swallow	UA	Limited evidence; No disconfirming evidence	D	4	1%	6%	-
Esophageal transit time	UA	Not patient oriented	X	x	-	-	-
Eating problems NOS	Severe	Unclear definition and use; May comprise multiple experiences	X	x	-	-	-
STOMACH SYMPTOMS		Proposed concept category					
Acid reflux/heartburn	UA	Limited evidence; No disconfirming evidence	X	4	-	7%	-
Early fullness (saiety)	Severe	Unclear definition of concept	X	3	-	15%	[5-21%]
Abdominal pain/discomfort	UA	Limited evidence; No disconfirming evidence	D	4	1%	9%	-
Nausea & Vomiting	Severe	Double barreled; One Tier 1 study disconfirming in early PD; Measure separately	C -	4	1%	5%	[2-11%]
Bloating/fullness	UA	Limited evidence; No disconfirming evidence	D	4	1%	15%	-
Appetite changes	Severe	May overlap with early saiety/fullness; Two Tier 1 studies disconfirming in early PD	D -	4	-	10%	[5-15%]
BOWEL SYMPTOMS		Proposed concept category					
Constipation	-	Strong evidence all Tiers	A +	1	7%	29%	[10-46%]
Tenesmus	-	Limited evidence; No disconfirming evidence; Not patient oriented	X	4	-	20%	-
Straining during BM	Moderate	Limited evidence; No disconfirming evidence; may overlap with constipation	X	3	-	42%	[29-55%]
Problems with bowel emptying		Proposed concept	D	4		13%	[6-17%]
Bowel urgency	Moderate	One Tier 1 study disconfirming presence in early PD <3 YSD	X -	x	-	-	-
Bowel incontinence	Severe	Inconsistent and disconfirming evidence in all Tiers for early PD <3YSD	X -	3 -	-	5%	[1-7%]
Anal sphincter control	UA	Limited evidence; No disconfirming evidence; Not patient oriented	X	4	-	11%	-

DIGESTIVE DOMAIN (SYMPTOMS)

Diarrhea	-	Limited evidence; No disconfirming evidence	X	4	-	4%	-
General GI dysfuntion	Severe	Non-specific; Comprises many diverse symptom experiences	X	4	-	58%	[17-81%]

Notes. *PD= Parkinson's disease; UA=Unable to assess due to limited data; YSD=Years since diagnosis of Parkinson's disease;* ***Tier 1 Grade*** *A+=100%, A=75-99%, B=50-74%, C=25-49%, D=1-24%, X=No studies supporting presence in early PD;* ***Tier 2 & 3 Level*** *1=75-100%, 2=50-74%, 3=25-49%, 4=1-24%, x=No Tier 2 or 3 studies supporting presence in early PD. Minus sign "-" in Grade or Level indicates presence of disconfirming evidence.*

SOFT 8. Urinary Domain

Category/Concept	Coherence in Measurement & Classification		Adequacy of Data		Relevance of Concept		
	Concerns	Explanation	*Tier 1 Grade*	*Tier 2 & 3 Level*	*Bothersome mean %*	*Prevalence mean %*	*Prevalence [Range]*
URINARY DYSFUNCTION	Moderate	Composite concept may include multiple experiences	A+	3	5%	40%	[17-97%]
Urinary frequency	Moderate	Appears to be individually defined; Not clearly defined	D	4	13%	56%	[26-80%]
Urinary urgency	-	Limited evidence; No disconfirming evidence	D	4	2%	23%	[14-69%]
Nocturia	Moderate	One Tier 3 study disconfirming presence in early PD <3 YSD; Not clearly defined	C	3 -	14%	47%	[17-87%]
Incomplete voiding	UA	No evidence in early PD <3 YSD	X	x	-	32%	[17-40%]
Urinary incontinence	-	Limited evidence; No disconfirming evidence	C	4	3%	23%	[2-35%]
Urinary infections	UA	No evidence in early PD <3 YSD	X	x	-	-	-
Weak urine stream	UA	Limited evidence; No disconfirming evidence	X	4	-	40%	[39-41%]

Notes. *PD= Parkinson's disease; UA=Unable to assess due to limited data; YSD=Years since diagnosis of Parkinson's disease;* ***Tier 1 Grade*** *A+=100%, A=75-99%, B=50-74%, C=25-49%, D=1-24%, X=No studies supporting presence in early PD;* ***Tier 2 & 3 Level*** *1=75-100%, 2=50-74%, 3=25-49%, 4=1-24%, x=No Tier 2 or 3 studies supporting presence in early PD. Minus sign "-" in Grade or Level indicates presence of disconfirming evidence.*

SOFT 9 . Sexual Domain

Category/Concept	Coherence in Measurement & Classification		Adequacy of Data		Relevance of Concept		
	Concerns	Explanation	*Tier 1 Grade*	*Tier 2 & 3 Level*	*Bothersome mean %*	*Prevalence mean %*	*Prevalence [Range]*
SEXUAL DYSFUNCTION	Moderate	Concept category; comprises multiple concepts and experiences	A	2	2%	18%	[3-62%]
Anorgasmia	-	Limited evidence; No disconfirming evidence	X	4	-	35%	[6-62%]
Ejaculatory dysfunction	-	Limited evidence; No disconfirming evidence	X	4	-	32%	[25-42%]
Erectile dysfunction (Male)	-	Limited evidence; No disconfirming evidence	D	4	1%	43%	[36-52%]
Impaired libido	-	One Tier 2 study disconfirming presence in early PD <3 YSD	X	4 -	-	5%	[1-10%]
Vaginal dryness (Female)	-	Limited evidence; No disconfirming evidence	X	4	-	29%	[6-53%]

Notes. *PD= Parkinson's disease; UA=Unable to assess due to limited data; YSD=Years since diagnosis of Parkinson's disease;* ***Tier 1 Grade*** *A+=100%, A=75-99%, B=50-74%, C=25-49%, D=1-24%, X=No studies supporting presence in early PD;* ***Tier 2 & 3 Level*** *1=75-100%, 2=50-74%, 3=25-49%, 4=1-24%, x=No Tier 2 or 3 studies supporting presence in early PD. Minus sign "-" in Grade or Level indicates presence of disconfirming evidence.*

SOFT 10. Autonomic Domain

Category/Concept	Coherence in Measurement & Classification		Adequacy of Data		Relevance of Concept		
	Concerns	Explanation	*Tier 1 Grade*	*Tier 2 & 3 Level*	***Bothersome mean %***	***Prevalence mean %***	***Prevalence [Range]***
CARDIOVASCULAR SYMPTOMS		Proposed concept category	X	4	-	28%	-
Blood pressure regulation	UA	Limted evidence; no disconfirming evidence	D	x	-	5%	-
Hypotension	Moderate	Thresholds not provided in sources	D	4			
Orthostatic hypotension	Moderate	Contextual variation of hypotension; Not patient oriented term	D	4	-	-	-
Orthostatic symptoms	Moderate	Presumed symptoms; unclear defintion in sources; Not patient oriented term	X	4	-	18%	[16-19%
Hypertension	Moderate	Thresholds not provided in sources; no evidence in early PD <3YSD	X	x	-	-	-
Supine hypertension	UA	Contextual variation of hypertension; Not patient oriented term	X	x	-	-	-
Nocturnal hypertension	UA	Contextual variation of hypertension; Not patient oriented term	X	x	-	-	-
Change in nocturnal BP	UA	Contextual variation of hypertension; Not patient oriented term	X	x	-	-	-
Lower extremity swelling	Moderate	Unclear if correctly categorized; One Tier 1 study disconfirming in early PD <3YSD	D -	4	-	12%	[9-14%]
LIGHTHEADED, DIZZY, FAINTING		Proposed concept category					
Dizziness	Moderate	May overlap with lightheadedness from patient perspective	B	4	3%	16%	[13-23%]
Lightheadedness	Moderate	May overlap with dizziness from patient perspective	A+	3	3%	20%	[3-31%]
Lightheadedness with long standing	UA	Contextual variation of lightheadedness	X	4	-	14%	[12-15%]
Fainting/Syncope	UA	Limted evidence; no disconfirming evidence	D	4	-	2%	[1-3%]
SWEATING/HYPERHIDROSIS	Moderate	One Tier 1 study disconfirming presence in early PD <3 YSD	D -	3	1%	13%	[3-28%]
AUTONOMIC SYMPTOMS NOS	Severe	Comprises many diverse concepts; unclear what is being measured	X	4	-	71%	-

Notes. *PD= Parkinson's disease; UA=Unable to assess due to limited data; YSD=Years since diagnosis of Parkinson's disease;* ***Tier 1 Grade*** *A+=100%, A=75-99%, B=50-74%, C=25-49%, D=1-24%, X=No studies supporting presence in early PD;* ***Tier 2 & 3 Level*** *1=75-100%, 2=50-74%, 3=25-49%, 4=1-24%, x=No Tier 2 or 3 studies supporting presence in early PD. Minus sign "-" in Grade or Level indicates presence of disconfirming evidence.*

SOFT 11. Physical Functioning Domain (Impacts)

Category/Concept	Coherence in Measurement & Classification		Adequacy of Data		Relevance of Concept		
	Concerns	Explanation	*Tier 1 Grade*	*Tier 2 & 3 Level*	*Bothersome mean %*	*Prevalence mean %*	*Prevalence [Range]*
MOBILITY		Proposed concept category	A	4	31%	70%	[51-88%]
Getting out of bed/chair/car	-	No issues	A	4	3%	21%	[13-34%]
Turning in bed	Moderate	One Tier 1 study disconfirming presence in early PD <3YSD	C -	4	-	28%	[13-58%]
Standing	Moderate	Encompasses getting to standing position and maintaining standing	B	x	2%	21%	[16-26%]
Kneeling/bending	Moderate	Composite concept encompassing two activities	D	x	-	3%	-
Climbing stairs	-	No issues	B	x	1%	17%	[5-25%]
Lifting/holding/carrying	Moderate	Composite concept encompassing several activities	B	x	1%	23	[9-42%]
Gripping and opening	Moderate	Composite concept; One Tier 1 study disconfirming presence in early PD <3YSD	B -	x	-	25%	[8=40%]
Handwriting	-	No issues	A	4	5%	69%	[51-95%]
Using a computer	Moderate	Composite: Includes keyboard and mouse/trackpad use	B	x	3%	52%	[34-69%]
Using smartphone/tablet	-	No issues	B	x	1%	12%	[9-14%]
Exercise/sports	Minor	Includes range of activities	B	4	23%	61%	50-66%]
PHYSICAL COMFORT		Proposed concept category	C	x	13%	38	-
Feeling unwell	-	Limited evidence	D	x	2%	-	-
Difficulty relaxing	-	Limited evidence	D	x	2%	-	-
EFFORT OF LIVING		Patient panel proposed category to capture increased work of daily living	D	x	29%	-	-
Functional slowness	Minor	Variable terminology including "Longer to do things"	B	x	16%	28%	[5-51%]
Everything takes more effort	UA	Component of concept category effort of living; limited evidence	C	x	28%	41%	-
Having to plan around PD	UA	Limited evidence; One Tier 1 study disconfirming presence in early PD <3YSD	C -	x	-	15%	[11-19%]
SELF-CARE		Proposed concept category					
Dressing	Minor	Patient panel recommendation to identify specific aspects of dressing	B	4	2%	30%	[10-41%]
Personal hygiene/self-care	Minor	Encompasses range of specific experiences	B	4	3%	24%	[5-38%]
Eating tasks	Minor	Encompasses range of specific experiences	B	4	3%	48%	[28-71%]
SAFETY		Proposed concept category					
Accidental self-injury	UA	Limited evidence	C	x	5%	3%	-
Tripping & Falling	Moderate	Double barrelled; Two Tier 2 studies disconfirming presence in early PD <3YSD	A	4 -	5%	18%	[10-27%]
Weight change	Moderate	Unclear best categorical or domain fit for concept	C	4	-	8%	[4-15%]

Notes. *PD= Parkinson's disease; UA=Unable to assess due to limited data; YSD=Years since diagnosis of Parkinson's disease;* ***Tier 1 Grade*** *A+=100%, A=75-99%, B=50-74%, C=25-49%, D=1-24%, X=No studies supporting presence in early PD;* ***Tier 2 & 3 Level*** *1=75-100%, 2=50-74%, 3=25-49%, 4=1-24%, x=No Tier 2 or 3 studies supporting presence in early PD. Minus sign "-" in Grade or Level indicates presence of disconfirming evidence.*

SOFT 12. Psychosocial Functioning Domain (Impacts)

Category/Concept	Coherence in Measurement & Classification		Adequacy of Data		Relevance of Concept		
	Concerns	Explanation	*Tier 1 Grade*	*Tier 2 & 3 Level*	*Bothersome mean %*	*Prevalence mean %*	*Prevalence [Range]*
INDEPENDENCE	-	Patient panel proposed concept category	B	x	24%	13%	-
Cooking/meal preparation	-	Important aspect of indepence per patient panel	B	x	2%	29%	[13-28%]
Shopping	-	Important aspect of indepence per patient panel; Limited research	D	x	2%	-	-
Housework/home maintenance	-	Important aspect of indepence per patient panel; Includes gardening	B	x	2%	39%	[32-43%]
Travel/driving	-	Important aspect of indepence per patient panel	B	x	-	40%	[18-53%]
SELF-CONCEPT	Minor	Concept category; May comprise multiple aspects or specific experiences	B	x	35%	49%	[26-72%]
Embarassment/self-conscious	Minor	May have overlap with concept of stigma	B	x	11%	53%	[43-63%]
Feeling stigmatized	Minor	May have overlap with embarassment/self-conscious; Limited research	C	x	22%	44%	-
Self-efficacy		Proposed concept encompassing several aspects of perceived ability to manage	B	x	-	-	-
Self-confidence	UA	Limited research	C	x	8%	65%	-
Sense of helplessness	UA	Limited research	C	x	-	18%	[11-25%]
Sense PD limits what you can do	UA	Limited research	C	x	28%	91%	-
COPING	Minor	Concept category; May comprise multiple aspects or specific experiences	B	x	29%	18%	[11-25%]
Living with uncertainty	UA	Limited research	D	x	-	50%	-
Preoccupation with disease	Moderate	Limited research: Unclear what constitutes preoccupation; definitions needed	C	x	-	41%	[23-59%]
Fear	Minor	May encompass different specific experiences; definitions needed	A	x	9%	46%	[27-59%]
Fear of falling	Minor	May overlap with fear of future	D	x	7%	-	-
Fear of the future	Minor	May overlap with fear of falling	B	x	11%	46%	[27-59%]
Avoidance	Moderate	Unclear in reference to what; definitions needed	C	x	-	12%	[6-17%]
Denial	Minor	One Tier 1 study disconfirming presence in early PD <3YSD	D -	x	-	34%	-
Concealing diagnosis	UA	Limited research	D	x	-	19%	-
Annoyance/bothered	Moderate	May overlap with Frustration/anger; definitions needed	D	x	-	69%	-
Frustration/Anger	Moderate	May overlap with Annoyance/bothered; definitions needed	B	x	6%	24%	[20-27%]
Stress/distress	Moderate	May overlap with Annoyance/bothered; definitions needed	B	x	9%	27%	[14-44%]
Finding ways to compensate	UA	Limited research; Patient panel recommendation to include positive impacts	D	x	-	53%	-
Positive changes to take control	UA	Limited research; Patient panel recommendation to include positive impacts	D	x	-	47%	-
INTERPERSONAL INTERACTIONS	-	Patient panel proposed concept category	D	x	19%	-	-
Relationships with others	Minor	Variably includes family, friends, co-workers	B	x	9%	53%	[30-66%]
Others perceptions/reactions	Severe	Ambigous concept; Needs definition	D	x	-	11%	-
Communication	Moderate	May included written or spoken; Needs definition	A	x	9%	39%	[19-75%]
Loneliness/isolation	-	No concerns	A	x	1%	22%	[16-31%]

PSYCHOSOCIAL FUNCTIONING DOMAIN (IMPACTS)

ROLES & RESPONSIBILITIES		Patient panel proposed concept category					
Taking care of family	UA	Limited research; No disconfirming evidence	C	x	2%	3%	-
Taking care of pets	UA	Limited research; No disconfirming evidence	C	x	1%	3%	-
Job/profession	-	No disconfirming evidence	B	x	11%	54%	[40-72%]
Financial impact	Moderate	One Tier 1 study disconfiming presence in early PD	D -	x	-	3%	-
IMPORTANT ACTIVITIES		Patient panel proposed concept category					
Pleasurable activities	Moderate	Very limited research; may overlap with other concepts in category	D	x	19%	-	-
Loss of things you enjoy	Moderate	Very limited research; may overlap with other concepts in category	D	x	14%	-	-
Social life	UA	Very limited research	D	x	17%	-	-
Playing an instrument	UA	Limited research; may overlap with other concepts in category	C	x	2%	13%	-
Spiritual/Religious activities	UA	Very limited research	D	x	-	9%	-
Hobbies & Liesure	Moderate	May overlap with other concepts in category	A	4	2%	47%	[34-86%]

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Figures for Print

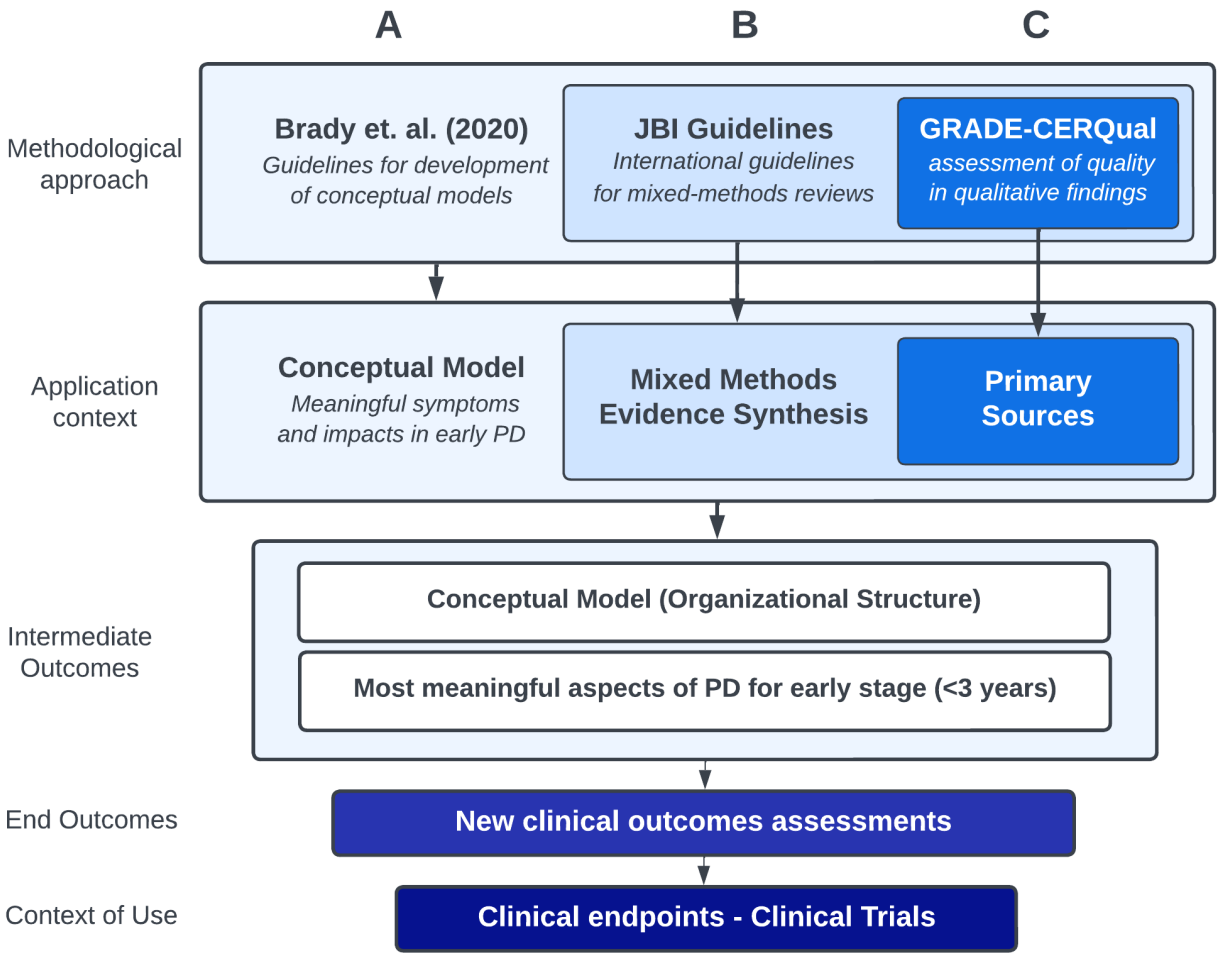


Figure 1. Inductive approach to a conceptual model of early Parkinson's that can support development of meaningful outcome measures for clinical trials

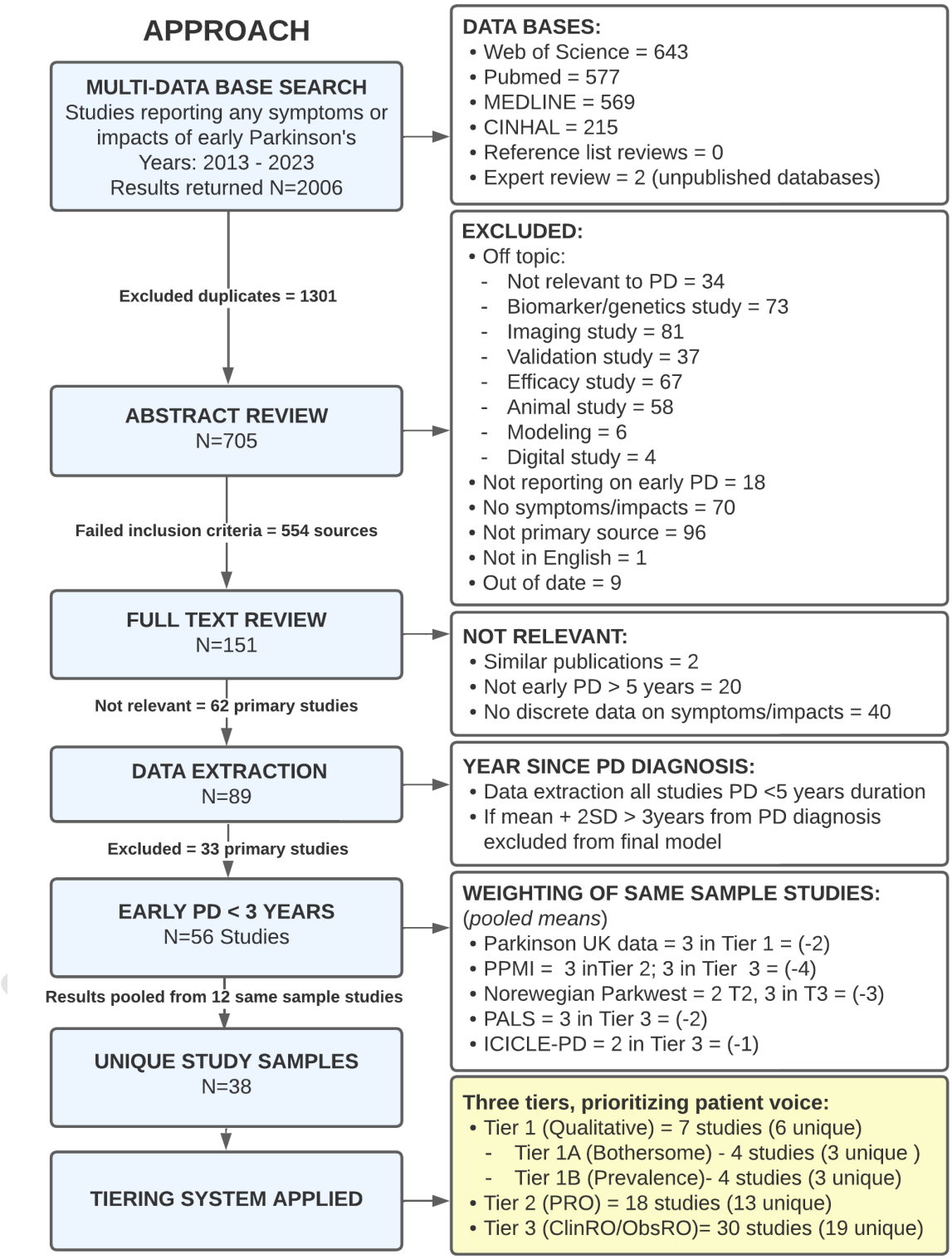


Figure 2. Flowchart for identification and screening of sources included in model

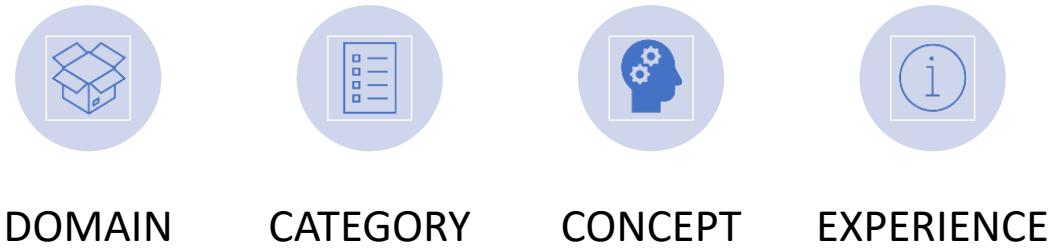


Figure 3. Conceptual model schema

Online Supplements

Supplement A. Multi-database search strategy

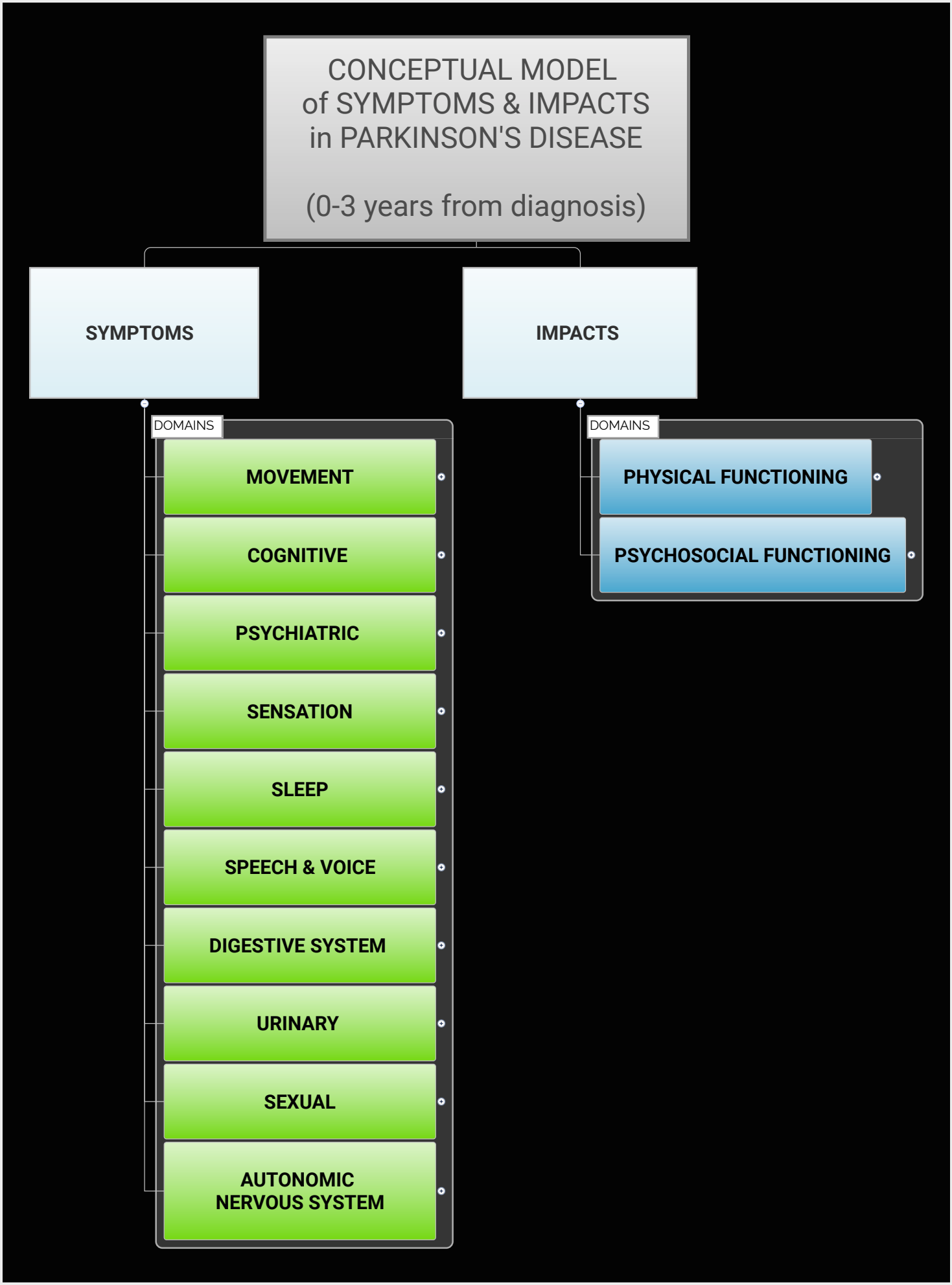
Database	Search terms	Date	Hits	Duplicates	Unique
	SEARCH STRATEGY 1: Symptoms & Impacts in early PD				
Web of Science	1. "early parkinson*" (Title) OR "early parkinson*" (Abstract) 2. "early PD*" (Title) OR "early PD*" (Abstract) 3. #2 OR #1 4. ((AB=(symptom*)) OR AB=(impact*)) AND #3 ***Filtered***: within 10 years (2013—2023)	4/4/2023	595	-	595
PubMed	(("early PD"[Title/Abstract]) OR ("early Parkinson*"[Title/Abstract])) AND ((symptom*[Title/Abstract]) OR (impact*[Title/Abstract])) ***Filtered***: within 10 years (2013—2023)	4/4/2023	551	497	54
MEDLINE/OVID	1. ("early parkinson*" or "early parkinson*").ab. 2. ("early PD" or "early PD").ab. 3. ("early parkinson*" or "early parkinson*").ti. 4. ("early PD" or "early PD").ti. 5. (symptom* or symptom*).ti. 6. (impact* or impact*).ti. 7. (symptom* or symptom*).ab. 8. (impact* or impact*).ab. 9. 7 or 8 10. 5 or 6 11. 3 or 4 12. 1 or 2 13. 11 or 12 14. 9 or 10 15. 13 and 14 ***Filtered***: within 10 years (2013—2023)	4/4/2023	546	540	6
EBSCO/CINHAL	1. TI "early parkinson*" OR AB "early parkinson*" 2. TI "early PD" OR AB "early PD" 3. 1 OR 2 4. TI impact* OR AB impact* 5. TI symptom* OR AB symptom* 6. 4 OR 5 7. 3 AND 6 8. (PY>2012) AND 7	4/4/2023	209	209	0
	SEARCH STRATEGY 2 – Qualitative in early PD				
Web of Science	(((((((AB=(qualitative)) OR AB=(conceptual model)) OR AB=(conceptual framework)) OR AB=(lived experience)) OR AB=(illness experience)) OR AB=(phenomena)) OR AB=(phenomenon)) AND **((AB=("early PD")) OR AB=("early Parkinson*"))**	5/4/2023	48	10	38 (*4 relevant*)
PubMed	(((((((("conceptual model"[Title/Abstract]) OR ("conceptual framework"[Title/Abstract])) OR (phenomena[Title/Abstract])) OR ("lived-experience"[Title/Abstract])) OR ("lived experience"[Title/Abstract])) OR ("illness experience"[Title/Abstract])) OR ("illness-experience"[Title/Abstract])) OR (qualitative[Title/Abstract])) AND (("early PD"[Title/Abstract]) OR ("early Parkinson*"[Title/Abstract]))	5/4/2023	26	16	10 (*2 relevant*)
MEDLINE/OVID	((ab: early w PD) or (ab: early w Parkinson*)) and (ab: qualitative or ab: phenomena) or ((ab: conceptual and ab: model)) or (((ab: lived and ab: experience)) or ((ab: illness and ab: experience)) or ((ab: conceptual and ab: framework)))	5/4/2023	23	23	0
EBSCO/CINHAL	(AB "early PD" OR AB "early Parkinson") AND (AB qualitative OR AB "conceptual model" OR AB "conceptual framework" OR AB phenomena OR AB "lived experience" OR AB "illness experience")	5/4/2023	6	6	0
	SEARCH STRATEGY 3				
Reference lists	Sources identified from reference lists in systematic and scoping reviews on symptoms or impacts of early PD.				
	SEARCH STRATEGY 4				
Expert review	Ahead of press and prepublication. Seminal works older than 10 years.				2
	TOTALS				
					705

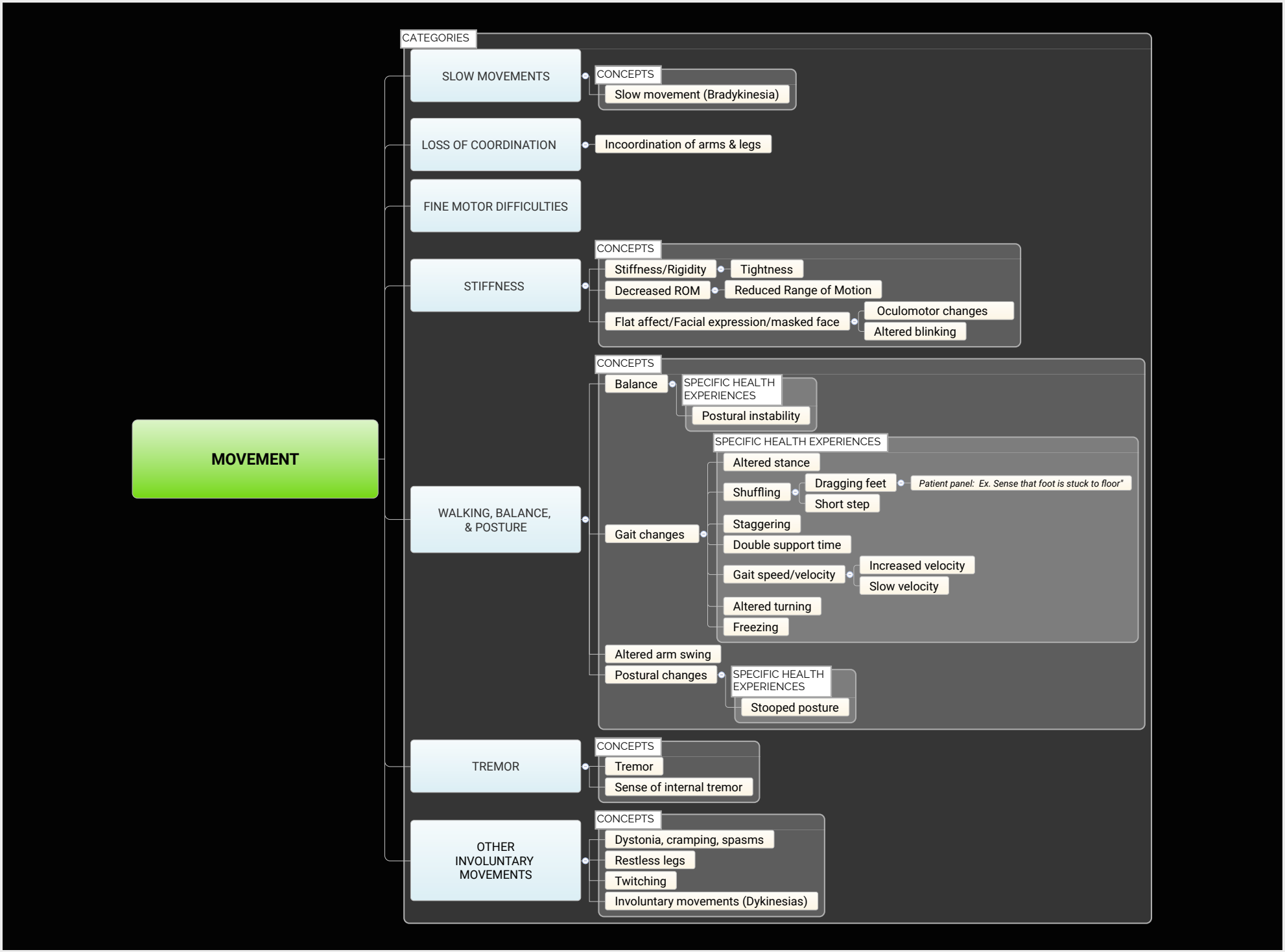
Supplement B. Supporting data files

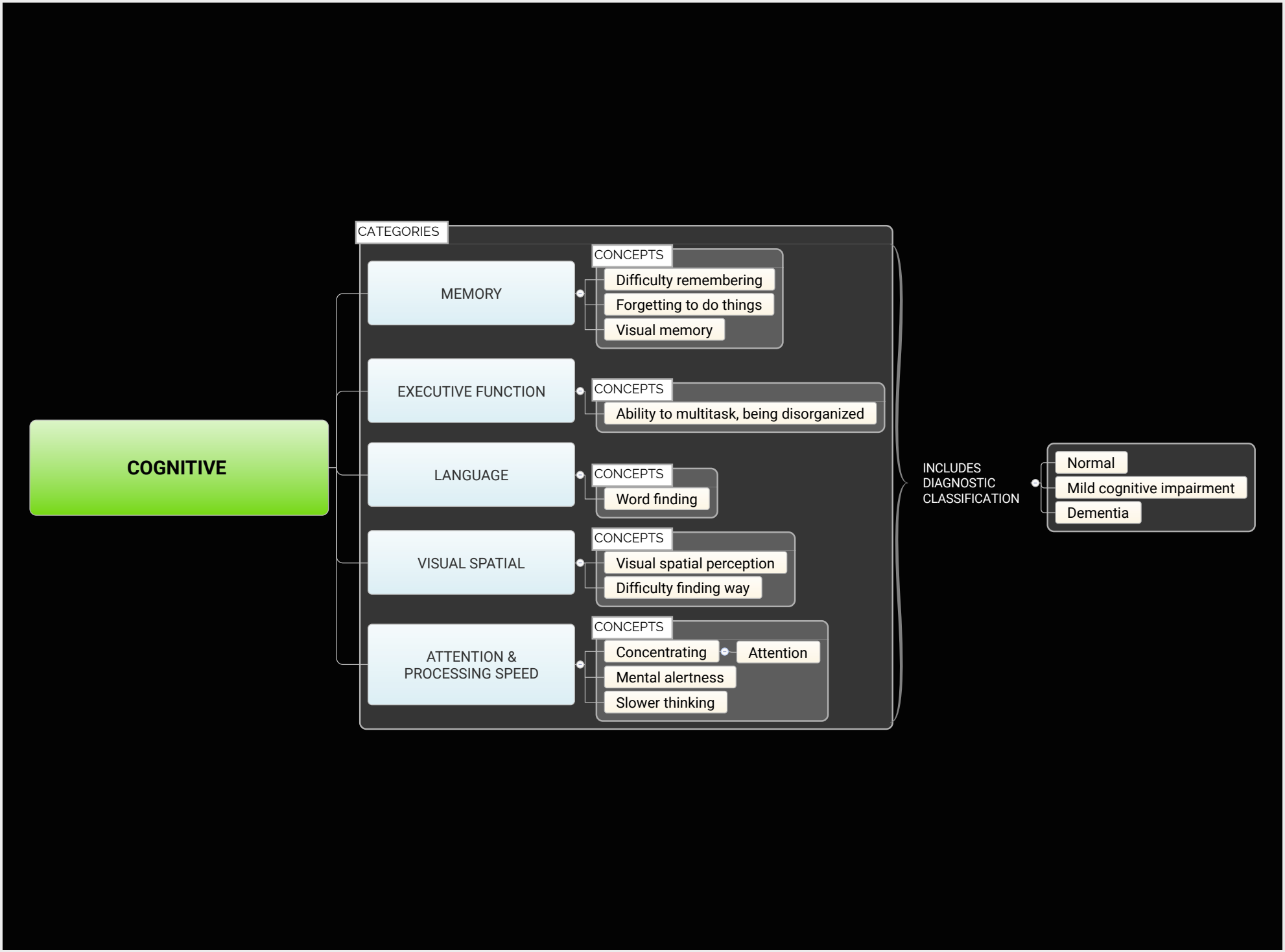
See attached XL file with data for all sources by Tier and supporting metrics.

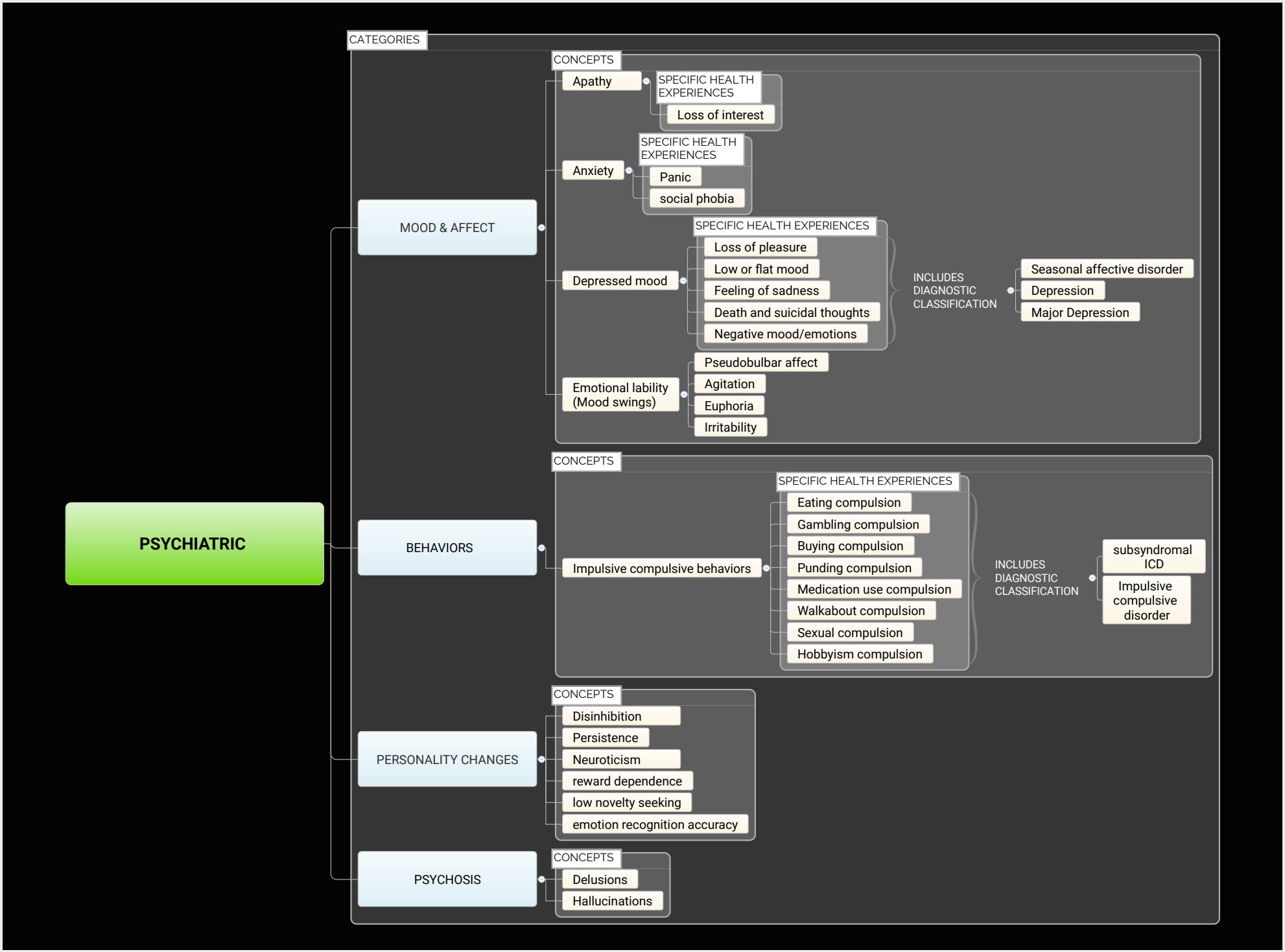
Supplement C. Domain maps for conceptual model

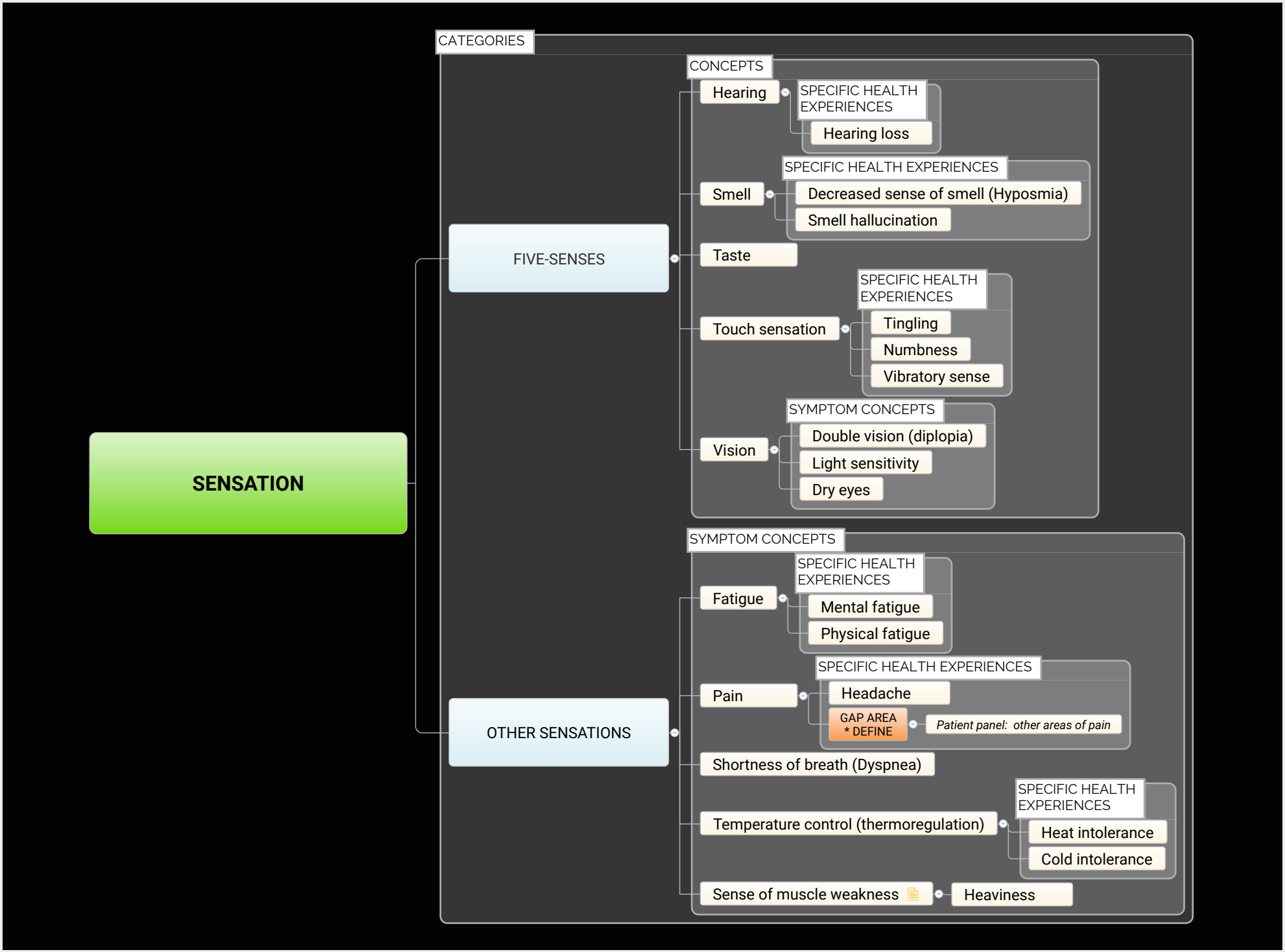
See attached PDF files with Xmind Maps for each domain section.

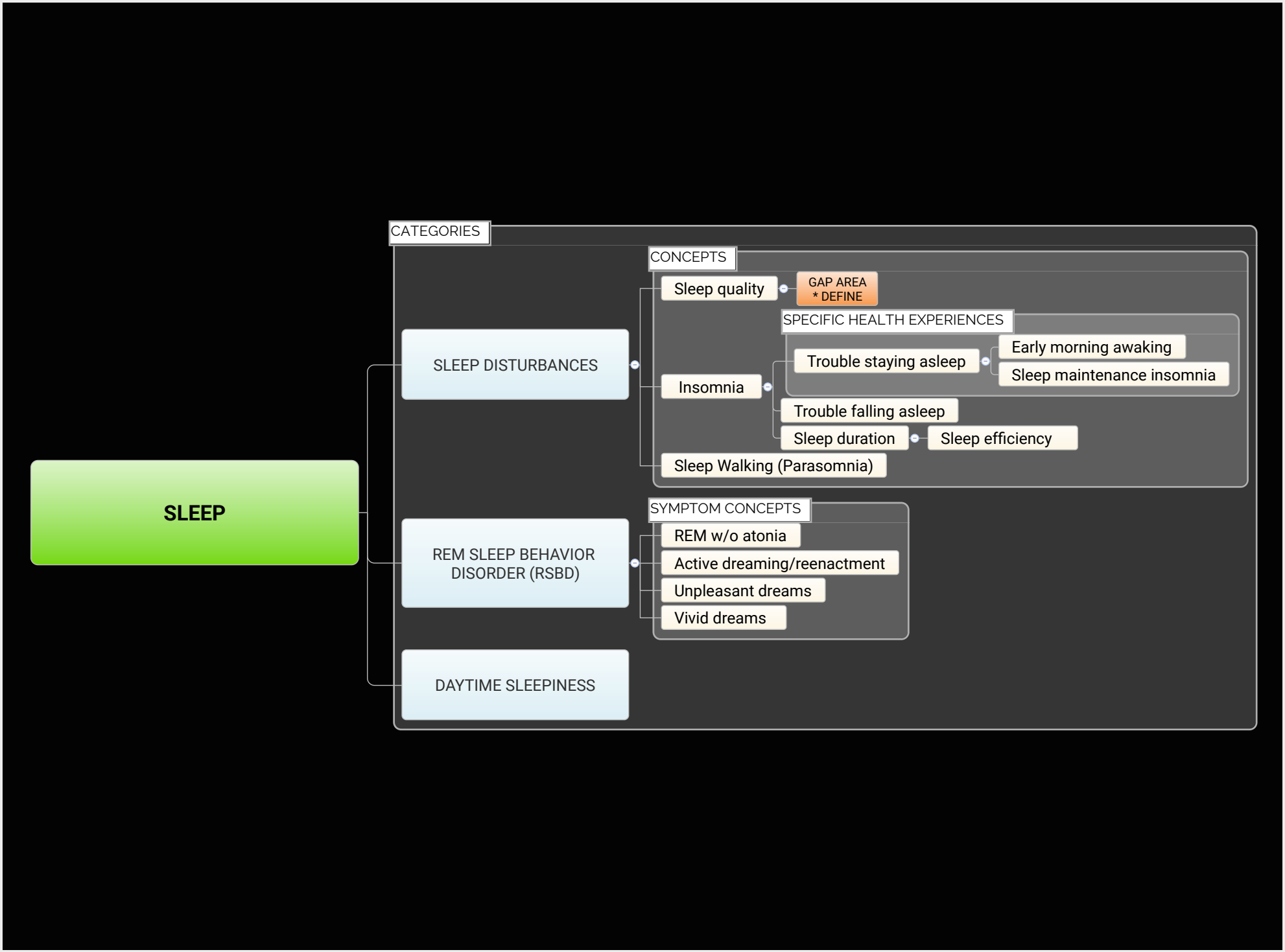

CONCEPTUAL MODEL
of SYMPTOMS & IMPACTS
in PARKINSON'S DISEASE
(0-3 years from diagnosis)
SYMPTOMS
IMPACTS
DOMAINS
MOVEMENT
COGNITIVE
PSYCHIATRIC
SENSATION
SLEEP
SPEECH & VOICE
DIGESTIVE SYSTEM
URINARY
SEXUAL
AUTONOMIC
NERVOUS SYSTEM
DOMAINS
PHYSICAL FUNCTIONING
PSYCHOSOCIAL FUNCTIONING

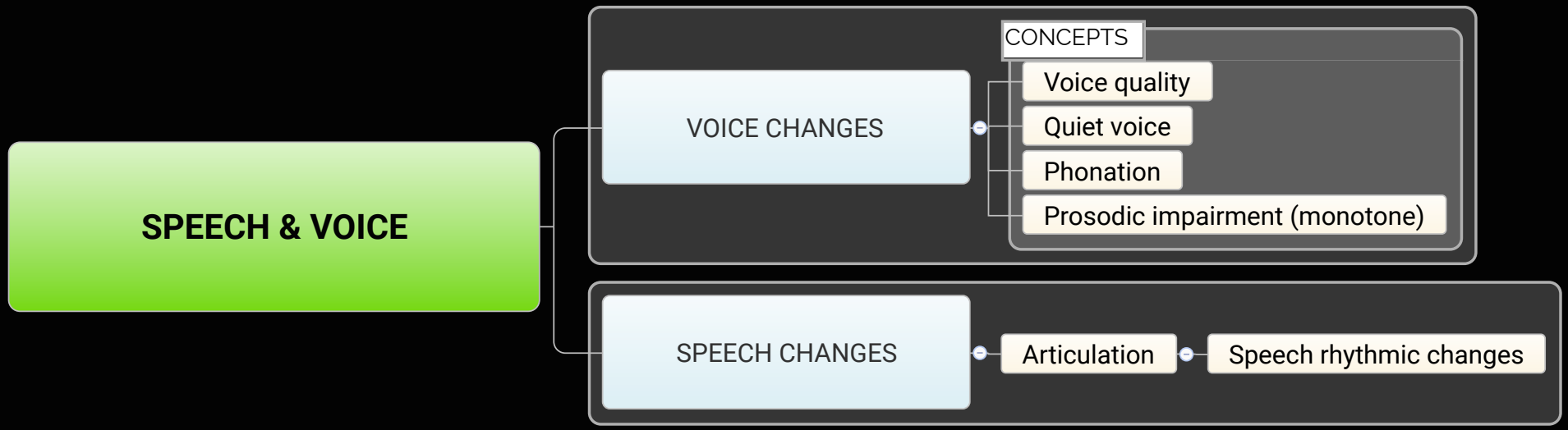

MOVEMENT
CATEGORIES
SLOW MOVEMENTS
CONCEPTS
Slow movement (Bradykinesia)
LOSS OF COORDINATION
Incoordination of arms & legs
FINE MOTOR DIFFICULTIES
STIFFNESS
CONCEPTS
Stiffness/Rigidity
Tightness
Decreased ROM
Reduced Range of Motion
Flat affect/Facial expression/masked face
Oculomotor changes
Altered blinking
WALKING, BALANCE, & POSTURE
CONCEPTS
Balance
SPECIFIC HEALTH EXPERIENCES
Postural instability
Gait changes
SPECIFIC HEALTH EXPERIENCES
Altered stance
Shuffling
Dragging feet
Patient panel: Ex. Sense that foot is stuck to floor"
Short step
Staggering
Double support time
Gait speed/velocity
Increased velocity
Slow velocity
Altered turning
Freezing
Altered arm swing
Postural changes
SPECIFIC HEALTH EXPERIENCES
Stooped posture
TREMOR
CONCEPTS
Tremor
Sense of internal tremor
OTHER INVOLUNTARY MOVEMENTS
CONCEPTS
Dystonia, cramping, spasms
Restless legs
Twitching
Involuntary movements (Dykinesias)

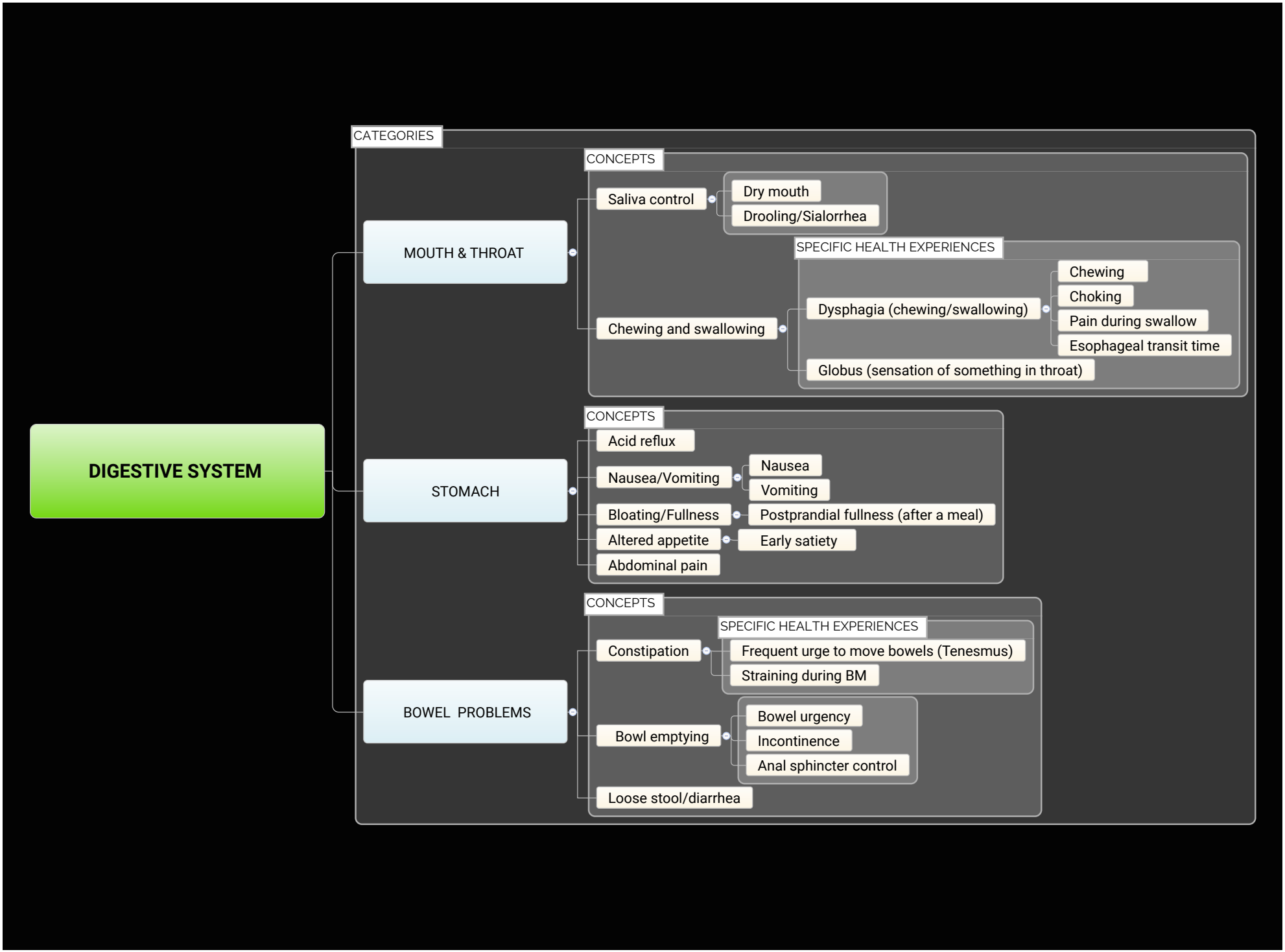

COGNITIVE
CATEGORIES
MEMORY
CONCEPTS
Difficulty remembering
Forgetting to do things
Visual memory
EXECUTIVE FUNCTION
CONCEPTS
Ability to multitask, being disorganized
LANGUAGE
CONCEPTS
Word finding
VISUAL SPATIAL
CONCEPTS
Visual spatial perception
Difficulty finding way
ATTENTION & PROCESSING SPEED
CONCEPTS
Concentrating
Attention
Mental alertness
Slower thinking
INCLUDES DIAGNOSTIC CLASSIFICATION
Normal
Mild cognitive impairment
Dementia

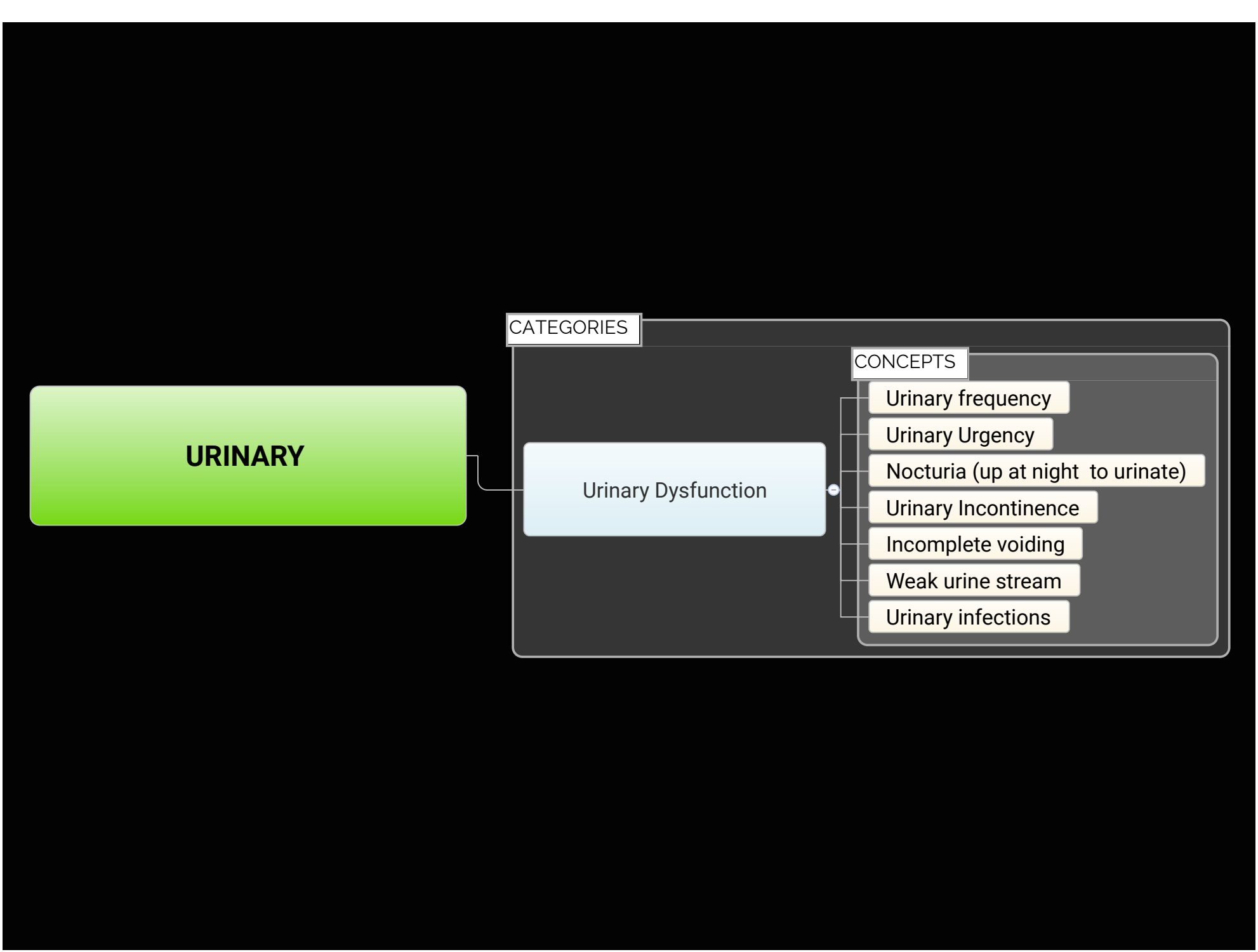

PSYCHIATRIC
CATEGORIES
MOOD & AFFECT
CONCEPTS
Apathy
SPECIFIC HEALTH EXPERIENCES
Loss of interest
Anxiety
SPECIFIC HEALTH EXPERIENCES
Panic
social phobia
Depressed mood
SPECIFIC HEALTH EXPERIENCES
Loss of pleasure
Low or flat mood
Feeling of sadness
Death and suicidal thoughts
Negative mood/emotions
INCLUDES DIAGNOSTIC CLASSIFICATION
Seasonal affective disorder
Depression
Major Depression
Emotional lability (Mood swings)
Pseudobulbar affect
Agitation
Euphoria
Irritability
BEHAVIORS
CONCEPTS
Impulsive compulsive behaviors
SPECIFIC HEALTH EXPERIENCES
Eating compulsion
Gambling compulsion
Buying compulsion
Punding compulsion
Medication use compulsion
Walkabout compulsion
Sexual compulsion
Hobbyism compulsion
INCLUDES DIAGNOSTIC CLASSIFICATION
subsyndromal ICD
Impulsive compulsive disorder
PERSONALITY CHANGES
CONCEPTS
Disinhibition
Persistence
Neuroticism
reward dependence
low novelty seeking
emotion recognition accuracy
PSYCHOSIS
CONCEPTS
Delusions
Hallucinations


SENSATION
CATEGORIES
FIVE-SENSES
CONCEPTS
Hearing
SPECIFIC HEALTH EXPERIENCES
Hearing loss
Smell
SPECIFIC HEALTH EXPERIENCES
Decreased sense of smell (Hyposmia)
Smell hallucination
Taste
Touch sensation
SPECIFIC HEALTH EXPERIENCES
Tingling
Numbness
Vibratory sense
Vision
SYMPTOM CONCEPTS
Double vision (diplopia)
Light sensitivity
Dry eyes
OTHER SENSATIONS
SYMPTOM CONCEPTS
Fatigue
SPECIFIC HEALTH EXPERIENCES
Mental fatigue
Physical fatigue
Pain
SPECIFIC HEALTH EXPERIENCES
Headache
GAP AREA * DEFINE
Patient panel: other areas of pain
Shortness of breath (Dyspnea)
Temperature control (thermoregulation)
SPECIFIC HEALTH EXPERIENCES
Heat intolerance
Cold intolerance
Sense of muscle weakness
Heaviness

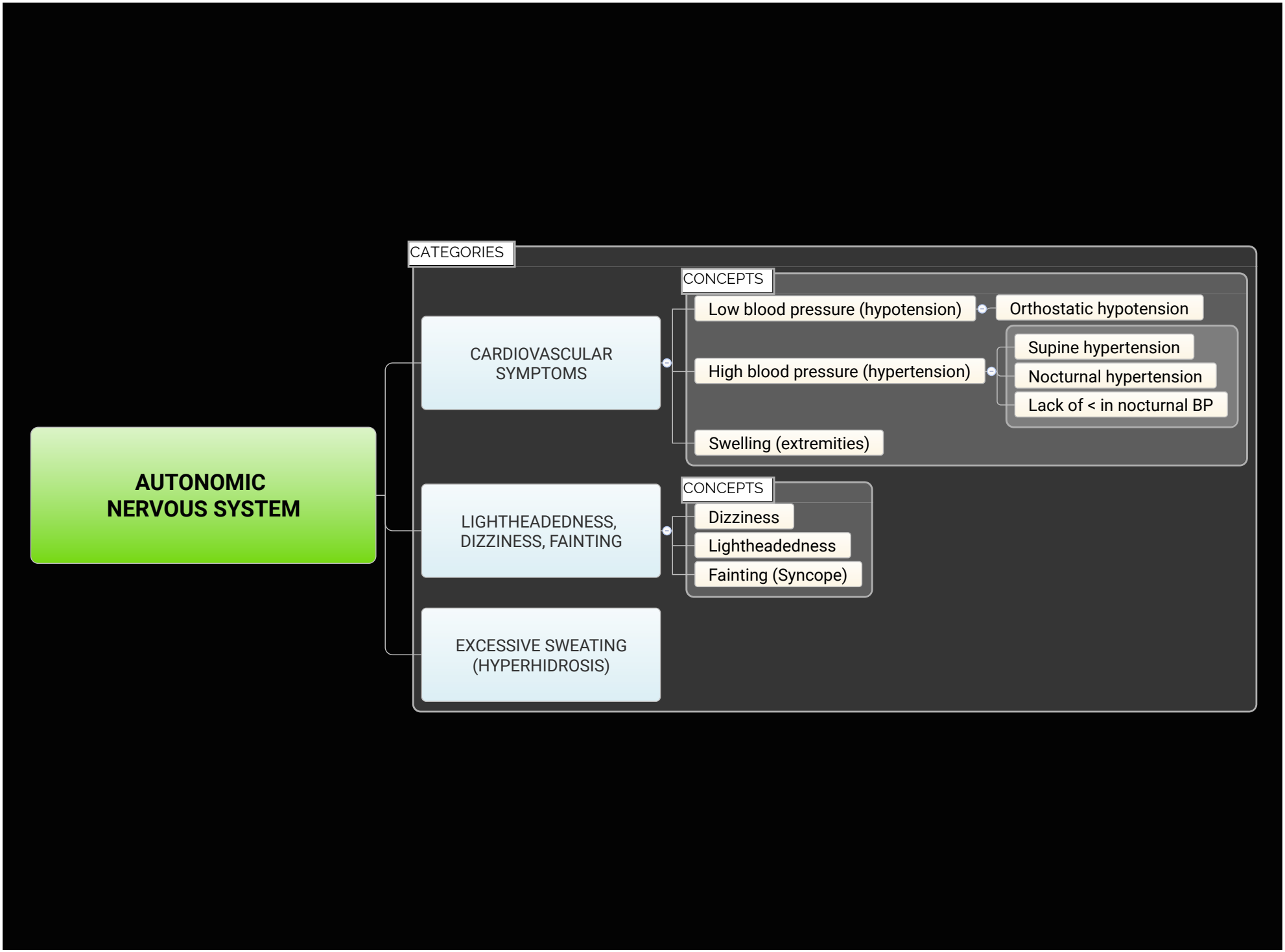

SLEEP
CATEGORIES
SLEEP DISTURBANCES
CONCEPTS
Sleep quality
GAP AREA
* DEFINE
SPECIFIC HEALTH EXPERIENCES
Trouble staying asleep
Early morning awaking
Sleep maintenance insomnia
Insomnia
Trouble falling asleep
Sleep duration
Sleep efficiency
Sleep Walking (Parasomnia)
REM SLEEP BEHAVIOR DISORDER (RSBD)
SYMPTOM CONCEPTS
REM w/o atonia
Active dreaming/reenactment
Unpleasant dreams
Vivid dreams
DAYTIME SLEEPINESS

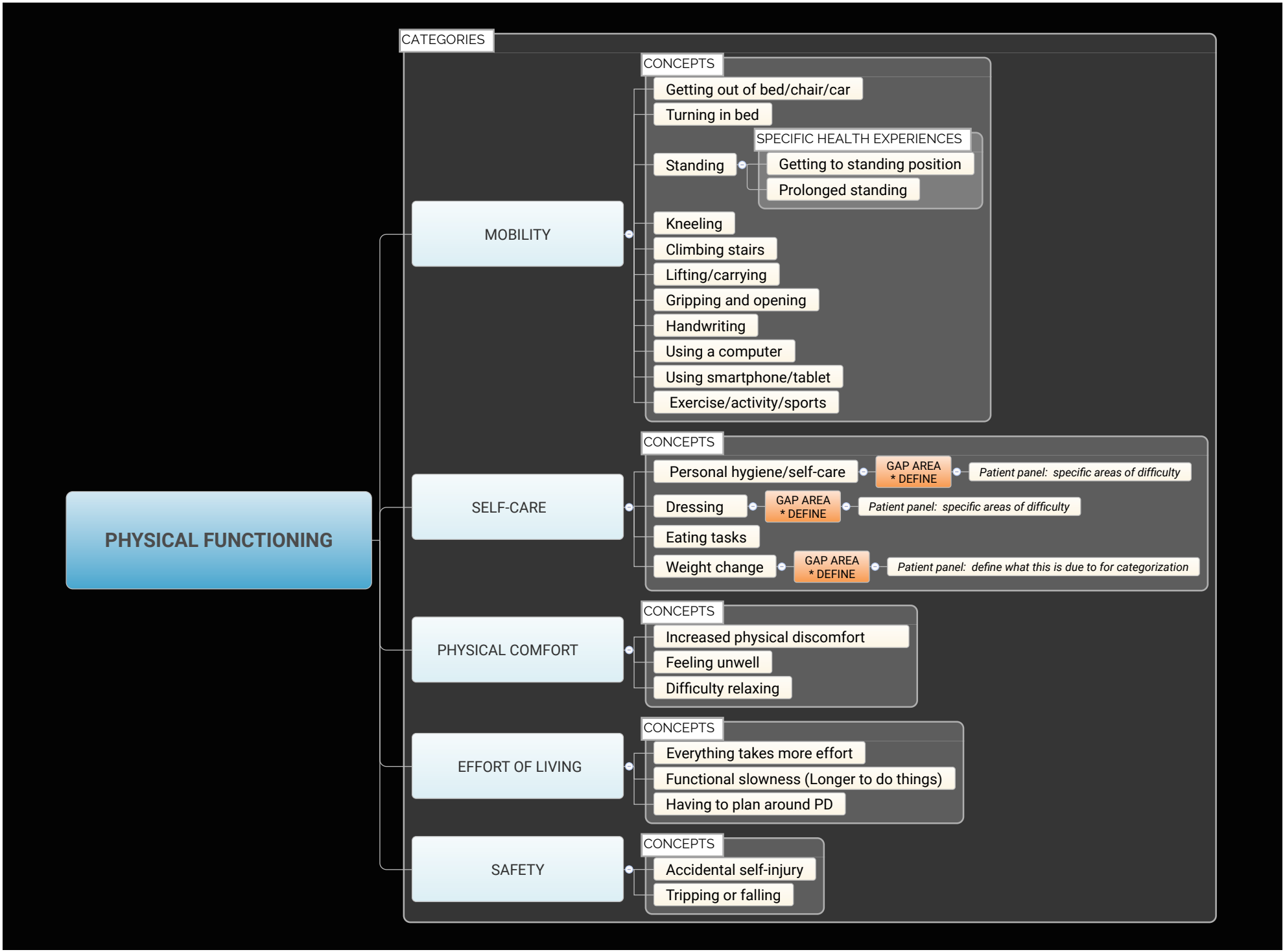

SPEECH & VOICE
VOICE CHANGES
CONCEPTS
Voice quality
Quiet voice
Phonation
Prosodic impairment (monotone)
SPEECH CHANGES
Articulation
Speech rhythmic changes

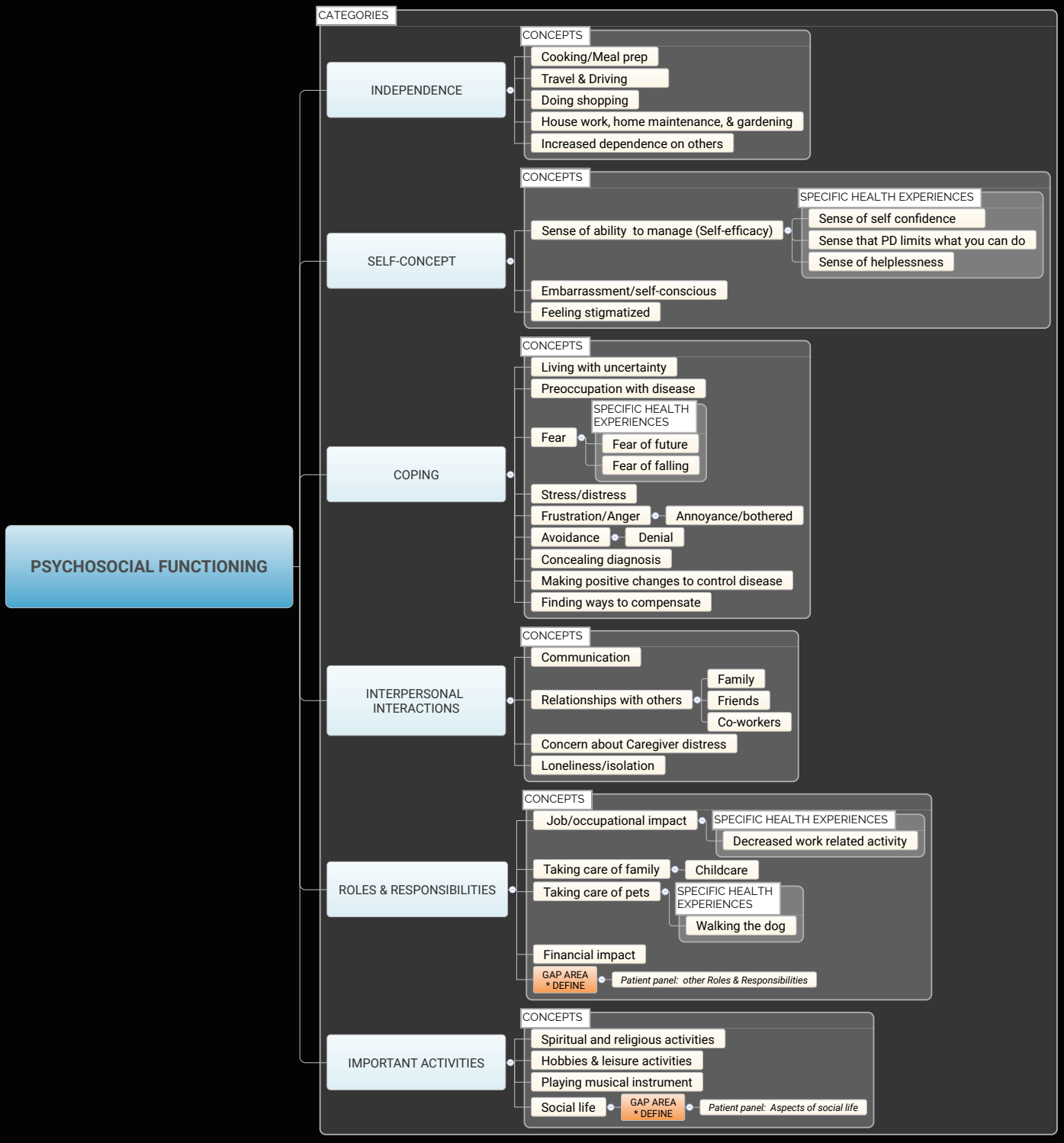

DIGESTIVE SYSTEM
CATEGORIES
MOUTH & THROAT
CONCEPTS
Saliva control
Dry mouth
Drooling/Sialorrhea
Chewing and swallowing
SPECIFIC HEALTH EXPERIENCES
Dysphagia (chewing/swallowing)
Chewing
Choking
Pain during swallow
Esophageal transit time
Globus (sensation of something in throat)
STOMACH
CONCEPTS
Acid reflux
Nausea/Vomiting
Nausea
Vomiting
Bloating/Fullness
Postprandial fullness (after a meal)
Altered appetite
Early satiety
Abdominal pain
BOWEL PROBLEMS
CONCEPTS
SPECIFIC HEALTH EXPERIENCES
Constipation
Frequent urge to move bowels (Tenesmus)
Straining during BM
Bowl emptying
Bowel urgency
Incontinence
Anal sphincter control
Loose stool/diarrhea


URINARY
CATEGORIES
Urinary Dysfunction
CONCEPTS
Urinary frequency
Urinary Urgency
Nocturia (up at night to urinate)
Urinary Incontinence
Incomplete voiding
Weak urine stream
Urinary infections


SEXUAL
CATEGORIES
Sexual dysfunction
CONCEPTS
Libido changes (sex drive)
Vaginal dryness (F)
Erectile dysfunction
Ejaculatory dysfunction (M)
Inability to have an orgasm (Anorgasmia)


AUTONOMIC NERVOUS SYSTEM
CATEGORIES
CARDIOVASCULAR SYMPTOMS
CONCEPTS
Low blood pressure (hypotension)
Orthostatic hypotension
High blood pressure (hypertension)
Supine hypertension
Nocturnal hypertension
Lack of < in nocturnal BP
Swelling (extremities)
LIGHTHEADEDNESS, DIZZINESS, FAINTING
CONCEPTS
Dizziness
Lightheadedness
Fainting (Syncope)
EXCESSIVE SWEATING (HYPERHIDROSIS)


PHYSICAL FUNCTIONING
CATEGORIES
MOBILITY
CONCEPTS
Getting out of bed/chair/car
Turning in bed
SPECIFIC HEALTH EXPERIENCES
Standing
Getting to standing position
Prolonged standing
Kneeling
Climbing stairs
Lifting/carrying
Gripping and opening
Handwriting
Using a computer
Using smartphone/tablet
Exercise/activity/sports
SELF-CARE
CONCEPTS
Personal hygiene/self-care
GAP AREA * DEFINE
Patient panel: specific areas of difficulty
Dressing
GAP AREA * DEFINE
Patient panel: specific areas of difficulty
Eating tasks
Weight change
GAP AREA * DEFINE
Patient panel: define what this is due to for categorization
PHYSICAL COMFORT
CONCEPTS
Increased physical discomfort
Feeling unwell
Difficulty relaxing
EFFORT OF LIVING
CONCEPTS
Everything takes more effort
Functional slowness (Longer to do things)
Having to plan around PD
SAFETY
CONCEPTS
Accidental self-injury
Tripping or falling


PSYCHOSOCIAL FUNCTIONING
CATEGORIES
INDEPENDENCE
CONCEPTS
Cooking/Meal prep
Travel & Driving
Doing shopping
House work, home maintenance, & gardening
Increased dependence on others
SELF-CONCEPT
CONCEPTS
Sense of ability to manage (Self-efficacy)
SPECIFIC HEALTH EXPERIENCES
Sense of self confidence
Sense that PD limits what you can do
Sense of helplessness
Embarrassment/self-conscious
Feeling stigmatized
COPING
CONCEPTS
Living with uncertainty
Preoccupation with disease
Fear
SPECIFIC HEALTH EXPERIENCES
Fear of future
Fear of falling
Stress/distress
Frustration/Anger
Annoyance/bothered
Avoidance
Denial
Concealing diagnosis
Making positive changes to control disease
Finding ways to compensate
INTERPERSONAL INTERACTIONS
CONCEPTS
Communication
Relationships with others
Family
Friends
Co-workers
Concern about Caregiver distress
Loneliness/isolation
ROLES & RESPONSIBILITIES
CONCEPTS
Job/occupational impact
SPECIFIC HEALTH EXPERIENCES
Decreased work related activity
Taking care of family
Childcare
Taking care of pets
SPECIFIC HEALTH EXPERIENCES
Walking the dog
Financial impact
GAP AREA * DEFINE
Patient panel: other Roles & Responsibilities
IMPORTANT ACTIVITIES
CONCEPTS
Spiritual and religious activities
Hobbies & leisure activities
Playing musical instrument
Social life
GAP AREA * DEFINE
Patient panel: Aspects of social life

Supplement D. Concept dictionary

See attached file with definitions for concepts in Conceptual model.

Term derived from literature review	Proposed Ammendment to Concept	Proposed Definition	Definition Source	Excludes	Relevant Clinical Terminology	Patient Friendly Definition	Comments
MOVEMENT DOMAIN							
Slowed movements		Slowness of the limbs or generalized whole body movements including slowness performing activities	Common language and expert review	cognitive slowing	Hypokinesia, akinesia, bradykinesia	Slow Movements	
Fine motor dexterity		Impaired ability to do tasks requiring fine movement of the hand such as dressing, eating, writing, typing, etc.	Common language and expert review		Micrographia	Fine Motor Control; Hand dexterity	
Loss of coordination	Coordination	Impaired coordination of extremities or trunk, may including missing target when attempting to reach for objects, bumping into things	Common language and expert review	fine motor; hand dexterity		Generalized clumsiness	
Stiffness		Increased resistance with motion, may also be reported as stiffness or tightness	Common language and expert review	spasms, cramping, bending, twisting, dystonia	Rigidity, May included cogwheeling	Stiffness	
Decreased range of motion (ROM)	Range of Motion	Reduced ability to fully extend or flex body/extremities	Common language and expert review	stiffness, rigidity		Inability to fully extend or flex body parts	
Altered facial expression	Facial expression	Flat affect, expressionless facial movements	Common language and expert review		Masked facies, Hypomimia	Reduced facial expression	
Altered eyemovements	Eye movements	Altered eye muscle movements that include decreased blink rate or restriction of oœular movements	Common language and expert review		Oculomotor dysfunction	Changes in movement of eyes and eyelids, NOT including double vision	
Altered balance	Balance	Difficulty maintaining balance while not being supported, which may or may not include requiring support to maintain balance, and may include a tendency to trip or fall	Common language and expert review		Retropulsion, Postural Instability	Impaired balance, trouble balancing	
Gait changes	Gait	Changes in quality of walking not otherwise specified	Common language and expert review			Other changes in walking	
Shuffling		Diminished foot clearance when walking resulting in dragging of the feet	Common language and expert review			Dragging feet when walking	
Altered stride Length	Stride length	abnormal shortened distance between steps	Common language and expert review		Festination	Shortened length of steps	
Altered stance	Stance	Abnormal ability to stand independently upright on two feet which may result in compensatory foot placement	Common language and expert review				
Altered turning	Turning	Interrupted or segmented turning, non-fluid changes in direction	Common language and expert review		En bloc turning	Non-fluid turns	
Double support time		Amount of time spent while walking with two feet stabilized on the ground	Common language and expert review			Time spent with both feet on ground	
Staggering		Unsteady gait with redirection to maintain balance resulting in deviation from walking in a straight line	Common language and expert review			Wavering, staggering	
Freezing		Failure to initiate or delay of initiation of movement, may also be the temporary arrest of ongoing movement	Common language and expert review	the 'fear of' freezing		Stuck when walking	
Gait velocity		Slowed gait with increase transit time or faster gait with decreased transit time	Common language and expert review		Festination	Change in walking speed	
Altered arm swing	Arm swing	Irregular or reduced arm swing during walking	Common language and expert review				
Postural changes	Posture	Deviation of trunk; any change in posture resulting in person being not fully upright	Common language and expert review		Camptocormia, Pisa Syndrome	Stooped Posture, leaning	
Tremor		Oscillating, rhythmic involuntary movement of any body part	Common language and expert review	involuntary movements not specified as tremor or shaking, 'shakiness' related to an anxiety-related condition or internal sensation	Rest tremor, postural tremor, action tremor	Tremor	
Internal tremor		Invisible rhythmic sensation, may be of any body part, not visually observable, but felt	Common language and expert review	shakiness or jitteriness reported to be due to anxiety, restlessness		Inner sense of tremor	
Twitching		Brief, sudden, involuntary contraction of a group of muscle fibers	Common language and expert review		Myoclonus, fasiculations		
Dystonia, Cramping & Spasms	1. Dystonia 2. Cramping & Spasm	1. Abnormal posture of a body part due to involuntary sustained muscle contraction, includes leaning 2. Painful contractions of muscle(s)	Common language and expert review	Cramping in the context of abdominal pain or gastrointestinal discomfort	Dystonia	Cramping, spasms, or sustained involuntary muscle contraction resulting in abnormal posture of a body part	
Dyskinesia		Involuntary writhing/dancing/swaying movement of the face, arms, legs or trunk; can be secondary to medication wearing off or peak dose effect	Common language and expert review	inner restlessness/akasthisia	Motor fluctuation, chorea, athetosis, Dyskinesia	Involuntary swaying movements	
Restless leg		Urge to move legs that is only temporarily relieved with movement, often more severe at night but may be present during the day	Common language and expert review	dyskinesias involving the legs		leg discomfort with urge to move	
COGNITIVE DOMAIN							
Cognitive changes		Improvement or decline in cognitive abilities	Common language and expert review		Mild cognitive impairment	Thinking changes	
Dementia		Impairment of cognitive function leading to significant limitation in domains of living	Common language and expert review		Severe cognitive impairment	Thinking changes leading to difficulty doing tasks of daily life	
Memory		Memory function, including ability/difficulty remembering information, orientation to time/date, and short and long term recall	Common language and expert review			Difficulty remembering information	
Forgetting to do things	Forgetfulness	Forgetting to follow up and complete desired tasks	Common language and expert review			Forgeting to do things; forgetfulness	
Visual memory		Difficulties with visual recall may result in challenges navigating spaces that were once familiar	Common language and expert review			Difficulty remembering what things look like; difficulty visually recalling how to get places	
Executive function		Ability to engage in multi-level planning and decision-making to allow for successful completion of tasks	Common language and expert review		Frontal lobe function	Difficulty planning and making decisions	
Ability to multitask	Multitasking	Ability to adapt and switch from one cognitive task to another	Common language and expert review				
Word finding		Abilities for expressing oneself verbally or recalling intended words for conversation	Common language and expert review	difficulties understanding due to hearing impairment, dysarthria	Aphasia		
Depth perception		Ability to judge distances or depth includes orienting onself in space and identifying spatial relationships amoung objects	Common language and expert review	freezing in doorways or thresholds	Visual spatial	Depth perception	
Difficulty finding way	Ability to find one's way	Becoming lost or disoriented with navigation	Common language and expert review				
Attention		Ability to maintain focus on stimuli, tasks or conversation	Common language and expert review			Attenion or trouble staying focused	
Concentration		Ability to maintain focus during task completion or questioning	Common language and expert review			Focus	
Cognitive slowing		Slowing of mental processing. Includes difficulty keeping up with conversations or slowness to respond	Common language and expert review			Slower thinking	

Mental alertness		Feeling mentally sharp and alert, or difficulty with cognitive processing that may include confused, muddled, or mixed up	Common language and expert review	Daytime sleepiness		Brain fog	
PSYCHIATRIC DOMAIN							
Apathy		Lack of desire, motivation, or interest to participate in hobbies, socialization, or activities of daily living	Common language and expert review			Loss of interest/motivation	
Anxious mood		Excessive worry or fear that persists often resulting in unease or avoidance behavior	Common language and expert review		Anxiety	Nervousness, feeling anxious, anxiety	
Social phobia		Excessive and irrational fear/anxiety when faced with social interaction	Common language and expert review		Specific phobia	Fear of social interaction	
Panic		Sudden uncontrollable and often irrational fear, intense worry that is often debilitating	Common language and expert review				
Depressed mood		Persistent saddness, helplessness, worthlessness, or empty mood	Common language and expert review		Depression	Feeling down or depressed	
Low or flat mood		Lessened reactivity to emotion, limited emotional expression	Common language and expert review	Excludes feeling depressed	Blunted affect	Flat mood with little variation	
Feeling of sadness		Feelings of sadness or hopelessness, may be associated with increased tearfulness	Common language and expert review	suicidal ideation	Depression	Feelings of being sad	
Loss of pleasure		Inability or diminished ability to feel pleasure or find enjoyment	Common language and expert review		Anhedonia	Lack of joy and pleasure	
Negative feelings & emotions		Persisent negative thoughts or feelings	Common language and expert review	exludes feeling depressed or sad or suicidal ideation	Pessimism	Negative thoughts, feeling more negative	
Suicidal ideation or thoughts of death		Thoughts of personal death either passively or with intended plan	Common language and expert review		Suicidality	Thoughts of death or suicide	
Pseudobulbar affect		Sudden uncontrollable strong emotional expression (ex. crying/laughing) at times seemingly unprovoked and not matching internal feelings	Common language and expert review		Emotional lability	Sudden laughing/crying that does not relate to your feelings	
Irritability		Easily frustrated or annoyed often over seemingly small matters	Common language and expert review			Easily frustrated or annoyed	
Euphoria		Feeling of extreme happiness or excitement	Common language and expert review			Intense happiness that may be excessive for the situation	
Agitation		Heightened restlessness/nervousness which may more easily lead to an angered response	Common language and expert review			Restless and on edge	
Impulsive behaviors		Difficulty controlling behaviors resulting in inability to resist temptation, often resulting in actions that are atypical for the person	Common language and expert review		Impulsivity	Doing things impulsively in response to urges that are difficult to control	
Medication use compulsion		Pattern of medication use of dysregulated over consumption and loss of control or urge towards increased intake	Common language and expert review		Dopamine dysregulation syndrome	Medication overuse due to an urge to take more than prescribed	
Buying compulsion		Excessive urge or tendency to shop or spend money often with adverse consequence	Common language and expert review		Oniomania	Excessive shopping urge	
Eating compulsion		Intense urge or tendency to over eat despite not being hungry	Common language and expert review		Hyperphagia	Excessive food cravings	
Sexual compulsion		Heightened focus on sexual urges or behaviors often with limited self-control	Common language and expert review		Hypersexuality	Excessive sexual urge	
Punding compulsion		Intense fascination of repetitive non-goal oriented mechanical tasks, may include assembling/disassembling and sorting	Common language and expert review	Obsessive Compulsive Disorder		Doing tasks repetitively without a reasonable goal (e.g. repetitive sorting)	
Gambling compulsion		Excessive urge or tendency to bet or gamble often with adverse consequence	Common language and expert review		Pathological gambling	Excessive urge to gamble	
Walkabout compulsion		Persisent urge to walk often aimlessly without intended destination	Common language and expert review			Excessive urge to wander about	
Hobbyism compulsion		Uncontrollable urge to carry out or pursue a hobby often prioritizing above other responsibilities	Common language and expert review			Excessive urge to do a hobby	
Psychosis		Condition in which thoughts, emotions, or perceptions are lost to reality and often with limited insight	Common language and expert review			Difficulty telling what is real and what is not real	
Delusions		False belief or distortion of reality that persists despite evidence to the contrary	Common language and expert review			mistaken beliefs about things that aren't real	
Hallucinations		Seeing, hearing, feeling, tasting, or smelling something that is not actually present, includes sensations of someone or something passing nearby in periphery	Common language and expert review	Misperception due to visual impairment		Seeing and hearing things that aren't real (e.g. visions or sounds)	
Smell hallucinations		Smelling something that is not present or perceived by others; Subset of hallucinations	Common language and expert review		Olfactory hallucination	Smelling things that are not there.	
Personality changes		Altered manner in how one thinks, acts, or feels that are distinctly uncharacteristic, may affect interactions with others	Common language and expert review			Personality changes	
Persistence		Determination to complete tasks often with inflexibility or with fixated thought	Common language and expert review		Perseveration	Feeling compelled to keep doing something	
Reward seeking behavior		Increased tendency to seek approval or respond to rewarding stimuli	Common language and expert review		Reward dependence	Reward seeking behavior	
Disinhibition		Inability to regulate behaviors or thoughts within bounds of socially acceptable behavior	Common language and expert review		Frontal lobe function	Inability to control behaviors in a way that is socially acceptable; Loss of filter	
Neuroticism		Increased distress or dissatifaction with oneself or external circumstance	Common language and expert review			Easily frazzled	
Emotion recognition accuracy		Ability to successfully recognize and interpret others emotions	Common language and expert review			Trouble recognizing others feelings and emotions	
Low novelty seeking	Novelty seeking	Tendency to avoid the pursuit of new or exciting experiences and situations	Common language and expert review			Limited interest in trying new things	
SENSORY DOMAIN							
Double Vision		Seeing two of the same objects simultaneously	Common language and expert review		Diplopia	Double vision	
Light sensitivity		Discomfort when placed in bright environments	Common language and expert review		Photosensitivity	Visually sensitive to light; light sensitivity	
Dry eyes		Limited tear production which may result in eye irritation or discomfort	Common language and expert review		Xerophthalmia	Dry eyes	
Taste		Changes in quality of the taste of food	Common language and expert review		Gustation	Altered sense of taste	
Smell		Changes in quality of smell, may include food but also surrounding environment	Common language and expert review		Olfaction	Altered sense of smell	

Hearing		Changes in quality of hearing, may include distortions of sound or diminished ability to perceive/interpret sound	Common language and expert review	Does not include auditory hallucination	Auditory perception	Altered sense of hearing	
Touch sensation		Changes in quality of touch sensation, may include light touch, pressure, or sensory disturbance not otherwise specified below	Common language and expert review		Tactile perception	Altered sensitivity to touch	
Altered sentation in hands and feet		Numbness or sensory disturbance most pronounced of distal arms/legs	Common language and expert review		Peripheral neuropathy	Numbness or tingling of hands/feet	
Vibratory sense		Ability to perceive vibratory stimuli	Common language and expert review			Loss of ability to feel vibrations (skin)	
Numbness		Diminished ability to perceive to tactile stimuli	Common language and expert review			Loss of sensation in skin	
Tingling		Sensory disturbance that may be compared to pins and needles or when an extremity 'falls asleep' following restricted blood flow	Common language and expert review			Tingling sensation in skin	
Temperature sensation		Ability to differentiate between hot and cold	Common language and expert review		Thermosensation	Altered ability to feel hot and cold	
Pain		Body pain or discomfort due to any cause including cramping, spasms, or neuropathy	Common language and expert review		Nociception	Pain, physical discomfort	
Headache		Head pain or discomfort due to any cause	Common language and expert review			Headache	
Fatigue - General		Overall lack of energy not otherwise specified	Common language and expert review	sleepiness		lack of energy; feeling too tired to do things	
Fatigue - Mental		Sense of mental exhaustion not explained by drug effects or other psychiatric condition, includes feeling exhausted during intellectually challenging tasks or decreased capacity to sustain cognitively challenging activites	Common language and expert review	sleepiness		Feeling mentally exhuasted	
Fatigue - Physical		Exhaustion or tiredness of the body	Common language and expert review	sleepiness		Feeling physically exhausted	
Shortness of breath		Difficult or labored breathing	Common language and expert review	Does not included proportionate exercise induced SOB	Dyspnea	Feeling abnormally short of breath	
Muscle weakness		Diminished ability to produce maximal motor strength	Common language and expert review			Loss of strength; feeling weak	
Heaviness		Maximal strength is preserved but takes more effort or energy to exert force or make movement	Common language and expert review			Sensation of heavy limbs such that physical tasks require more effort	
Body temperature control		Feeling (perception) of being either excessively hot or cold, may include generalized sensation or be specific to certain parts of the body	Common language and expert review	chills or sensory disturbances secondary to fever/infection	Thermoregulation	Difficulty managing body temperature; Feeling excessively hot or cold	
Heat intolerance		Significant discomfort when placed in warm temperature environments	Common language and expert review			Feeling abnormally hot	
Cold intolerance		Significant discomfort when placed in cold temperature environments	Common language and expert review			Feeling abnormally cold	
SLEEP DOMAIN							
Altered Sleep		Changes in patterns or behaviors when trying to sleep	Common language and expert review			Sleep changes	
Sleep disturbances (general term)		Undesired interruptions or disruptions of sleep	Common language and expert review			Disturbed or interrupted sleep	
Sleep quality		Perception of having a good night of sleep	Common language and expert review			Quality of sleep; sleeping well	
Sleep onset insomnia		Difficulty falling asleep at the beginning of the sleep period	Common language and expert review	difficulties initiating sleep due to restless legs		Difficulty falling asleep	
Sleep maintenance insomnia		Difficulty staying asleep; Awakening during the night with difficulty falling asleep again	Common language and expert review	brief awakenings (ex. due to trips to the bathroom) without difficulty falling back asleep		Difficulty staying asleep; interrupted sleep; broken sleep	
Early morning awakening		Waking up too early with difficulty falling back to sleep	Common language and expert review	Does not included planned early morning wakening, such as for occupation		Waking up too early	
Sleep duration & efficiency		How long one sleeps and overall time one maintains sleep, how restful one feels upon awakening	Common language and expert review			How long you stay asleep	
Sleep talking/walking		Vocalizations, talking, or walking during sleep without awareness of behavior	Common language and expert review	dream enactment, sleep paralysis			
RSBD		Acting out dreams, movements or vocalizations during sleep; may only be aware due to partner report; may at times cause patient to awaken	Common language and expert review	moving in sleep without further specification	REM Sleep Behavior Disorder	Acting out dreams	
Vivid dreams		Any report of vivid or detailed dreams, dreams that seem real or can recall in great detail upon awakening	Common language and expert review			Intense memorable dreams	
Unpleasant dreams		Intense dreams, nightmares	Common language and expert review				
Daytime sleepiness		Urge or need to sleep in situations when is sleep not desired or appropriate, may lead to intentional or unintentional sleep during the day	Common language and expert review	tiredness or fatigue without needing to sleep/nap	Hypersomnia		
SPEECH & VOICE DOMAIN							
Articulation		Ability to form clear distinct sounds, clarity of speech production	Common language and expert review		Dysarthria	Clarity of speech	
Phonation		Ability to produce sound from the vocal tract	Common language and expert review			Ability to produce sound	
Monotone voice		Lack of vocal fluctuation in tone or rhythm	Common language and expert review		Monotone; Prosodic impairment	Intonation/rhythm of speech	
Hypophonia		Low speech volume/amplitude, difficulty projecting voice	Common language and expert review			Quiet voice	
Voice quality		Changes in character or quality of voice not otherwise specified	Common language and expert review				
Verbal fluency		Ability to produce desired vocabulary when communicating	Common language and expert review			Ease of word production	
DIGESTIVE SYSTEM DOMAIN							
Drooling		Difficulty managing saliva with overflow out of the mouth	Common language and expert review		Sialorrhea		
Dry mouth		Sensation of inadequate saliva production	Common language and expert review		Xerostomia		
Globus sensation		Sensation of having something stuck in one's throat	Common language and expert review		Globus pharyngis		
Swallowing difficulties		Swallowing impairment that may result in coughing/choking when trying to ingest food and drink	Common language and expert review		Aspiration; Dysphagia	Swallowing difficulties	
Chewing		Changes in ability to masticate food to allow for succesful feeding	Common language and expert review		Mastication		
Pain during swallow		Pain or discomfort of any part of the oropharynx or digestive tract provoked by swallowing	Common language and expert review		Odynophagia		
Esophageal transit time		The amount of time it takes for food/drink to traverse down the esophagus into the stomach	Common language and expert review			Time it takes for food to enter stomach	

Acid reflux		Upper abdominal/chest discomfort caused by stomach acid irritating the lower part of the esophagus often worsened following meals or when laying down	Common language and expert review		GERD	Heartburn	
Early fullness		Inability to eat a full meal due to feeling full after only a small amount of food intake	Common language and expert review		Early saiety	Feeling full easily	
Abdominal pain		Pain or discomfort attributed to the GI tract	Common language and expert review			Stomach or belly pain or ache	
Nausea & Vomiting		Sensation of stomach discomfort with concern that one may vomit or progression to vomiting	Common language and expert review		Emesis		
Bloating/Fullness		Feeling of abdominal fullness/tightness often with associated distention	Common language and expert review		Gastroparesis	Belly feeling full or large	
Appetite changes		Changes in desire to eat, may result in either weight loss or weight gain	Common language and expert review				
Constipation		Difficulty with passage of stool, often accompanied by hardened feces	Common language and expert review		Fecal impaction		
Tenesmus		Urge to pass stool accompanied by pain/cramping and often unsuccessful with limited defecation	Common language and expert review	pain passing hard stool		Feeling the need to pass stool without being able to; may be painful	
Straining		Increased required force or effort exerted during bowel movements	Common language and expert review				
Bowel urgency		The need to suddenly relieve bowels to prevent accidental soiling	Common language and expert review				
Bowel incontinence		Loss of ability to hold bowels often without forewarning leading to involuntary soiling	Common language and expert review		Encopresis	Losing control of stool leading to soiling	
Anal sphincter control		Ability to willingly tighten or loosen one's anal sphincter to allow for coordination of bowel movements	Common language and expert review				
Diarrhea		Bowel movements of loose or watery consistency	Common language and expert review			Loose stool	
URINARY DOMAIN							
Urinary Frequency		The need to pass urine more frequently than typical or desired	Common language and expert review			Urge to urinate frequently	
Urinary Urgency		The need to suddenly relieve urine often without forewarning	Common language and expert review			Urge to urinate suddenly	
Nocturia		Awakening at night to urinate, may occur multiple times per night and disrupt sleep	Common language and expert review			Need to urinate at night	
Incomplete voiding		Inability to fully void urine from bladder	Common language and expert review			Incomplete bladder emptying	
Urinary Incontinence		Loss of ability to hold urine or regulate desired timing of urination	Common language and expert review			Loss of bladder control	
Urinary Infections		Associated infections of the urinary system	Common language and expert review		Urinary tract infection		
Weak urine stream		Diminished outflow velocity when urinating	Common language and expert review		Urinary hesitancy		
SEXUAL DOMAIN							
Sexual dysfunction		Difficulties with sexual response, desire, or performance not otherwise specified	Common language and expert review				
Trouble achieving orgasm	Ability to achieve orgasm	Absent, delayed, or diminished orgasm following adequate sexual stimulation	Common language and expert review		Anorgasmia	Difficulty achieving orgasm	
Ejaculatory dysfunction		Absent, delayed, diminished, or premature ability to ejaculate during sexual intercourse	Common language and expert review			Difficulty ejaculating or early ejaculation	
Erectile dysfunction		Difficulty achieving or maintaining an erection during sex	Common language and expert review		Impotence		
Impaired libido		Lack of interest in sexual activity	Common language and expert review			Low sex drive	
Vaginal dryness		Dryness of the vagina, often may lead to irritation or pain with intercourse	Common language and expert review		Vaginal atrophy		
AUTONOMIC NERVOUS SYSTEM DOMAIN							
Orthostatic hypotension		Low blood pressure provoked with standing from sitting or lying down, may result in lightheadedness or episodes of passing out	Common language and expert review			Low blood pressure when standing	
Hypotension		Low blood pressure	Common language and expert review			Low blood pressure	
Hypertension		Elevated blood pressure	Common language and expert review			high blood pressure	
Supine hypertension		Elevated blood pressures noted particularly when laying down	Common language and expert review			High blood pressure when laying down	
Nocturnal hypertention		Elevated blood pressures noted overnight when attempting to sleep	Common language and expert review			High blood pressure overnight	
Swelling of extremities		Swelling due to retention of fluid commonly involving distal legs but may also involve arms	Common language and expert review		Peripheral edema	Swelling of arms or legs	
Dizziness		Altered sense of self perceived place, may be described as either the room or the person spinning which may cause one to lose balance	Common language and expert review	lightheadedness		Abnormal sensation of movement	
Lightheadedness		Altered sensation that one may faint, often positionally provoked and may improve when seated from standing or laying flat	Common language and expert review	dizziness		Faintness	
Syncope		Loss of consciousness, often brief with quick recovery	Common language and expert review			Passing out	
Hyperhidrosis		Excessive sweating that may involve the entire body or specific areas such as under arms, soles, face, etc.	Common language and expert review	sweating secondary to panic, distress, or anxiety related events		Excessive sweating	

Term derived from literature review	Proposed ammendment to Concept	Proposed Definition	Definition Source	Excludes	Relevant Clinical Terminology	Patient Friendly Definition	Comments
PHYSICAL FUNCTIONING DOMAIN							
MOBILITY							
Mobility		Purposeful physical movement used to navigate one's enviroment including gross simple movements, fine complex movements, and muscle coordination	Adopted from Giddens, 2017		Ambulation, dexterity	Movement; walking	
Getting out of bed/chair/car		Ability to get up from a seated position and from different heights or surfaces	Best interpretation of common language				Potential distinctions between these concepts may or may not be meaningful and there may be room to blend with aspcets of getting to standing position.
Turning in bed		Ability to roll over and change positions in bed	Best interpretation of common language				
Standing		1. Ability to get to standing position; and 2. Ability to maintain erect posture	Best interpretation of common language				Subconcept 1 could possibly be combined with "getting out of bed/chair" as the concept "Getting up from sitting or lying down"
Kneeling/bending	Divide: 1. Kneeling 2. Bending	1. Use of musculoskeletal system to assume a position where the body is supported by the knees 2. Use of the musculoskeletal system to incline the body downward from a standing position	Best interpretation of common language				combines two concepts that are not clearly related
Climbing stairs		1. Ability to independently walk upwards on a set of stairs or steps; 2. Ability to independently walk downwards on a set of stairs or steps	Best interpretation of common language				
Lifting/holding/carrying	1. Lifting 2. Holding 3. Carrying	1. ability to use musculoskeletal system to pick up and move an object to a different position 2. ability to keep an object in one's hand or arms 3. ability to move an object while holding it	Best interpretation of common language				Distinction may be germane to measurement of a single underlying concept (i.e., ability to move objects); these three constituent definitional elements would be likley more relevant to a performance outcome measure than a self reported one
Gripping and opening	Divide: 1. "ability to open a container" 2. "gripping"	1. Functional ablity or muscular force in hands needed to remove the lid from a jar, bottle, or container 2. How firmly a person can hold items and apply tension, maximum strenght generated by forearm muscles	Best interpretation of common language				[rationale; actions required different muscle group]
Handwriting		Use of a writing instrument, such as a pen, pencil, or marker and fine motor skills of the hand	Best interpretation of common language			Penmanship	
Using a computer		Ability to operate a computer	Best interpretation of common language	Limitations secondary to lack of technological knowledge			
Using smartphone/tablet		Ability to navigate use of a handheld electronic device	Best interpretation of common language	Limitations secondary to lack of technological knowledge			
Exercise/activity/sports		Engagement in physical activity to improve health and fitness, or for social and leisure purposes	Best interpretation of common language			running; hiking; biking	
PHYSICAL COMFORT							
Increased physical discomfort	Physical discomfort	An unpleasant sensory experience; inability to achieve physical comfort, such as feeling relaxed, at ease, and able to hold a normal physical position without distress"	Adopted from Giddens, 2017		Pain, discomfort	Pain	
Feeling unwell		General malaise; sensation of not feeling well or not at baseline	Best interpretation of common language	Emotional distress			
Difficulty relaxing	Ability to relax	State of increased tension with inability to fully resolve; Ability to reduce muscle tension, slow breathing, and calm thought process	Best interpretation of common language				
EFFORT OF LIVING							
Effort of living		Energy or effort (mental or physical) expended to perform usual daily living activities	Best interpretation of common language				
Longer to do things/Functional slowness		Prolonged time required to complete tasks, often due to slow effortful movements and decreased motor control	Adapted from Parkinsons literature		Bradykinesia		
Everything takes more effort		Increased energy expended to perform all tasks (overlaps with categorical concept)	Best interpretation of common language			Feeling drained	
Having to plan around PD		Having to coordinate schedule and alter plans to accommodate impact of symptoms	Best interpretation of common language		Motor fluctuations, ON/OFF time		
SELF-CARE							
Dressing		Ability to put on or take off clothing	Best interpretation of common language				
Personal hygiene/self-care		Tasks to maintain personal cleanliness ex. showering, brushing teeth, grooming, etc.	Best interpretation of common language				
Eating tasks		Ability to feed oneself or independently consume food/beverages	Best interpretation of common language		Nutrition		
SAFETY							
Accidental self-injury	Unintentional self-injury	Injuries to oneself that are not inflicted purposely, commonly resulting from cognitive or motor impairments	Best interpretation of common language	Self-harm			
Tripping & Falling	Consider dividing: 1. Tripping 2. Falling	1. Difficulties with foot clearance, motor control, or imbalance which may result in near or actual falls 2. In ability to maintain or regain balance in standing position; Falling as a result of tripping, bending over	Best interpretation of common language	Falling out of bed	Gait imbalance, freezing, falls	Unsteadiness	Additional evidence may be needed to understand what the concept really is and to what extent they are separate. Tripping may occur without falling. However, "tripping-and-then-falling-because-of-tripping" could be a germane concept for PD
Weight change		Unplanned weight loss or gain that may or may not be secondary to changes in appetite	Best interpretation of common language				
PSYCHOSOCIAL FUNCTIONING DOMAIN							
INDEPENDENCE							
Independence		Ability to be self-reliant and complete necessary and desirable tasks and activities without undue assistance from others	Best interpretation of common language			Needing more help	
Cooking/Meal prep		Act of preparing a meal for consumption	Best interpretation of common language				
Doing shopping		Act of purchasing goods from a store or online	Best interpretation of common language				
House work/home maintenance/garden		Activities required for maintenance of a house, i.e. vaccuming, cleaning, cooking, laundry, lawn care	Best interpretation of common language				
Travel/Driving		Act of going from one place to another by walking or different modes of transportation	Best interpretation of common language				
SELF-CONCEPT							
Altered self-concept		Change in beliefs/perception about oneself, feeling that one's identity or essential self has changed	Best interpretation of common language			Change in self-image	
Embarrassment/self-conscious		Uncomfortable feeling generated from perceiving that one's condition draws attention from others or results in unwelcome or taboo occurances; a state of shame or worry about ones condition or symptoms	Best interpretation of common language				
Feeling stigmatized	Percieved stigma	Self perception of being negatively viewed, unfairly being treated or having done something wrong	Best interpretation of common language				
SELF EFFICACY							
Decreased Self confidence	Self-confidence	Diminished pride in oneself or belief in ability to be successful	Best interpretation of common language				
Sense of helplessness		Feeling or preception that one's actions have limited ability to change or affect future outcomes	Best interpretation of common language				
Sense that PD limits what you can do	Sense of being limited	Perception that one's abilities are limited by symptoms	Best interpretation of common language				
COPING							

Altered coping	Coping	Ability to manage stress or adverse conditions	Best interpretation of common language				
Living with uncertainty		Acknowledgement and awareness of the unpredictable and potentially undesirable nature of disease outcomes that may or may not cause anticipatory distress	Best interpretation of common language				
Preoccupation with disease		Intrusive thoughts or worry about the impact of disease burden/progression	Best interpretation of common language				
Increased fear	Fear	Unpleasant strong emotion and increased autonomic activity caused by anticipation or awareness of danger	Adopted from Merriam-Webster Dictonary, 2024				
Fear of falling		Anticipation and concern about the act of falling and its consequences	Best interpretation of common language				
Fear of future		Anticipation and dread about future or upcoming events or outcomes	Best interpretation of common language				
Avoidance		Behaviors that limit social interaction or pursuit of activities	Best interpretation of common language				
Denial		Refusal to accept diagnosis or reality of one's condition	Best interpretation of common language				
Concealing diagnosis		Choosing not to disclose one's diagnosis	Best interpretation of common language				
Annoyance/bothered		Emotional state of feeling irritated or bothered about something	Best interpretation of common language				
Frustration/Anger		Emotional state of displeasure or animosity towards something	Best interpretation of common language				
Stress, distress, overwhelmed		Percieved emotional feeling and hormonal reaction to a life event such as adversity, hardship, or illness where resources and abilites for management are available, exceeded, or exhausted	Adopted from Giddens, 2017				
Finding ways to compensate		Actions that compensate for the impact of one's symptoms or diagnosis	Best interpretation of common language				
Making positive changes to take control of disease		Adaptive behaviors to promote self empowerment and address uncertainty	Best interpretation of common language		Empowerment		
INTERPERSONAL INTERACTIONS							
Interpersonal interactions (all)		Social involvement or engagement with others	Best interpretation of common language				
Relationships with others (friends, family, colleagues)		Perception of major roles and responsibilites in current life situation	Adapted from Alfaro-LeFevre (2014)				
Others perceptions and reactions		Views and feelings about how other people perceive and react to one's symptoms, impairments, and needs or requirements	Best interpretation of common language				Term may benefit by clarification
Communication		Abilty to express thoughts verbally or by writing or typing and to receive language and understand others	Best interpretation of common language				
Loneliness/isolation		Limited or unsatisfying social interaction with others	Best interpretation of common language				
ROLES AND RESPONSIBILITIES							
Taking care of family		Ability to provide for family, may include physical/emotional means	Best interpretation of common language				
Taking care of pets		Ability to provide for pets, may include feeding, elimination, exercise, veterinary care	Best interpretation of common language			Pet care	
Impact on job/career/profession		Influence symptoms/disease has on career aspirations or ability to achieve desired professional goals, as well as ability to attend work and complete work-related tasks accurately and on time	Best interpretation of common language				
Financial impact/paying bills		Economic strain or influence on affording costs of living	Best interpretation of common language			Worrying about money or finances	
IMPORTANT ACTIVITIES							
Pleasurable activities		Ability to engage in activities that bring enjoyment, may include recreational activities or tasks that provide greater sense of fufillment	Best interpretation of common language				
Loss of things you enjoy		Sense of loss due to inability to engage in desired enjoyable activities"	Best interpretation of common language		Apathy		
Social life		Social interactions with others spent doing enjoyable activities	Best interpretation of common language		Socialization		
Playing musical instrument		Ability to position oneself to hold or operate a musical instrument	Best interpretation of common language				
Spiritual and Religious Activities		Ability to participate in an organized or independent spiritual or religious life"	Best interpretation of common language				
Hobbies/leisure		Ability to engage in desired hobby or leisure activities	Best interpretation of common language				
CONTEXTUAL FACTORS							
Symmetrical symptom onset		Motor deficits that affect both sides of the body at beginning of disease or perceived awareness of symptoms	Adopted from Parkinsons literature				
Most dominant/obvious issues		Most prevalent or dominant symptom(s) that causes the greatest impact on daily life, health, and wellbeing	Best interpretation of common language				
Frequency and severity of symptoms		Frequency refers to the number of times a symptom occurs and severity refers to how severe a symptoms is when present	Best interpretation of common language				
Medication dose failure/delayed on		Limited efficacy following medication dosing either due to delay or limit in peak benefit	Best interpretation of common language				
Nocturnal motor symptoms		Motor symptoms that occur primarily at night often while trying to sleep	Best interpretation of common language				
Motor fluctuations		Changes in motor performance often in context of varied drug absorption/availability of dopamine	Adopted from Parkinsons literature		dyskinesias		
Energy intake		Total daily consumption of nutritional caloric intake	Best interpretation of common language		Nutrition	Eating	
"Off" periods		Moments of worsened motor symptoms resulting in functional limitation	Adopted from Parkinsons literature		Wearing off syndrome		
Medication side effects		Unintended adverse effect occuring at a normal dose	Best interpretation of common language		Pharmacological adverse effect		
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Giddens, J.F. (2017). *Concepts for nursing practice* (2nd Ed.). Elsevier							
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Supplement E. Audit trail of sources included in the systematic review

Included in Full Review (all "early" PD)

Tier 1 (N=8): [4, 10-13, 32-34]
Tier 2 (N=28) and 3 (N=52) : [35-114]

Pooled Data from Same Sample studies (Full review)

Tier 1: Parkinson's UK survey data [4, 33]
Tier 2:

- Chinese PSG [98, 111]
- ICICLE-PD [50, 51, 77]
- Norwegian Parkwest [76, 79, 104]
- OPDC [40, 41, 102]
- PPMI [69, 83, 96]

Tier 3

- Norwegian Parkwest [63, 75, 103, 106]
- ICICLE-PD [66, 74]
- PALS [46, 56, 60]
- PPMI [37, 38, 49, 55, 62, 65, 93, 95]
- Sichuan University [80, 81]

Removed from final model due to PD time since PD diagnosis >3 years (model constraints)

- Tier 1: [34]
- Tier 2: [40, 76, 83, 89, 91, 98, 102, 107, 108, 111]
- Tier 3: [37, 41-43, 45, 54, 57-59, 61, 64, 68, 70, 73, 78, 80-82, 88, 92, 97, 106, 110]

Excluded from Review:

Excluded during full text review [123-186]

- Not early PD
- Not methodologically generalizable
- Not reporting symptoms or impacts

Excluded during Abstract review:

- Biomarker/genetic study [187-258]
- Conference abstract [259]
- Digital monitoring, no symptoms [260-263]
- Imaging study [264-344]
- Modeling study [345-350]
- Not early PD population [351-367]
- Not reporting symptoms or impacts [368-436]
- Not a primary source [437-529]
- Out of data and not qualitative [530-538]
- Protocol/methods paper [539-547]
- Reference list - Review [548-566]
- Unrelated to Parkinson's [567-600]
- Validation study [601-635]
- Efficacy study (effect of X on Y) [636-702]
- Animal model study [703-760]
- Unsure/not usable [761]

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