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RESEARCH ARTICLE

Integrated Alzheimer's Disease Rating Scale: Clinically meaningful change estimates

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Abstract

Introduction: The Integrated Alzheimer's Disease Rating Scale (iADRS) has been used to detect differences in disease progression in early Alzheimer's disease (AD). The objectives of this study were to enhance understanding of iADRS point changes within the context of clinical trials, and to establish a minimal clinically important difference (MCID) on the iADRS.

Methods: Data from AMARANTH and EXPEDITION3 were analyzed using various approaches, including anchor-based, distribution-based, regression analyses, and cumulative distribution function (CDF) plots. Three potential anchors were examined, including the Clinical Dementia Rating—Sum of Boxes, Mini-Mental State Examination, and Functional Activities Questionnaire. Triangulation of all results was used to determine the MCID for participants with mild cognitive impairment (MCI) due to AD and AD with mild dementia.

Results: All three anchors met criteria for "sufficiently associated" ($|r| = 0.4–0.7$). Cumulatively, results from anchor-based and distribution-based results converged to suggest an iADRS MCID of 5 points for MCI due to AD and 9 points for AD with mild dementia. Regression analyses and CDF plots supported these values.

Discussion: These findings suggest the iADRS can be used in clinical trials to detect a clinically meaningful outcome of AD progression.

KEYWORDS
Alzheimer's disease, clinical meaningfulness, cognitive/functional composite endpoint, Integrated Alzheimer's Disease Rating Scale, minimal clinically important change, minimal clinically important difference

1 | BACKGROUND

Alzheimer's disease (AD) clinical trials are enrolling participants earlier on the disease continuum (i.e., patients with mild cognitive impairment [MCI] due to AD, or earlier). However, earlier intervention introduces a key challenge in clinical trials of AD: identifying a clinical outcome assessment (COA) to assess cognition and function that is sensitive, responsive, and able to detect clinically meaningful changes across the disease continuum (for a more detailed historical background, see Appendix A.1 in supporting information). Some commonly used COAs in clinical trials of MCI and/or AD with mild dementia include the Clinical Dementia Rating Scale–Sum of Boxes

Research in context

1. **Systematic Review**: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. While previous studies have identified a minimal clinically important difference (MCID) for clinical outcome assessments used in clinical trials of Alzheimer's disease (AD), no study has identified a MCID for the integrated Alzheimer's Disease Rating Scale (iADRS).
2. **Interpretation**: Data from two large, randomized clinical trials and a combination of anchor, distribution, and supportive analyses were used to determine iADRS MCID. A five-point worsening on the iADRS for participants with mild cognitive impairment due to AD, and nine-point worsening for participants with mild AD dementia can be considered clinically meaningful. These results suggest the iADRS captures meaningful cognitive and functional changes.
3. **Future directions**: Clinical trials can use the iADRS and these established MCIDs to detect a clinically meaningful outcome of AD progression.

Highlights

- For mild cognitive impairment due to Alzheimer's disease (AD), a five-point worsening on the integrated Alzheimer's Disease Rating Scale (iADRS) is clinically meaningful.
- For mild AD dementia, a nine-point worsening on the iADRS is clinically meaningful.
- Clinical trials can use the iADRS to detect clinically meaningful AD progression.

(CDR-SB), the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog), the Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living scale (ADCS-iADL), the Mini-Mental State Examination (MMSE), and the Functional Activities Questionnaire (FAQ).[1,2] While each COA has benefits, there are also limitations in each existing scale. For example, the CDR-SB is sensitive to detect disease progression within participants with a range of disease severity,[3] but limited in its ability to consistently detect a treatment effect in clinical trials.[2] The ADAS-Cog and MMSE are measures of global cognition but do not assess the impact of cognition on daily function, while the ADCS-iADL and FAQ measure daily function, but do not directly assess the impact of treatment on cognition.[4–8] While it is well accepted that changes in cognition underlie changes in daily function,[9] oftentimes separate scales are used to assess these two highly related outcomes. A challenge of using separate COAs as co-primary endpoints is increased Type II error, thereby decreasing the chance to detect a true treatment effect in clinical trials.[5] These challenges highlight the need to identify an integrated scale that can assess cognition and function, is reliable and sensitive to detect cognitive and functional changes within and between participants, and that can be meaningfully interpreted across a broad disease spectrum. Doing so will allow uniform recognition of potential treatment effects in participants with AD in clinical trials.

Using a combination of theory-driven and data-driven approaches, the integrated Alzheimer's Disease Rating Scale (iADRS) was developed. The iADRS is a composite of two widely accepted measures, the ADAS-Cog 13-item version (ADAS-Cog13) and the ADCS-iADL. The iADRS has been validated;[10,11] its statistical properties described;[5] and it has been used, and is currently in use, as a clinical outcome measure in previous and ongoing phase 2 and 3 clinical trials in AD.[7,12–17] Cumulatively, these data demonstrated the iADRS was effective in capturing disease progression from MCI throughout moderate AD,[2] as well as treatment effects across the early disease spectrum.[4–6] A more detailed description of the iADRS can be found in Appendix A.1. However, questions remain, including what magnitude of change on the iADRS represents a meaningful change in AD.

A minimal clinically important difference (MCID) is an individual, within-patient change in a COA, and is different than a between-group treatment effect.[18] While between-group treatment effects are important clinical trial endpoints, used to determine the efficacy of an investigational treatment, the within-patient change is equally important because it measures the patient or physician perspective. Specifically, the MCID is a threshold for outcome scores (either patient-reported or physician-measured) over which a patient or physician would consider a given change in score to be meaningful and worthwhile.[18,19] An MCID provides context around a patient's progression and is therefore important to various stakeholders, including the patient, caregivers, and health-care decision makers (e.g., treating clinicians).[18,20] In the case of iADRS, a MCID would provide details around an individual's progression related to both cognition and function, over time.

The objectives of this study were to enhance understanding of iADRS point changes within the context of clinical trials, and to establish a MCID on the iADRS. As an increase in disease severity is associated with a faster cognitive and functional decline, the iADRS MCID will be calibrated by disease severity (i.e., MCI vs. AD with mild dementia).

2 | METHODS

2.1 | Study design

Data from two phase 3 trials, EXPEDITION3 and AMARANTH, were used (Table 1). Details on the population and study design from each trial have been described previously.[12,13] Briefly, AMARANTH was a multicenter, randomized, double-blind, placebo-controlled study of lanabecestat in participants with early AD, defined as MCI due to AD or

TABLE 1 Summary of data used in this retrospective analysis

	AMARANTH (lanabecestat)	EXPEDITION3 (solanezumab)
Design	104-week, phase 2/3 randomized, placebo-controlled trial	80-week, phase 3, placebo-controlled trial
Indication	Early AD (MCI due to AD and AD with mild dementia)	AD with mild dementia
Key inclusion criteria		
Age	55–85	55–90
AD diagnostic criteria	AD with mild dementia: meet NIA-AA criteria with CDR GS of 0.5 or 1, with memory box score of ≥0.5 MCI due to AD: meet NIA-AA criteria with a CDR GS of 0.5, with memory box score of ≥0.5	AD with mild dementia: meet probable AD criteria per NINDS-ADRDA
MMSE score	20-30	20-26
RBANS DMI	≤85	N/A
Amyloid positive	CSF, florbetapir amyloid PET, or historical amyloid PET (florbetaben, florbetapir, flutemetamol, NAV-4694, PiB)	Florbetapir amyloid PET scan or Aβ1-42 measurements in CSF

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; GS, Global Score; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; N/A, not applicable; NAV-4694, fluorine 18-labeled flutafuranol; NIA-AA, National Institute on Aging–Alzheimer's Association; NINDS-ADRDA, National Institute of Neurological Disorders and Stroke and Alzheimer's Disease and Related Disorders Association; PET, positron emission tomography; PiB, Pittsburgh compound B; RBANS DMI, Repeatable Battery for the Assessment of Neuropsychological Status Delayed Memory Index.

AD with mild dementia.[13] EXPEDITION3 was a double-blind, placebo-controlled trial of solanezumab among participants who had AD with mild dementia.[12]

Participants from the treatment and placebo arms of both trials were included in analyses if they had iADRS assessments at baseline and at endpoints of 52 and 78 weeks (AMARANTH) or at baseline and 52 and 80 weeks (EXPEDITION3), and a baseline plus endpoint assessment of at least one other cognitive or functional assessment—either the CDR-SB, the MMSE, or the FAQ. These assessments were chosen because they were considered potential anchors (described in Section 2.3), as these were the three COAs collected at baseline and endpoints in both trials.

2.2 | Clinical outcome assessments

For a scale-by-scale comparison of all clinical outcome assessments described in Section 2.2, see Table A.1 in supporting information.

2.2.1 | iADRS

The iADRS is a linear combination of its two components: the ADAS-Cog13 (range: 0–85; higher scores indicating greater deficit of global cognition)[21] and the ADCS-iADL (range: 0–59; lower scores indicating greater impairment; items: 6a and 7–23).[22,23] For more details on these individual components and iADRS development, see Appendix A.1. Because worse outcomes are indicated by higher scores on the ADAS-Cog13 and lower scores on the ADCS-iADL, the ADAS-Cog13 score is multiplied by −1 when calculating the iADRS score, such that lower iADRS scores indicate greater impairment. iADRS scores range from 0 to 144.

2.2.2 | CDR

The CDR is a clinician reported outcome measure designed as a staging instrument and is a semi-structured interview of participants and informants, after which a clinician rates the severity of symptoms across six domains of cognition and function.[9,24,25] The CDR-SB is a continuous measure of dementia severity (range: 0–18; higher scores indicate greater impairment).[6]

2.2.3 | MMSE

The MMSE is a brief instrument used to assess global cognitive function in participants (range: 0–30; lower scores indicate greater impairment).[26] The instrument measures five areas: orientation, short term memory, attention, short term recall, and language.[26]

2.2.4 | FAQ

The FAQ is an assessment used to measure complex functional activities of daily living, such as ability to shop, cook, and pay bills.[6,27] The FAQ is an informant rating of performance changes in 10 complex activities of daily living (range: 0–30; higher scores indicate greater impairment).[6,27]

2.3 | Anchor- and distribution-based approaches

The Food and Drug Administration (FDA) has recommended using primarily anchor-based methods, supplemented with empirical, distribution-based approaches and cumulative distribution function

TABLE 2 MCID estimates by disease severity over 1 year

	MCI due to AD	AD with mild dementia	Moderate/severe AD dementia
CDR-SB*			
(Range: 0–18; higher = worse)	+1	+2	+2
MMSE†			
(Range: 0–30; lower = worse)	−1	−2	−3
FAQ†			
(Range: 0–30; higher = worse)	+3	+3	+3

Abbreviations: AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; FAQ, Functional Activities Questionnaire; MCI, mild cognitive impairment; MCID, minimal clinically important difference; MMSE, Mini-Mental State Examination.
*Reference for CDR-SB MCID values is Lansdall et al.[29].
†Reference for MMSE and FAQ MCID values is Andrews et al.[4]

(CDF) plots to estimate the MCID.[18] Integration of MCID estimates from each of these approaches is known as triangulation.[18]

An anchor-based approach links change scores on an outcome measure to a meaningful external criterion (i.e., anchor) corresponding to participants' or clinicians' perception of meaningful change. The previously identified level of meaningful change on the anchor is then used to derive a threshold or range of score changes reflecting a clinically meaningful change on the new scale of interest, which in this case is the iADRS. Per guidance, an anchor should be: (1) plainly understood, (2) easier to interpret than the clinical outcome of interest, and (3) sufficiently associated with the target outcome.[18] Based on previously established thresholds, a correlation (negative or positive) between 0.40 and 0.70 indicates two measures are "sufficiently associated,"[28] suggesting appropriateness as an anchor. For these analyses, the CDR-SB, the MMSE, and the FAQ were each identified a priori as potential anchors, as they were available measures of cognition or function, are plainly understood in the context of cognition and/or function in AD clinical trials, and have established MCIDs. Furthermore, incorporating physician input, MCIDs have been established for the CDR-SB, MMSE, and FAQ (Table 2),[4,29] allowing us to classify a change on the iADRS based on a previously established meaningful change on an existing scale. Multiple anchors were investigated per guidance suggesting multiple anchors are advantageous to refine and build confidence around a proposed threshold.[20] For example, the iADRS was developed in an effort to improve upon existing COAs for AD clinical trials, given the limitations of existing COAs, described in Section 1. However, to acknowledge limitations to existing COAs, such as the CDR-SB, MMSE, and FAQ, is to acknowledge limitations of the anchors proposed here. Although each anchor may be limited in some way, if several imperfect anchors each correspond to the same proximate threshold or range of threshold values, it increases confidence in the proposed MCID.[20]

Distribution-based methods consider score changes in the context of variability and reliability of scores.[18,20] Distribution-based parameters were selected based on previously published guidance.[18] Distribution-based parameters are considered supportive evidence because they do not consider the patient's or clinician's perspective.[18,20] Included distribution-based parameters were: effect size (ES), defined as the mean difference in score divided by the standard deviation (SD) of baseline scores; standardized response mean (SRM), defined as the mean difference in score divided by SD of the change; and half the SD (0.5 × SD) of baseline scores. ES and SRM are the most common responsiveness measures. For both, a value of ≥0.80 is considered large, 0.50 to 0.79 moderate, 0.20 to 0.49 small, and 0.00 to 0.19 very small.[30]

Per established guidance, the goal of triangulation is to identify a reasonable threshold value or range of values, using evidence from both anchor- and distribution-based approaches.[18,20,31] Triangulation is not a formal analysis, but rather an expert review of anchor-based results combined with the distribution-based results and additional supportive analyses, including CDF plots. In this step, results from anchor- and distribution-based approaches are examined to determine whether there is convergence of results, pointing to a value or range of values that can be confidently identified as the within-patient MCID. While all results are considered, the relative importance of results varies during this step. Typically, anchor-based results are considered primary.[18,20] Because multiple anchors are often explored simultaneously, they are based on previously established and clinically accepted thresholds, and they incorporate the patient perspective (i.e., are informed by patient, caregiver, or clinician judgment of disease status).[18,20] Furthermore, results of various anchors are all considered, but the importance of anchors varies depending on the context in which the anchor may be most appropriate.[20] In these analyses, the CDR-SB was identified a priori as the anchor of most relative importance out of the three considered anchors, given it measures both cognition and function, similar to the iADRS.

2.4 | Statistical analysis

Baseline descriptive characteristics were calculated for each trial and reported by participants with MCI due to AD versus AD with mild dementia.

Pearson's correlation coefficients between the iADRS and each potential anchor (CDR-SB, MMSE, and FAQ) were evaluated to determine appropriateness of each scale as an anchor. Mean iADRS change over 1 year was estimated for each cohort and each respective anchor threshold (e.g., 1-point worsening on CDR-SB in MCI over 1 year; Table 2). For EXPEDITION3, an 18-month iADRS mean change was

TABLE 3 Baseline age, sex, iADRS, CDR-SB, MMSE, and FAQ, by trial

	AMARANTH MCI due to AD	AMARANTH AD with mild dementia	EXPEDITION3 AD with mild dementia
Age, mean (SD)	71.3 (6.6)	70.7 (7.3)	72.7 (7.8)
Female sex, %	51.5%	54.6%	57.9%
Education level, ≥13 years	53.7%	54.4%	66.7%
iADRS BL, mean (SD)	110.9 (10.2)	101.5 (11.5)	106.6 (13.5)
CDR-SB BL, mean (SD)	2.7 (1.1)	4.1 (1.4)	3.8 (1.8)
MMSE BL, mean (SD)	24.9 (2.6)	23.1 (2.3)	22.8 (2.8)
FAQ BL, mean (SD)	6.2 (4.6)	11.2 (5.9)	10.3 (6.9)

Abbreviations: AD, Alzheimer's disease; BL, baseline; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; FAQ, Functional Activities Questionnaire; iADRS, Integrated Alzheimer's Disease Rating Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SD, standard deviation.

calculated for the CDR-SB anchor (the CDR-SB was not collected at 1 year). For each of the anchors and respective populations, ES, SRM, and 0.5 × SD baseline score were calculated.

Given the CDR-SB was considered a more important anchor than the MMSE or the FAQ, additional (supportive) analyses were performed with only this anchor. Analyses regressed change score on the iADRS versus CDR-SB unit changes. The regression model was fit without an intercept (i.e., the model assumed no change on CDR-SB equated to no change on iADRS). All participants with changes on both scales were included in the models. CDF plots provide an overall picture of change on an outcome measure against change on various anchor levels. CDF plots of change in iADRS from baseline to 52 weeks (AMARANTH) or 80 weeks (EXPEDITION3) by change in various CDR-SB anchor levels were created to determine the percentage of participants within each trial cohort that met the iADRS MCID criteria corresponding to each CDR-SB anchor level.

3 | RESULTS

Baseline characteristics were similar across both trials, including baseline CDR-SB, MMSE, and FAQ (Table 3).

At baseline, week 52 (AMARANTH), week 78 (AMARANTH), and week 80 (EXPEDITION3), the CDR-SB, MMSE, and FAQ all met criteria to be considered sufficiently associated[28] with iADRS (Table A.2 in supporting information). Correlations were stronger as disease progressed.

The iADRS mean change varied slightly across anchors and by disease severity (Table 4). In AMARANTH, among participants with MCI due to AD who progressed +1 point/year on the CDR-SB, the mean (SD) change in iADRS was −5.5 (7.8; Table 4). Estimates were similar in AMARANTH and EXPEDITION3 for patients with AD with mild dementia (9.5 points/year or 12.2 points/1.5 years, respectively). Distribution-based results supported anchor-based results (Table 4).

Regression analyses examining the change in iADRS for every unit change in the CDR-SB from baseline to week 52 (AMARANTH) or week 80 (EXPEDITION3) aligned with anchor-based and distribution-based results (Table 5). A 1-point CDR-SB decline was associated with an approximate reduction of 4 points on the iADRS for participants with MCI due to AD (Table 5), slightly less than the anchor-based approach. For participants with AD with mild dementia, a 2-point CDR-SB decline was associated with an approximate 10-point decline on the iADRS (Table 5), slightly more than the anchor-based approach.

Figure 1 shows the percentage of participants within each CDR-SB anchor level who met the established iADRS MCID within respective trial cohorts. In AMARANTH, among participants with MCI due to AD, approximately 50% of participants with a 1-point increase on the CDR-SB met the iADRS MCID of 5 points (Figure 1A). Among participants with mild AD with mild dementia, 50% of participants with a 2-point increase on the CDR-SB met the iADRS MCID of 9 points (Figure 1B). In EXPEDITION3, among participants with AD with mild dementia, approximately 60% of participants with a 2-point increase on the CDR-SB met the iADRS MCID of 9 points (Figure 1C).

As stated in Section 2.3, anchor-based results were generally weighted more heavily than distribution-based results, and results from the CDR-SB anchor were weighted more heavily than MMSE or FAQ. With this in mind, results from all approaches aligned to support an iADRS MCID of 5 points for participants with MCI due to AD and 9 points for participants with AD with mild dementia.

4 | DISCUSSION

Triangulation of various MCID thresholds obtained via anchor- and distribution-based methods indicated an iADRS MCID of 5 points for MCI due to AD, and 9 points for AD with mild dementia. Across two studies and all methods used, MCID estimates generally aligned. Additional regression analyses and CDF plots supported these iADRS MCIDs.

The iADRS MCIDs established here reflect a decline over time that, if met, is considered clinically meaningful. It is important to note a MCID is not the same as a potential treatment effect detected at a study endpoint. As stated previously, a MCID is an individual, within-patient change in a COA, indicative of a clinically meaningful change whereby the patient is expected to require either additional treatment or additional supportive care. This differs from a between-group

TABLE 4 iADRS change score versus change score of the CDR-SB, MMSE, and FAQ

	AMARANTH MCI due to AD			AMARANTH AD with mild dementia			EXPEDITION3 AD with mild dementia		
	CDR-SB (+1pt/yr)	MMSE (−1 pt/yr)	FAQ (+3 pt/yr)	CDR-SB (+2 pt/yr)	MMSE (−2 pt/yr)	FAQ (+3 pt/yr)	CDR-SB (+2 pt/18 mos)	MMSE (−2 pt/yr)	FAQ (+3 pt/yr)
N	96	74	63	102	141	84	128	223	153
Anchor-based results									
iADRS mean (SD) change	−5.5 (7.8)	−3.5 (8.4)	−5.2 (7.9)	−9.5 (8.7)	−5.9 (9.5)	−7.5 (8.1)	−12.2 (11.5)	−7.0 (9.7)	−7.2 (9.7)
95% CI	−7.1, −3.9	−5.4, −1.5	−7.2, −3.2	−11.2, −7.8	−7.5, −4.3	−9.2, −5.7	−14.2, −10.2	−8.3, −5.7	−8.8, −5.7
Range	−33, 11	−32, 16	−31, 10	−33, 10	−36, 21	−32, 11	−53, 10	−63, 15	−40, 14
Distribution-based results									
ES	−0.57	−0.42	−0.60	−0.83	−0.58	−0.59	−1.07	−0.56	−0.54
SRM	−0.70	−0.42	−0.66	−1.09	−0.62	−0.93	−1.06	−0.72	−0.74
0.5*SD baseline	4.84	4.17	4.34	5.76	5.10	6.32	5.74	6.21	6.70

Abbreviations: AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CI, confidence interval; ES, effect size; FAQ, Functional Activities Questionnaire; iADRS, Integrated Alzheimer's Disease Rating Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; mos, months; pt, patient; SD, standard deviation; SRM, standardized response mean; yr, year.

TABLE 5 Regression analysis showing change in iADRS from baseline to 52, 78, or 80 weeks on change in CDR-SB score

	AMARANTH week 52		AMARANTH week 78		EXPEDITION3 week 80
	MCI due to AD	AD with mild dementia	MCI due to AD	AD with mild dementia	AD with mild dementia
N	622	1062	360	634	1776
Estimate	−3.67*(Δ in CDR-SB)	−4.52*(Δ in CDR-SB)	−4.30*(Δ in CDR-SB)	− 4.92*(Δ in CDR-SB)	−5.25*(Δ in CDR-SB)
95% CI of slope	(−4.05, −3.30)	(−4.76, −4.28)	(−4.74, −3.87)	(−5.19, −4.65)	(−5.43, −5.07)

Abbreviations: AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating Scale–Sum of Boxes; CI, confidence interval; iADRS, Integrated Alzheimer's Disease Rating Scale; MCI, mild cognitive impairment.

treatment effect, which is indicative of a clinically meaningful measure of efficacy between placebo and treatment arms (a treatment effects difference of 20%–30% is generally viewed as meaningful[32–34]). Thus, it is essential to understand the interrelationship of a MCID and a treatment effect when evaluating a MCID in the context of a disease-modifying intervention study. For example, if the iADRS is a COA used in a new clinical trial of MCI due to AD, one could evaluate whether the placebo group met the 5-point iADRS MCID, and if so, how long it took to reach that point. This provides a measure of average "expected" meaningful decline in a given patient population, against which a delay in progression due to a disease-modifying agent can be assessed. If this interventional study showed a 30% slowing of disease progression, and assuming the placebo group reached the MCID at month 18, one could infer the investigational treatment group would meet the MCID at 23.4 months (18 × 30%). In other words, it takes the investigational treatment group 5.4 months longer to reach meaningful decline. As is the case with disease modifying treatments, the savings noted above will grow over time. Another way to think about this is to calculate the proportion of participants meeting the MCID in both study arms. The placebo-treated group is expected to show a greater proportion of participants meeting a meaningful decline, compared to participants in the treatment group. In other words, fewer participants in the treatment group will experience a decline considered meaningful.

The iADRS has a wide range of possible scores (0–144), with lower scores indicating a greater deficit in cognition and function. When used in the intended population, floor and ceiling effects are avoided, making this an appropriate outcome assessment for a broad range of disease severity or over longer investigation periods. In spite of the wide range, a baseline dynamic range (i.e., mean ± 1 SD; capturing 68% of the distribution, assuming normality) has been estimated as 20 points for MCI and 24 to 28 points for AD with mild dementia.[7,12,13,35,36] Thus, within the context of the dynamic ranges, a MCID of 5 points for MCI due to

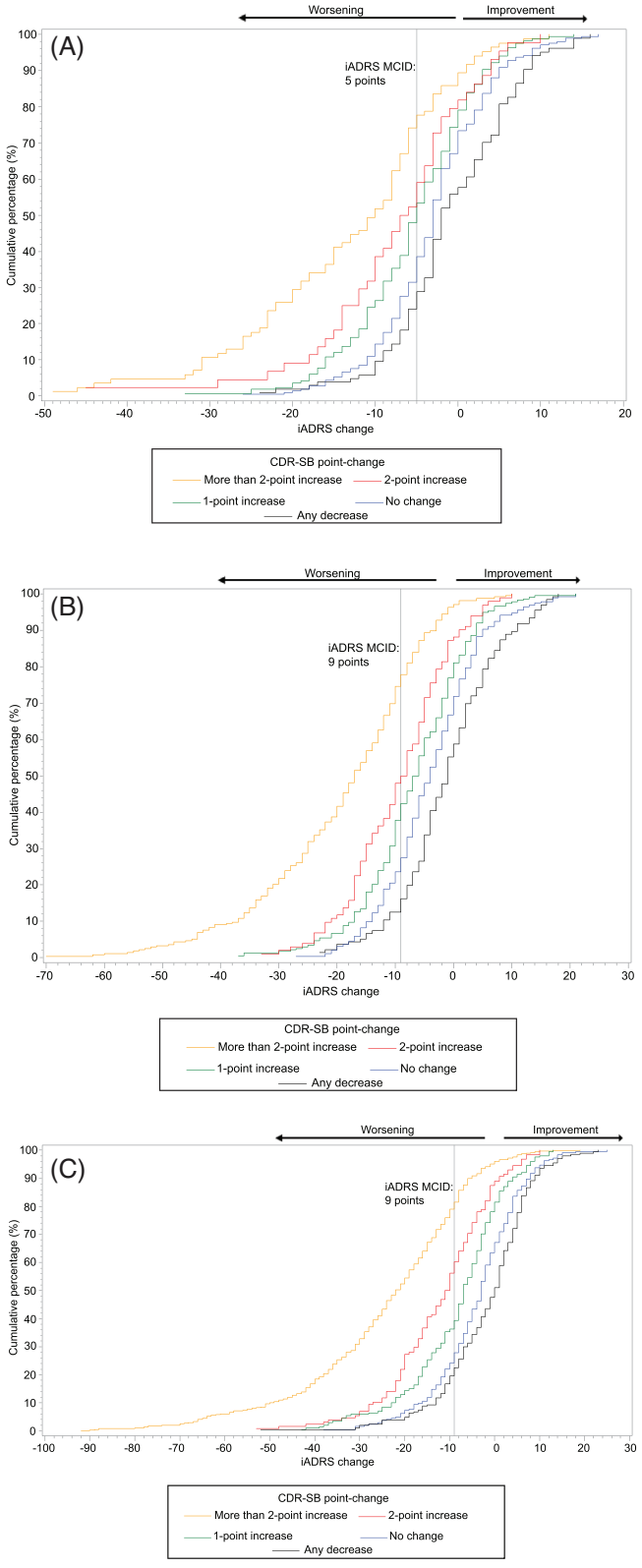

FIGURE 1 Cumulative distribution function curves of change in iADRS from baseline to 52 weeks (AMARANTH) by change in CDR-SB, for participants with MCI due to AD (A), AD with mild dementia (B), and 80 weeks (EXPEDITION3) by change in CDR-SB for participants with AD with mild dementia (C). AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating–Sum of Boxes; iADRS, Integrated Alzheimer's Disease Rating Scale; MCI, mild cognitive impairment; MCID, minimal clinically important difference

AD or 9 points for AD with mild dementia will be useful in interpreting clinical trial data, and treatment effects across the disease severity spectrum.

As discussed in Section 2.3, anchor-based results are considered primary per established guidance.[18,20] It was important to consider multiple anchors, each chosen on "face value" because it measures a construct similar to the COA of interest (i.e., iADRS).[18,20] While strong correlations between potential anchors and the COA of interest are anticipated, it must always be investigated to be certain of anchor appropriateness.[18,20] These results showed the iADRS was sufficiently correlated with all three potential anchors, and the strength of each association increased over time, a previously demonstrated relationship[37] indicating the anchor remains an appropriate choice as disease progresses. Within anchor-based results, the CDR-SB was considered the most appropriate anchor[20] because, like the iADRS, it measures both cognition and function.[6,9,24,25] Alternatively, the MMSE measures global cognition but not function, and the FAQ measures daily function but not cognition.[6,26,27] That said, providing iADRS data against all three anchors was important because it allowed researchers and clinicians to make inferences about the performance of iADRS against well-established, well-accepted, and widely understood outcome measures.

CDF plots examined an overall picture of iADRS change over time for relevant CDR-SB anchor levels. This approach approximates the percentage of responders at other potential CDR-SB anchor levels and allows a visual comparison of separation between CDR-SB anchor levels, relative to the proposed iADRS MCID. For example, in AMARANTH, among participants with AD with mild dementia, 50% of participants with a 2-point worsening on the CDR-SB met the 9-point iADRS MCID. For participants with AD with mild dementia and a >2-point worsening on the CDR-SB, approximately 80% met the 9-point iADRS MCID, and 40% with a 1-point worsening on the CDR-SB met the 9-point iADRS MCID. Even among participants with AD with mild dementia who showed "improvement" on the CDR-SB, 16% met the 9-point iADRS MCID. These results show granularity of the iADRS versus the CDR-SB and support the usefulness of a wide score range that avoids floor and ceiling effects. The CDF plots support the iADRS detecting a clinically meaningful difference with more sensitivity than the CDR-SB. CDF plots support anchor- and distribution-based results, and a 9-point iADRS MCID for AD with mild dementia and 5 points for MCI due to AD.

Results from this study should be considered within the context of potential limitations. In Andrews et al.,[4] the CDR-SB MCID estimate is based on a group mean (1.63 points for AD with mild dementia[4]), whereas in analysis of participant-level data, CDR-SB scores occur on a continuous scale with 0.5-point increments. To allow differentiation from MCI (which had a MCID of 0.984), we analyzed our data based on a 2-point CDR-SB change for the AD with mild dementia group. Therefore, the established iADRS MCID for AD with mild dementia (9 points) may be slightly overestimated. Additionally, these (post hoc) analyses were limited to previously collected clinical trial measures. Some anchors (CDR and MMSE) were used in study screening or diagnostic process of the clinical trials; therefore, it cannot be ruled out that

results may be impacted by participant selection. A variable capturing "clinician-based judgment of meaningful decline" or an anchor reflecting patient/care partner input regarding "meaningfulness" was missing from existing clinical trial data. Finally, and as mentioned in Section 2.3, triangulation is not a formal statistical test, rather an interpretation of available evidence. In these analyses, we chose to more heavily weight anchor-based analyses and the CDR-SB, and use distribution-based analyses, regression analyses, and CDF plots as supportive data. Different assumptions may have resulted in different MCID estimates.

Using data from two large, randomized clinical trials and a combination of anchor, distribution, and supportive analyses, we presented performance on the iADRS in relation to well-established, well-accepted, and widely understood outcome measures. These data will aid researchers and clinicians in the interpretation of iADRS scores and score changes in future clinical trials and existing data. Results show a 5-point worsening on the iADRS for participants with MCI due to AD and 9 points for participants with AD with mild dementia can be considered a clinically meaningful change. These findings suggest the iADRS is a valid cognitive and functional endpoint that can be used in clinical trials to detect a clinically meaningful outcome of AD progression.

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CONFLICTS OF INTEREST

Alette M. Wessels, Michael Case, Steve Lauzon, and John R. Sims are all employees and minor shareholders at Eli Lilly and Company. Dorene M. Rentz reports consulting relationships with Biogen IDEC and Digital Cognition Technologies; she also serves on the Scientific Advisory Board for Neurotrack.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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