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Outcome Measures for Dementia with Lewy Body Clinical Trials: A Review

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Abstract

Background: Dementia with Lewy bodies (DLB) is one of the most common degenerative dementias. Clinical trials for individuals with DLB are increasing. We aimed to identify commonly used outcome measures for trials in DLB.

Methods: A pragmatic literature search of PubMed and clinicaltrials.gov identified interventional studies including populations with DLB. Studies were included if they enrolled participants with DLB and met the National Institutes of Health criteria for a clinical trial. Data were collected using standardized forms. Outcome measures were categorized according to core and supportive features of DLB.

Results: After de-duplication, 58 trials were identified. The most common cognitive outcome measures were the Mini Mental State Examination (n=24) and Cognitive Drug Research computerized Assessment System (n=5). The Clinician's Assessment of Fluctuations was the most commonly employed measure for fluctuations (n=4). Over half of studies used the Neuropsychiatric Inventory to assess behavioral symptoms (n=31). The Unified Parkinson's Disease Rating Scale was frequently used for motor assessment (n=23).

Conclusions and Relevance: Clinical trial outcomes used in DLB are rarely validated in this population and some lack face validity. There is a need to validate existing scales in DLB and develop DLB-specific outcome measures.

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Keywords

Dementia with Lewy bodies; Lewy body disease [MeSH term]; Outcome Assessment – Health Care [MeSH term]; outcome measure; clinical trials as topic [MeSH term]

INTRODUCTION

Lewy body dementia (LBD) is the second most common neurodegenerative dementia after Alzheimer disease (AD).[1] LBD consists of dementia with Lewy bodies (DLB) and Parkinson disease dementia (PDD). There exist ongoing debates regarding the relationship of DLB, Parkinson disease (PD), and PDD.[2,3] However, recent research found that ideal clinical trial outcomes are distinct between DLB and PDD, suggesting value to separating these two diagnoses in clinical trials.[4] Outcome measures are rarely formally validated for use in DLB. It is possible that the lack of validated outcome measures is one contributor to recent trials showing no benefit (e.g. the HEADWAY-DLB study of RVT-101 [NCT02669433]). No treatments are Food and Drug Administration (FDA)-approved for individuals with DLB. Donepezil and zonisamide are approved for DLB treatment only in Japan. Developing symptomatic and disease-modifying therapies for LBD is a national clinical research priority established by the 2019 Alzheimer's Disease–Related Dementias Summit,[5] but the ideal outcome measures for such trials are yet to be established. In this setting, we aimed to identify the outcome measures used in prior DLB clinical trials in order to inform future trial planning.

METHODS

This review employed a pragmatic literature search. Pragmatic searches adapt conventional systematic review processes to take into consideration limited time or resources, typically by applying additional limits to search or eligibility criteria.[6,7] In this review, we restricted the literature search to two sources (PubMed and clinicaltrials.gov) as these are likely to capture the majority of clinical trials in DLB (see Figure, Supplemental Digital Content 1, which demonstrates the selection process of publications and clinical trials in this review). Additionally, we limited key search terms to those directly related to dementia with Lewy bodies rather than using search terms related to dementia more broadly. In PubMed, the search included the terms "dementia with Lewy bodies" and "Lewy body dementia" combined with the clinical trial filter. The clinicaltrials.gov search used "dementia with Lewy bodies" as the condition/disease and study type was restricted to interventional studies. Studies were included if they (1) enrolled patients with DLB (with or without other populations) and (2) met the National Institutes of Health definition of a clinical trial ("a research study in which one or more human subjects are prospectively assigned to one or more interventions [which may include placebo or other control] to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes").[8] Open label and pilot studies were included if they met inclusion criteria. Excluded studies included case studies, case series, reviews, and studies using imaging modalities as an "intervention" or primary outcome. As this review focused on clinical trial outcome measures, biomarker outcomes (ie: imaging modalities) were not included. As this was a review of publicly

available data, institutional review board approval was not required. The protocol was not registered.

Data extraction was performed by a research assistant and investigator (BP). Search results, study characteristics, and outcome measures were organized using data extraction forms in Microsoft Excel® 2016. For PubMed entries, data collected included the publication reference, trial registration, whether the manuscript reported a protocol or clinical trial results, population, study intervention, comparator, duration, and primary and secondary outcome measures. For clinicaltrials.gov entries, data extraction included the study title, registration, study status (and date assessed), population, intervention, comparator, study duration, and primary and secondary outcome measures. For studies with multiple publications, each publication was counted separately if there were different outcome measures.

Outcome measures were categorized according to the core and supportive features of DLB: dementia/cognitive impairment, other cognitive-behavioral features (e.g. fluctuations, hallucinations, depression), REM sleep behavior disorder (RBD), and parkinsonism.[9] Other outcomes (e.g. quality of life, caregiver burden) were also categorized. As the review focused on identifying study outcomes, methodological quality of the clinical trials was not assessed.

RESULTS

Final searches were performed on February 27, 2020. The literature search identified 175 potentially relevant publications in PubMed and 67 potentially relevant studies on clinicaltrials.gov. After applying inclusion/exclusion criteria and removing duplicates, investigators included 58 studies in the review.

Study characteristics.

Twenty-three (40%) studies included individuals with PDD in addition to DLB. Eight (14%) included other populations such as AD, frontotemporal dementia, and Huntington disease dementia. No PubMed publications were protocol-only. Interventions (from both sources) included donepezil (8),[10–17] memantine (8),[18–25] rivastigmine (4),[26–29] levodopa (4),[30–33] nelotanserin (3),[34–36] intepirdine (3),[37–39] yokukansan (3),[40–42] armodafinil (2),[43,44] deep brain stimulation (2),[45,46] nilotinib (2),[47,48] and 1 each of galantamine,[49] olanzapine,[50] quetiapine,[51] ramelton,[52] zonisamide,[53] tacrine,[54] citalopram,[55] feru-guard,[56] tryptophan depletion,[57] treadmill walking,[58] cognitive rehabilitation,[59] cognitive stimulation,[60] and electroconvulsive therapy/transcranial magnetic therapy.[61] The comparators were placebo (26), [8,14–18,20–22,25,26,32,33,35,36,45,48–51,55,60–65] treatment as usual,[59,60], sham stimulation (2),[45,46] relaxation therapy (1),[59] risperidone,[55] and different doses of donepezil (1),[17] nelotanserin (1),[36] and intepirdine (1)[39]. In all 4 levodopa studies, comparisons were made to patients with PD and/or PDD.[30–33] One single-visit treadmill study lasted 20 minutes.[58] For the remaining studies, duration ranged from 4 to 52 weeks. Outcome measures included in at least 2 studies either as primary or secondary outcomes are listed in Tables 1–4.

Cognitive-behavioral outcome measures.

The most commonly used primary outcome measures for cognition were the Mini Mental State Examination (MMSE) and Cognitive Drug Research computerized Assessment System (COGDRAS) (Table 1). Frequently used secondary outcomes for cognition included the MMSE, Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), trail making test, and Controlled Oral Word Association Test (COWAT). Studies typically assessed cognitive fluctuations using the Clinician's Assessment of Fluctuations scale (CAF), but the Cognitive Fluctuation Inventory (CFI) and One Day Fluctuation Assessment Scale (ODFAS) were each used in two studies (Table 1).

For behavioral symptom assessment, 53% of studies used the Neuropsychiatric Inventory (NPI) (Table 2). Studies used various NPI versions, including the original NPI with two subdomains added (sleep/nighttime behavior disorders, appetite/eating disorders) or the questionnaire form (NPI-Q). Some studies used specific domain scores as outcome measures (e.g. the "NPI-4," including scores from the hallucinations, delusions, apathy, and agitation or dysphoria domains). Other measures of behavioral symptoms included the Unified Parkinson's Disease Rating Scale (UPDRS) part 1, Irritability-Apathy Scale, Problem Behaviors Assessment-short form, and Hospital Anxiety and Depression Scale (Table 2).

Sleep outcome measures.

The informant-completed Epworth Sleepiness Scale (ESS) was the most commonly used assessment of daytime sleepiness. Only two studies assessed changes in RBD frequency and severity based on a clinical evaluation (per clinicaltrials.gov; further details unavailable).[34,36]

Motor (parkinsonism) outcome measures.

Two studies used the newer Movement Disorder Society UPDRS (MDS-UPDRS), but analyzed the total score rather than the motor subscale independently (Table 3). The UPDRS motor subscale was almost always used for assessment of motor function in DLB clinical trials, followed by Timed Up and Go (TUG) test (Table 4).

Other outcome measures.

The most commonly used global measures of change included the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus) and Alzheimer's Disease Assessment Scale Cognitive subscale – clinical global impression of change (ADCS-CGIC). Two studies used the Clinicians Global Impression of Change in DLB (CGIC-DLB).

Caregiver outcomes were assessed using Zarit Caregiver Burden Interview, NPI caregiver distress score, and the Relatives' Stress Scale (Table 4).

DISCUSSION

Most outcome measures used in DLB clinical trials were developed for use in AD, PD, and/or general aging populations, with few efforts to validate these measures for DLB.

Without disease-specific outcome measures, selecting optimal outcomes relies on face validity (in which a test measures the specific construct it is intended to measure) for use in DLB, test characteristics when the outcome measures are used in other populations (e.g. interrater reliability, test-retest reliability, sensitivity to change), and prior experience with use in DLB. There are advantages to using outcome measures common to existing DLB cohorts, such as the U.S.-based National Alzheimer Coordinating Center (NACC) database, DLB Consortium, and the European Union-based EU Joint Programme – Neurodegenerative Disease Research (JPND).[68] The use of common measures was emphasized in the 2019 Alzheimer's Disease–Related Dementias Summit research priorities.[5] In this context, outcomes like the NPI and UPDRS may have particular benefits as their use allows comparison to existing DLB cohorts and comparison groups of AD and PD/PDD.

Cognitive outcome measures.

Cognitive outcomes are particularly challenging to select for DLB studies, due to the heterogeneity of cognitive impairment in DLB, impact of cognitive fluctuations, and outcome selection. The DLB clinical diagnostic criteria recommend neuropsychological testing covering the full range of potentially affected cognitive domains, with particular attention to the executive, attention, processing speed, and visuospatial/visuoperceptual impairments that are common in DLB.[9] Current recommendations focus on measures used to assess cognition in PD, including screening tools and individual tests with executive, attention, and visuospatial tasks.[69] The JPND report Level 1 recommendations for cognitive testing in Lewy body diseases included the Clinical Dementia Rating, MMSE, Montreal Cognitive Assessment (MoCA), and neuropsychological testing including the Consortium to Establish a Registry for Alzheimer's Disease word list, degraded letter test, WAIS similarities, adaptive digit ordering, and animal fluency.[68]

MMSE use identified in this review is congruent with the JPND report, but it has substantial limitations given its limited coverage of commonly affected domains (i.e., lacking face validity) and mixed results in studies assessing validity and sensitivity to change in LBD.[70] The MoCA, Mattis Dementia Rating Scale-2, and the Parkinson's Disease-Cognitive Rating Scale are recommended for cognitive screening in PD and have established reliability, validity, and sensitivity to change in PD populations.[70] However, the use of screening tests to measure responsiveness to interventions has limitations based on measure design and intended use. Advantages of the COGDRAS include the use of an automated computerized approach to test attention, working memory, episodic memory, executive tasks, and motor abilities, however potential disadvantages include participant discomfort with computer testing and lack of visuospatial domain coverage (thus, lacking face validity for use in DLB).

The breadth of cognitive outcomes identified in DLB trials may reflect lack of consensus regarding optimal domains to assess when studying individuals with DLB. Attention, executive, processing speed, and visuospatial/visuoperceptual impairments are common in DLB, particularly in early disease.[9] However, a recent study suggested that smaller sample sizes would be needed if using memory or language scores than visuospatial or executive scores for 2-year disease modification studies enrolling individuals with DLB.[4] Furthermore,

the presence of cognitive fluctuations can negatively affect performance – particularly during cognitive testing – but few trials incorporate this into study design.

Fluctuation Outcome Measures.

The relative rarity of fluctuation scale use is surprising given that fluctuations are a core DLB feature that can affect study result reliability. When last systematically reviewed, measures assessing cognitive fluctuations (the Mayo Fluctuations Scale, CAF, and ODFAS) lacked adequate testing of validity and reliability.[71] Since that time, the Mayo Fluctuations Scale, previously shown to distinguish DLB from AD,[72] was identified as having a sensitivity of 94% and a specificity of 71% for neurocognitive disorder with Lewy bodies in a Thai population when comparing it to blinded geriatric psychiatrists diagnoses based on the diagnostic and statistical manual of mental disorders (DSM)-5 criteria.[73] The DLB Consortium, NACC LBD module, and suggested JPND protocols use the Mayo Fluctuations Scale. A study of the CAF identified near-perfect interrater reliability in the setting of severe fluctuation cognition and fair interrater reliability for presence of fluctuations. Physician ratings achieved a sensitivity for severe fluctuating cognition of 70% and specificity of 96% when comparing it with the Fluctuating Cognition item from the DLB diagnostic criteria form adapted from McKeith, et al 1996.[74] Studies of these measures focus on screening rather than changes over time. The CAF, which includes frequency and duration scores, is likely better suited for assessing change over time than the 4-point Mayo Fluctuations Scale (which assesses the presence or absence of 4 symptoms). The CFI, developed in Japan and used in Japanese clinical trials, has good face/content validity and inter-rater reliability, but other validation is lacking.[75]

Behavior outcome measures.

The caregiver interview-based NPI is the most widely-used tool for assessing behavioral symptoms in DLB. It assesses the frequency and severity of 10–12 symptoms (depending on the version) and the degree of associated caregiver distress. The NPI-Q is a brief caregiver-completed questionnaire version that has acceptable reliability and correlation with the original NPI.[76] The NPI has the advantages of: assessing a variety of behavioral symptoms, use in NACC, the DLB Consortium, and JPND protocols, and established validity, reliability, and sensitivity to change in populations outside DLB, including some studies in PDD.[77] It is also a recommended scale for assessment of PD psychosis.[78] However, the degree to which it is responsive to change remains unknown. Furthermore, the NPI total score does not necessarily reflect specific treatment effects, which may be diluted by little or no effect on other symptoms. There is limited evidence regarding the use of subscales as outcome measures, something commonly done in DLB studies.

Sleep outcome measures.

Even though RBD is a core feature of DLB, RBD symptoms were an outcome measure in only one trial. The measure used in that study was a clinical assessment and not a validated scale. The Mayo Sleep Questionnaire (participant & co-participant/caregiver versions) is used by the NACC LBD module and DLB Consortium, but it is designed more as a screening measure than an assessment of RBD symptoms over time. Most of the available scales for RBD are screening tools with the exception of REM Sleep Behavior Disorder

Questionnaire Hong Kong (RBDQ-HK),[79] which is sensitive to change over time in studies of individuals with RBD[80] and PD.[81] The REM Sleep Behavior Disorder Severity Scale has been studied in PD with good interrater reliability[82] but requires polysomnography and longitudinal assessment is lacking. Additional scales are undergoing validation studies and may be useful for future trials.

Motor (parkinsonism) outcome measures.

The UPDRS (and more recently, the MDS-UPDRS) is the most commonly used measure of motor function in DLB, however there is limited information about the changes in motor function over time in DLB. The original UPDRS had strong clinimetric properties[83] and assessment of clinically important differences [84] but also inadequate rating instructions, ambiguous text, and missing non-motor symptoms.[83] These limitations led to MDS-UPDRS development.[85] However, the NACC Lewy body dementia module, DLB Consortium, and JPND recommendations still reference the original UPDRS. The MDS-UPDRS may have limited precision in early/mild parkinsonism.[86] A recent study using the UPDRS showed a significant difference between individuals with DLB treated with zonisamide as an adjunct to levodopa compared to those who received adjunctive placebo.[53]

Outcome measure selection.

This discussion focuses on which currently available measures are likely optimal, based on face validity in DLB, test characteristics in other populations, and prior experience with use in DLB. Even in the contexts for which they were designed, however, many of these outcome measures have limitations for use as clinical trial outcomes, including development as screening measures rather than longitudinal outcomes and lack of studies assessing clinically important changes. Currently there are insufficient data to support recommendations regarding the best outcome measures for DLB clinical trials, whether considering symptom-specific or global measures.

Ideal outcome measures would be validated specifically in DLB, including assessment of interrater reliability, test-retest reliability, means and standard deviations (to allow sample size calculations), and clinically important changes. It is worth considering whether existing scales truly fit the needs of DLB clinical trials or whether the best approach is to develop new DLB-specific outcome measures. The FDA has specific steps for developing and qualifying patient-focused outcome measures for use in clinical trials (Figure 1).[87,88] To use, revise, or develop a clinical outcome assessment (COA), investigators must identify a context of use. In the context of DLB, investigators must decide on their population (DLB specifically or combined with PDD) and their question (e.g. disease modification vs symptomatic treatment), which impacts appropriate outcome selection or development. Investigators must decide on the type of COA desired: patient-reported, observer-reported, clinician-reported, or performance-based (e.g. motor findings, cognition). Observer (caregiver)-reported, clinician-reported, and performance-based outcomes are all represented in the reviewed studies.

Once these key issues are decided, investigators must decide if the best approach is to validate an existing measure, modify an existing measure, or develop a new measure for

use in DLB. Regardless of the approach chosen, investigators and outcome developers must assess key test characteristics both cross-sectionally and longitudinally (Figure 1). For pharmaceutical companies desiring to use clinical trials to support FDA approval, submission of COAs for FDA qualification is recommended (Figure 1). This roadmap highlights the limitations of current measures used in DLB trials, particularly with regard to longitudinal evaluation of measurement properties. For DLB clinical trials to be successful, funding agencies need to support research developing and validating DLB outcome measures including measurements of change over time.

Lacking clinical trial outcome measures are not the only clinical trial design limitation in DLB. While the DLB population is considered a single entity for current trials and this review, DLB is heterogeneous. Researchers in PD are advocating studying PD subtypes for disease modification.[89] A similar approach in DLB could divide individuals with DLB into groups such as glucocerebrosidase (GBA) mutation carriers, individuals with AD co-pathology, or non-familial DLB without known co-pathology. Additionally, individuals with varying distributions of Lewy body pathology (e.g. diffuse vs. transitional, limbic vs. neocortical) have different trajectories of decline[90], but biomarkers to identify these subtypes are lacking. Further studies are needed to assess the validity of the clinical diagnostic criteria for DLB and whether individuals with DLB should be studied alone or in combination with PDD. A recent study suggested that optimal trial design would split these populations.[4]

Another major confounding issue is cognitive fluctuations. Fluctuations affect study visit performance and obscure the ability to detect change in response to therapeutic agents, particularly on measures that require attention. The existence of fluctuations may require novel trial approaches, such as serial (or “burst”) testing over hours-days, using an average to adjust for fluctuations. This would require outcome measures with multiple versions or the ability to change the exact nature of the task (e.g. changing where the subject needs to tap on a screen). Such measures would likely need to be home-based, as many participants travel long distances to study centers. None of the trials reviewed adopted this approach.

This review identified the outcome measures used most commonly in DLB clinical trials to inform future trial planning. Authors used a pragmatic literature search of two databases with available filters, so it is possible that studies not contained in these resources were missed. Additionally, authors relied on publicly-available data. For studies posted on clinicaltrials.gov but not published in manuscript form, outcome measures (or details of outcome measures) not described on clinicaltrials.gov were not included in this review. For example, the Lewy Body Dementia Association helped modify the Scale for the Assessment of Positive Symptoms (SAPS) and SAPS-caregiver and develop of a sleep diary for use in nelotanserin clinical trials, but this information was not available in clinicaltrials.gov listings. Limitations of this review include the lack of formal assessment of content validity and assessing change within outcome measures, as this was outside the scope of this paper.

Developing symptomatic and disease-modifying therapies for LBD is a national research prioritiy.[5] Most DLB clinical trials focus on treating symptoms, in contrast to AD, where more than half of studies are of potential disease-modifying interventions.[91] DLB lacks any FDA-approved intervention. The ability to identify and test promising therapies, however,

is constrained by a lack of outcome measures that reliably quantify symptoms in DLB and change in response to interventions. There is a need to validate existing scales for DLB-specific populations and develop DLB-specific outcome measures. Given the effort involved in measure development and validation, increased funding resources are needed to address this gap. Additionally, research is needed into other aspects of optimal DLB clinical trial design including population selection and how to mitigate the effects of cognitive fluctuations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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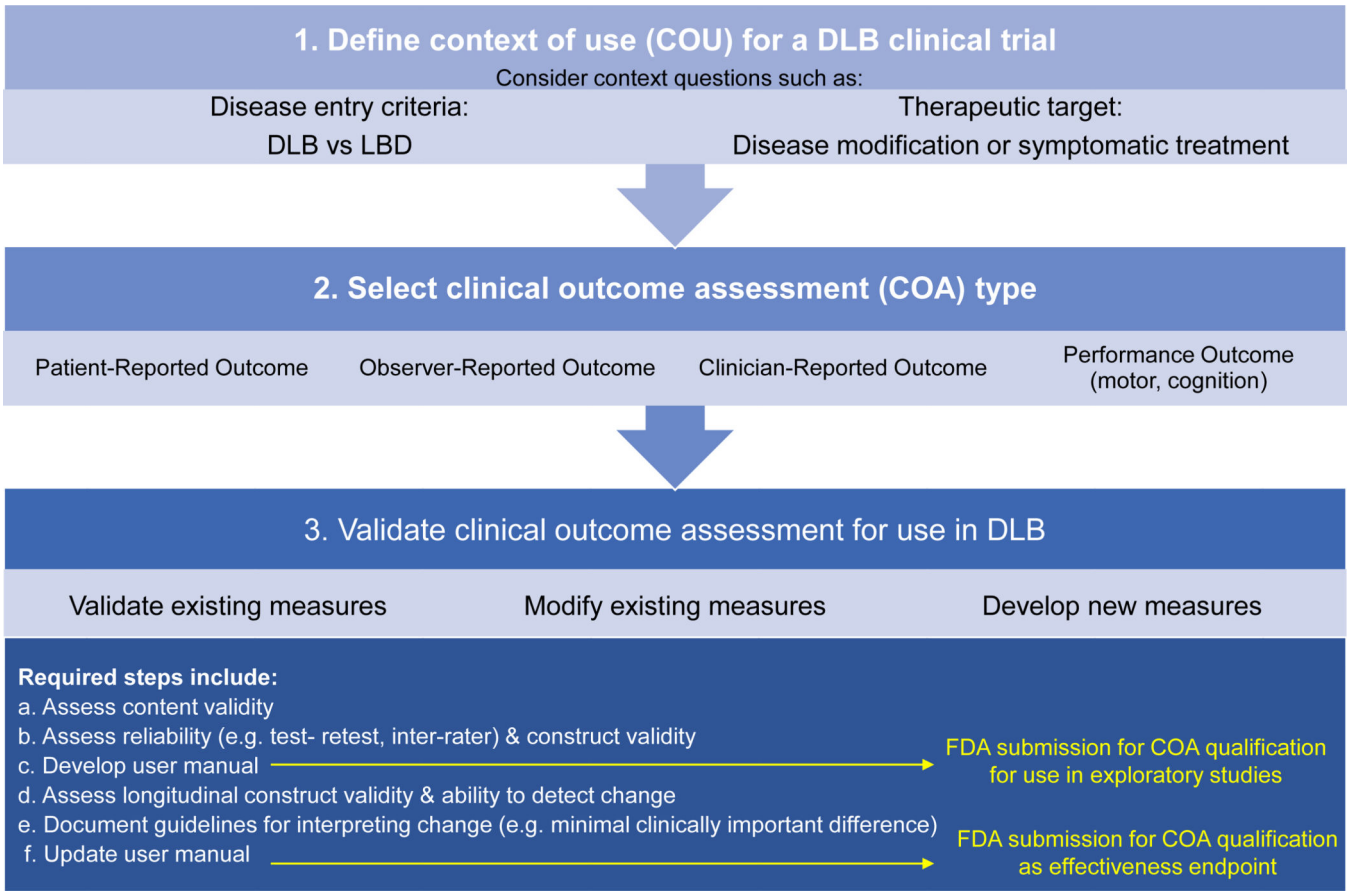

Figure 1.

Steps to Clinical Outcome Measure Development in DLB.*

Legend: *Adapted and modified from the U.S. Food and Drug Administration Center for Drug Evaluation and Research Office of New Drugs

Table 1.

Cognitive scales used as primary or secondary outcomes in DLB clinical trials

	Primary outcome frequency	Ref.	Secondary outcome frequency	Ref.
MMSE	6	10,13,14,17,26,41	18	15,18,25,27,30,32,40,43,45,48–50,53,55,57,63,64,67
COGDRAS	3	12,27,49	2	18,32
Verbal Fluency	2	10,45	0	n/a
COWAT or COWA	1	54	4	24,27,43,57
MoCA	1	63	3	47,65,66
Clinician's Assessment of Fluctuations scale	1	45	3	25,47,65
ADAS-Cog (memory)	0	n/a	6	11,24,43,47,49,65
Trail Making test (executive)	0	n/a	5	24,27,45,47,65
Stroop test	0	n/a	3	24,27,45
Benton Judgement of Line Orientation (visuospatial)	0	n/a	2	24,45
Clock drawing 10 point (executive)	0	n/a	2	24,25
Digit span forward/backward	0	n/a	2	43,57
Cognitive Fluctuation Inventory	0	n/a	2	15,63
One day fluctuation assessment	0	n/a	2	25,57

MMSE: Mini Mental State Examination, COGDRAS: Cognitive drug research computerised cognitive assessment system, COWAT or COWA: Controlled oral word association test measure of verbal fluency, MoCA: Montreal Cognitive Assessment, ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale

Table 2.

Behavioral scales used as primary or secondary outcomes in DLB clinical trials

	Primary outcome frequency	Ref.	Secondary outcome frequency	Ref.
NPI (total, 12, 11, 4, plus, NH)	9	10,13,14,17,26,27,41,49,56	22	11,15,18,24,27,30,32,40,43,45,47,50,53,55,60,63–67
UPDRS part 1	0	n/a	3	47,48,65
Irritability-Apathy Scale (IAS)	0	n/a	2	47,65
Problem behaviors assessment-short form	0	n/a	2	47,65
Hospital Anxiety and Depression Scale (HADS) - caregiver	0	n/a	2	59,60

NPI: Neuropsychiatric Inventory, UPDRS: Unified Parkinson's Disease Rating Scale

Table 3.

Global scales used as primary or secondary outcomes in DLB clinical trials

	Primary outcome frequency	Ref	Secondary outcome frequency	Ref
Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC+)	3	10,16,63	2	13,37
ADCS-CGIC	3	18,21,49	4	24,43,55,66
UPDRS total	0	N/A	3	27,48,53
Clinician's Global Impression of Change - In Dementia With Lewy Bodies (CGIC-DLB) Scale Score	0	N/A	2	45,63
MDS-UPDRS	0	N/A	2	45,66

ADCS-CGIC: Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change, UPDRS: Unified Parkinson's Disease Rating Scale, MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale

Table 4.

Additional scales used as primary or secondary outcomes in DLB clinical trials

Outcome Measure Category	Scale	Primary outcome frequency	Ref.	Secondary outcome frequency	Ref.
ADL	UPDRS Part II	1	[35]	6	[11,34,47,48,59,65]
	ADCS-ADL23	0	N/A	3	[24,49,65]
Caregiver burden	ZBI	2	[10,17]	5	[15,24,40,53,60]
	NPI caregiver distress score	0	N/A	2	[13,63]
	Relative stress scale	0	N/A	2	[59,61]
Motor symptoms	UPDRS-III	11	[10,13,14,21,26,30,31,35,37,53]	12	[11,18,24,25,32,34,47,48,52,59,63,65]
	TUG	0	N/A	4	[47,58,65,67]
Sleepiness	ESS	2	[33,43]	2	[18,66]

ADL: Activities of Daily Living, UPDRS: Unified Parkinson's Disease Rating Scale, ADCS-ADL23: Alzheimer's Disease. Cooperative Study-Activities of Daily. Living, ZBI: Zarit Burden Interview, NPI: Neuropsychiatric Inventory, TUG: Timed up and go, ESS: Epworth Sleepiness Scale